Effects of Inflammation on High-Density Lipoproteins

Philip Barter

High-density lipoproteins (HDLs) protect against the development of atherosclerotic coronary heart disease. In part, this reflects the ability of HDL to promote the efflux of cholesterol from macrophages in the artery wall but given that atherosclerosis is an inflammatory disorder, it may also reflect anti-inflammatory properties of HDL. Conversely, inflammation reduces the concentration of HDL and possibly compromises the anti-atherogenic functions of these lipoproteins. Given the pathophysiological implications of a potentially detrimental effect of inflammation on HDL function, it is clearly important to understand the mechanisms that may be involved. Such mechanisms are the subject of an article by Tietge et al in this issue of Arteriosclerosis, Thrombosis, and Vascular Biology.

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These authors provide compelling evidence that the effects of inflammation on HDL are the result mainly of activity of secretory phospholipase A2 (sPLA2), an acute phase reactant that is known to be present at increased concentration in plasma in a variety of inflammatory states and which has the ability to remodel HDL. Because remodeling of HDL by a variety of plasma factors is known to play a major role in regulating the concentration and subpopulation distribution of HDL, the possibility that inflammation may have an impact on this remodeling is of potentially great importance.

Remodeling of HDL in plasma plays a major part in the regulation of these lipoproteins. HDLs originate as lipid-free or lipid-poor apolipoproteins that acquire most of their lipid in the extracellular space. They accept phospholipids and cholesterol from cells in a process promoted by the ATP binding cassette A1 transporter (ABCA1) to form prebeta-cholesterol from cells in a process promoted by the ATP in the extracellular space. They accept phospholipids and lipid-poor apolipoproteins that acquire most of their lipid on this remodeling is of potentially great importance.

The remodeling of HDL may be responsible for the substantial changes to the lipoproteins during states of inflammation. These changes are mediated by acute phase reactants that circulate in plasma at such times. Two of these are serum amyloid A (SAA) protein and PLA2, both of which are present at increased concentration in plasma during inflammation.

SAA is an acute-phase reactant that is synthesized in the liver and is released into the plasma in a variety of inflammatory conditions. It is also released into plasma in response to major trauma or surgery. Within plasma, most of the SAA is transported as a component of HDL for which it has a high affinity. In vitro, SAA displaces apoA-I and, to a lesser extent, apoA-II from HDL and reduces the concentration of HDL cholesterol (HDL-C). The presence of SAA in HDL inhibits the LCAT-mediated esterification of HDL-C and decreases the ability of HDL to protect LDL against oxidation. These effects of SAA on cholesterol esterification in HDL and on the anti-oxidant properties of HDL both have the potential to diminish the anti-atherogenic properties of these lipoproteins. However, not all effects of SAA compromise their anti-atherogenic potential. For example, the presence of SAA in HDL does not reduce the ability of HDL to inhibit the expression of adhesion molecules in activated endothelial cells. Thus, the true impact of SAA on the protective properties of HDL remains uncertain.

The effects of SAA on HDL concentration and composition in vitro have not been confirmed in vivo. In studies in which the in vivo plasma concentration of SAA was increased in mice in the absence of an acute phase reaction, there was no effect on the concentration of HDL-C. It was noted, however, that this observation was made in mice that lacked endogenous sPLA2, leaving open the possibility that SAA may have an indirect effect on HDL during inflammation by activating sPLA2. This possibility has been largely excluded by the studies reported in this issue of the Journal by Tietge et al who conclude that sPLA2, but not SAA, accounts for the changes to HDL in inflammation.

sPLA2 originates in tissues throughout the body. Its synthesis and plasma concentration are increased in states of both acute and chronic inflammation, including acute coronary disease. Indeed, the plasma level of sPLA2 is predictive of coronary artery disease.

Secretory PLA2 has been clearly shown to remodel HDL in vitro. It hydrolyses HDL phospholipids and reduces HDL particle size, although, unlike CETP and PLTP, it does not generate prebeta-migrating apoA-I. The expression of sPLA2 in vivo in transgenic mice decreases the concentration...
of HDL-C and accelerates the development of atherosclerosis.

In the study reported by Tietge et al., the effects of sPLA2 on human-like HDL particles have been investigated in vivo in double transgenic mice expressing human sPLA2 and human apoA-I. The HDLs in these double transgenic mice were reduced in size, depleted in phospholipids and cholesterol esters, and enriched in triglyceride and protein when compared with the HDL in single transgenic animals expressing human apoA-I only. When an acute-phase response was initiated in these animals by intraperitoneal injection of LPS, there was an increase in plasma concentration of SAA in all animals. In the human apoA-I transgenic controls (lacking endogenous sPLA2), there was no change in the concentration of HDL-C. In contrast, in the double transgenic mice (possessing sPLA2), there was an increase in plasma concentration of sPLA2 and a decrease in HDL-C. To determine whether SAA has the capacity to activate sPLA2 in vivo, SAA was over-expressed in the double transgenic mice by using a technique of gene transfer. Despite high levels of SAA on a background of sPLA2, there was no evidence of an effect of SAA on HDL.

The results of the study reported by Tietge et al. provide clear evidence not only of a major effect of sPLA2 on the concentration and subpopulation distribution of HDL but also that these changes during acute phase reactions are unrelated to the presence of SAA. As discussed by the authors, this finding has important implications for our understanding of the pathophysiology of HDL in states of inflammation. It also identifies sPLA2 as a potential target for a therapeutic intervention designed to maintain the concentration and anti-atherogenic potential of HDL during inflammation.

References

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