C-reactive protein, inflammation and atherosclerosis: do we really understand it yet?

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During the past decade, it has become apparent that atherosclerosis is an inflammatory process. This fact has engendered a great deal of interest in identifying markers which may be detected in the blood that could reflect the state of the underlying inflammation present in the vascular wall\(^1\). In the current issue Tataru et al\(^2\) study the relationship between plasma C-reactive protein levels and the severity of atherosclerosis in 1112 male and 299 female survivors of acute myocardial infarction, as well as 326 male and 138 female controls. Patients in the study were divided into groups according to the severity of the manifestations of atherosclerosis. The worse the generalized manifestations of atherosclerosis, the higher the C-reactive protein levels. C-reactive protein was also shown to be higher in smokers and with increasing age. C-reactive protein also correlated with other risk factors for atherosclerosis, which in turn explain a modest amount of the variability in the C-reactive protein values.

This paper confirms a number of other studies that have shown a relationship between atherosclerosis and inflammation\(^1,3,4\). This is because C-reactive protein is an acute phase reactant, detectable in the plasma in numerous inflammatory processes. By themselves, such studies do not address the more fundamental nature of the association between inflammation and the pathogenesis of atherosclerosis. It is clear that lipids\(^5\), oxidation state\(^6\), mechanical stress\(^7\), thrombosis\(^8\), and perhaps even infection\(^9\) participate in the pathogenesis of atherosclerosis. The earliest event is thought to involve oxidative modification of lipoproteins in the subintimal space\(^10\). These modified lipoproteins elicit an immune-like response in the vessel wall, including stimulation of inflammatory cytokines and expression of vascular cell adhesion molecule-1 (VCAM-1) and the monocyte chemoattractant peptide-1 (MCP-1). The latter two are critical in recruiting monocytes into the subintimal space, where they become lipid-laden foam cells and release large amounts of reactive oxygen species, which in turn further oxidize lipoproteins. These heavily oxidized lipoproteins are avidly taken up by foam cells and are very biologically active.

Why do lipoproteins in the subintimal space evoke such an immune response? What does this have to do with C-reactive protein? It is fascinating to note that the antigenic proteins of several microbial agents are lipoproteins. In particular, mycobacterium tuberculosis secretes a 19 kD lipoprotein that stimulates the production of the inflammatory cytokine IL-12 from human monocytes via activation of the Toll receptor\(^11\). This receptor is present in many organisms, including Drisophila, suggesting that it is a fundamental defence mechanism that has been used by both vertebrates and invertebrates for millions of years. Of note, injection of mice with a heat shock protein of mycobacterium tuberculosis increases the development of atherosclerosis. Thus, it is interesting to speculate that the inflammation observed in atherosclerosis represents a very basic immune response originally designed to defend against invading microorganisms. Also of note, oxidation of lipoproteins is probably an attempt at an adaptive response. Unmodified lipoproteins are taken up via the LDL receptor of macrophages and other cells. This receptor is rapidly down-regulated by the presence of excess amounts of LDL. In contrast, oxidized LDL is taken up by the scavenger receptor, which is not subject to down-regulation. Thus, lipoprotein oxidation permits macrophages to ‘clean-up’ large amounts of lipids from the subintimal space. The problem facing our society in general is that our diet and other risk factors increase the amount of lipoproteins and, in particular, oxidatively modified lipoproteins in the subintimal space, promoting this very basic, and otherwise protective, immunological response. Some of these risk factors, such as diabetes\(^12\), cigarette smoking\(^13\), and hormonal influences, especially angiotensin II\(^14,15\), increase the oxidative state of the vessel wall, contributing to this cascade by amplifying the oxidation of lipoproteins.

Part of this inflammatory response is a loss of the endothelial production of nitric oxide, which results from several mechanisms. One involves down-regulation of the endothelial cell nitric oxide synthase mRNA by locally released cytokines\(^16\) and oxidized LDL\(^17\). A second involves oxidative destruction of nitric oxide by the superoxide anion, produced in excess quantities in several pathological states\(^18\). Nitric oxide has potent antioxidant and antiinflammatory roles in the blood vessel, and thus the loss of nitric oxide in these various conditions unMASKS and even promotes this inflammatory process.
Given these considerations, it is not at all surprising to find that a marker of the inflammatory milieu, such as the C-reactive protein, is elevated in individuals with atherosclerosis. The question that needs to be asked is whether or not this marker adds anything to our understanding of how sick an individual patient is, how advanced his or her disease is, or how aggressive we should be in subsequent evaluation or treatment. Of note, other blood-borne markers have been identified that may also prove to be useful. These include circulating antibodies against oxidized LDL\(^{19}\), antibodies against oxidized protein epitopes\(^{20}\) thought related to LDL oxidation, circulating soluble VCAM\(^{21}\), and others.

