Oxidized Lipoproteins and Infectious Agents
Are They in Collusion to Accelerate Atherogenesis?

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Recent epidemiological studies have documented an increased incidence of some forms of coronary artery disease (CAD) in patients who have chronic infections and inflammatory disorders. Chlamydia pneumonia1–3 and herpes viruses4–6 have been implicated in the pathogenesis of CAD on the basis of their detection in human atherosclerotic plaques and epidemiological evidence of a higher incidence of CAD in patients infected with these agents. In this regard, many investigative reports have focused on the proatherosclerotic effects of infectious agents on vascular cells in tissue culture and how they may affect the biology of the arterial wall. The panoply of changes induced include those that increase the thrombotic potential of the vessel wall,7 increase expression of macrophage scavenger receptors with subsequent enhanced uptake of cholesterol through oxidized lipoproteins,8 increase expression of adhesion molecules9 and inflammatory cytokines,10 and increase smooth muscle cell migration11 and proliferation. Moreover, products of certain pathogens can exert proatherosclerotic effects directly in the macrophage, thereby promoting transformation of macrophages into atherosclerotic foam cells and stimulating them to express cytokines that contribute to plaque instability and even rupture. Indeed, many of these pathological features fall within the rubric of an inflammatory response. Interestingly, evidence is now mounting that the acute-phase response (APR) is associated with oxidation of LDL. The hypothesis that increased modification of circulating LDL can lead to enhanced atherosclerosis specifically through the oxidation process is not novel; it has been tested in several in vitro and in vivo animal models of atherosclerosis over the last two decades.

In this issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Memon et al12 have demonstrated that the host response to infection and inflammation can lead to lipoprotein oxidation in vivo. They reason that this may be an important mechanism by which infection and inflammation promote CAD. In that report, they measured lipoprotein oxidation in three distinct models of infection and inflammation in vivo. Syrian hamsters were injected with lipopolysaccharide (LPS), zymosan, and turpentine to mimic acute infection, acute systemic inflammation, and acute localized inflammation, respectively. Levels of oxidized fatty acids in serum and lipoprotein fractions were carefully measured. Their results demonstrate a significant increase in serum levels of oxidative lipoprotein products in the form of conjugated dienes in all three models studied compared with controls. Often levels of conjugated dienes, thiobarbituric acid–reactive substances, and lipid hydroperoxides are reported as oxidative parameters of the pathophysiological outcome of the lipoproteins, although it is not entirely clear what the full effect is on the vessel wall of these substances found mainly in the serum. Notably, LPS and zymosan produced a ≈6-fold increase in conjugated dienes and lipid hydroperoxides in the LDL particle, and LPS produced a 17-fold increase in lysophosphatidylcholine during the oxidative modification process of LDL. Furthermore, Memon et al demonstrate that the LDL isolated from animals treated with bacterial LPS was significantly more susceptible to ex vivo oxidation with copper than LDL isolated from control animals. The mechanisms for this are unclear but may involve depletion of anti-oxidants from the lipoprotein.

The authors of this study raise the question of why lipoprotein oxidation would occur during a host reaction to infection and inflammation such as an acute-phase reaction (APR). An APR is a protective biochemical mechanism to prevent systemic injury and one that assists in repair processes. Indeed, reactive oxygen species and free radicals are part of the local host-defense mechanism, because they play a role in killing invading microorganisms. The authors reasonably conclude that the lipoproteins may scavenge these free radicals to prevent systemic toxicity and that a major enzyme that plays a key role in microbial killing, myeloperoxidase, is released by activated neutrophils and monocytes in response to bacterial infection or by other inflammatory stimuli. This explanation is well grounded, given that other studies have shown that LPS can also induce the expression of lipoxygenases required for the synthesis of several inflammatory mediators, such as leukotrienes.13 These substances, which are important signal-transduction mediators during inflammatory responses, also participate in LDL oxidation by oxidizing fatty acids and esterified lipids. Thus, it is possible that early activation of lipoxygenase may initiate the oxidative process that subsequently accelerates after the depletion of paraoxonase in the blood.13

The hypothesis that infection contributes to atherosclerosis is based on circumstantial evidence, albeit the evidence is compelling. At best, it is likely that only a relatively small percentage of CAD is a “direct” result of bacteria or viruses within the atheroma. However, one should not lose sight of

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the possibility that these infectious agents may also alter the physiology of the vessel wall indirectly, perhaps through other cellular pathways. Thus, these agents could participate in an inflammatory response either locally within the lesion or systemically to contribute to an accelerated atherosclerotic process. It is conceivable that infectious agents may work in tandem with known risk factors to accelerate atherogenesis. On the basis of these studies of Memon et al that showed increased levels of oxidative lipids in the serum as well as in circulating LDL in animal models of bacterial infection and inflammation, it is reasonable to conclude that a sustained host response to these pathophysiological events may be proatherogenic.

Of course, further studies are required to understand the changes in metabolism that occur and contribute to the lipoprotein oxidative process. It is widely believed that as LDL becomes oxidized, the rate of its influx into the vessel wall increases. Extracellular matrix can participate by trapping these modified lipoproteins, thereby contributing to extracellular lipid deposition. Progressive oxidation and the ensuing oxidative stress can continue because of the action of lipoxygenases, reactive oxygen species, peroxynitrates, and myeloperoxidase. Consequently, a range of oxidative LDL species is generated, which results ultimately in their recognition and internalization by macrophages and smooth muscle cells by means of specialized cellular receptors known as scavenger receptors on these cells. These oxidative lipoproteins (or molecular Trojan horses), which carry cellular saboteurs (or lipid peroxides), can contribute to the formation of “foam” cells in the vessel wall during atherogenesis. In addition to foam cell development, products of LDL peroxidation may activate endothelial cells and macrophages to release cytokines, which may participate in smooth muscle cell mitogenesis or enhance the binding of oxidized LDL to vascular cells. As this vicious cycle continues, spurred on, in part, by the chronic presence of infectious agents, the atheromatous plaque slowly develops.

References


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