While studies such as that of Tataru et al.\(^{17}\) suggest that C-reactive protein may prove useful, some of these other markers may be more specific for detecting the inflammation of atherosclerosis. It is also attractive to consider that combinations of these will be useful. One must also wonder how these various blood-borne markers measure up against time-proven methods for risk stratification such as exercise tolerance, nuclear-stress imaging, or stress echocardiography in allowing risk stratification of individuals with known or suspected coronary disease. Perhaps a useful approach for such blood tests will be the screening of asymptomatic individuals without known coronary disease on a large scale to determine who may benefit from more extensive non-invasive or invasive testing.

Whether inflammation in the development of atherosclerosis accelerates the process or is reparative is also uncertain. Clearly a deeper understanding of the process will need to be developed and certainly will be over the coming years. Risk factors for atherosclerosis even if involved in the causative path need not be totally independent. Thus, we see in the paper by Tataru et al.\(^{17}\) that lipid levels actually correlate with C-reactive protein levels.

Understanding each of the factors involved in the development of atherosclerosis has tremendous implications for prevention and therapy. While lipid lowering has been shown to decrease fatal and non-fatal cardiovascular events both in primary prevention and secondary prevention populations, available data from clinical trials would suggest that lipid lowering alone will not eliminate atherosclerosis\(^{22–26}\). Consequently, there has been interest in other factors as well. While the oxidative state may be important in the pathogenesis of atherosclerosis, to date there has not been an effective therapeutic strategy aimed at the oxidative state, and the few trials to involve antioxidants have so far been largely negative\(^{27–29}\). Mechanical stress cannot easily be addressed directly, except perhaps via controlling blood pressure. In that regard, recent guidelines have called for tighter control of blood pressure\(^{30}\). Reduction of events by controlling clotting, especially by the antiplatelet effect of aspirin and ADP blockers, has been successful\(^{31–33}\). However, this has been in patients who have atherosclerosis already, and the place of clotting in the early development and as an initial cause of atherosclerosis is much less certain. Antiplatelet agents will certainly not result in the elimination of atherosclerosis, however they remain important in decreasing events.

There is little evidence that antiinflammatory agents are useful in the treatment of atherosclerosis. Why this is so may relate to the limited experience, inadequate therapeutic agents, or the relationship of inflammation to atherosclerosis. If inflammation is reparative, antiinflammatory agents may not be useful. On the other hand, if inflammation in atherosclerosis goes beyond its protective and reparative functions to become destructive, then there may be a therapeutic window. In this regard, there is an important, if still somewhat uncertain, paper from the CARE study which showed that the HMG Co-A reductase inhibitor pravastatin could decrease plasma C-reactive protein independent of its effect on plasma lipid levels\(^{34}\). This offers the possibility, certainly without proof, that the effects of the HMG Co-A reductase inhibitors, which have so consistently lowered event rates in clinical trials, were in part mediated through a direct effect on atherosclerosis and, perhaps, on inflammation. Whether this can be adequately dissected out from current clinical trial data remains to be seen.

In conclusion, the paper by Tataru et al.\(^{17}\) raises more questions than it answers. The answer to the puzzle of atherosclerosis will lie largely with the basic scientists, perhaps with some help from their colleagues in the clinical trial and epidemiological community. There is a need to really understand the cause of atherosclerosis. There is also a need to understand whether at the bottom of the plethora of risk factors there is one final cause, perhaps still hidden to us, or whether atherosclerosis is, in the end, the final product of a multifactorial series of causes. Finally, there is a need to understand how the various pathophysiological factors function during the curse of the disease and how they interact.

There has long been a strong history in the treatment of coronary artery disease of advances in physiology leading to improved therapeutics, which are then shown to be beneficial in randomized clinical trials. As our understanding of the nature of both atherosclerosis and the role and relationships of the aetiological factors increases, we can expect to see the development of improved therapeutics and additional...
clinical trials aimed at proving benefit. As this process unfolds, the great plague of the late 20th century in the industrial world may recede and perhaps will not be the great plague of the 21st.

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References


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