Understanding Changes in High Density Lipoproteins During the Acute Phase Response

Brian J. Van Lenten, Srinivasa T. Reddy, Mohamad Navab, Alan M. Fogelman

During infection and inflammation there is a cascade of reactions that occurs in the host collectively known as the acute-phase response (APR).1 Besides alterations in acute-phase reactants (plasma proteins), the APR is also associated with changes in lipoproteins.2 Increasing evidence suggests that high density lipoproteins (HDL) are a critical part of the acute phase response (APR) of the innate immune system.3 During infection and inflammation, there is a reduction in levels of several plasma proteins involved in HDL-mediated reverse cholesterol transport and inhibiting plasma lipid oxidation, such as lecithin:cholesterol acyltransferase (LCAT), cholesterol ester transfer protein, phospholipid transfer protein, hepatic lipase, apolipoprotein acyltransferase (LCAT), cholesterol ester transfer protein, phospholipid transfer protein, hepatic lipase, apolipoprotein A-I (apoA-I), and paraoxonase (PON).2 Moreover, the composition of circulating HDL during an APR, also known as acute-phase HDL, is altered. Analysis of the lipid composition shows that acute-phase HDL is depleted in cholesterol ester but enriched in free cholesterol, triglyceride, and free tity acids.4 Changes in the phospholipid content of acute-phase HDL was shown to be more variable, having increased in one study5 but decreased in another.6 The levels of apolipoprotein J (apoJ or clusterin) and serum amyloid A (SAA) increase several fold in acute-phase HDL.7 Because of the marked changes in HDL during an APR, acute-phase HDL behaves differently from normal HDL in terms of its protective effect against atherosclerosis.8 Malle and coworkers have shown that acute-phase HDL was less effective in removing cholesterol from macrophages.9 Delivery of cholesterol ester to hepatocytes is also decreased during an APR because of changes in HDL composition and a reduction in hepatic scavenger receptor class B type.10

Van Lenten reported that the APR resulted in apoA-I being displaced from HDL by SAA, which was associated with a decrease in PON activity and the conversion of HDL to a proinflammatory state.7 Kisilevsky et al13 postulated that the principal role for SAA in acute inflammation is to enhance cholesterol removal from sites of tissue destruction, whereas Gonnermann et al14 proposed that SAA enrichment of HDL during the acute-phase response may cause HDL to deliver phospholipids and cholesterol to cells involved in tissue repair at sites of inflammation. In reviewing the changes in HDL induced by the APR, Khovidhunkit et al commented, “Because apoSAA can displace apoA-I from HDL16,17 and apoSAA-rich HDL particles are rapidly cleared from the circulation,18 it has been assumed that the several-fold increase in apoSAA content in HDL is the mechanism for the decrease in apoA-I and HDL levels. However, we have shown that the decrease in HDL is very rapid, occurring before the increase in SAA.19 Furthermore, a study in mice in which apoSAA levels were markedly increased to levels comparable to those seen in infection found no changes in HDL cholesterol or apoA-I levels.20 Thus, high levels of SAA per se do not decrease HDL or apoA-I levels in the absence of the other changes that occur during infection and inflammation.”

The notion that displacement of apoA-I from HDL during an APR may contribute to a less protective form of HDL was advanced by evidence from Burger and colleagues, who demonstrated an inhibition of cellular contact between stimulated T cells and monocytes by HDL-associated apoA-I.21 This mechanism inhibits monocyte activation and therefore both tumor necrosis factor (TNF)-α and interleukin (IL)-1β production. Noting that this inhibitory activity is present in plasma, the authors suggest that apoA-I controls the contact-mediated activation of monocytes in the blood stream. By inhibiting contact-mediated activation of monocytes, HDL-associated apoA-I displays antiinflammatory properties in a mechanism relevant to atherosclerosis.

In this issue of Arteriosclerosis, Thrombosis, and Vascular Biology Han et al22 demonstrate in an elegant series of in vitro and in vivo studies reciprocal and coordinate regulation of serum amyloid A versus apoA-I and PON-1 by inflammation in murine hepatocytes. These authors convincingly demonstrate that cytokines coordinately increase SAA and decrease apoA-I and PON-1. These reciprocal changes appear to be promoted by NF-κB and repressed by the nuclear receptor PPAR-α. As the authors note, neither apoA-I nor PON-1 promoters contain NF-κB sites,23–26 and the SAA promoters do not contain PPAR response elements.27 Thus, the mechanism for this coordinate regulation may be indirect both for PPAR-α and NF-κB. Despite the absence of a clear mecha-
nism for the all the steps involved, their experiments in PPAR-α-deficient mice convincingly demonstrate that PPAR-α does affect the expression of mouse apoA-I, and shows that PPAR-α activation can mitigate NF-κB activation by inflammatory stimuli.

The authors propose a model whereby reciprocal changes during cytokine-mediated inflammation are regulated by an interaction between PPAR-α and NF-κB, inducing counter-regulatory transcriptional responses through changes in expression of their target genes. Their work also suggests that PPAR-α expression exerts a chronic “braking” effect on inflammation, which can be reversed by inflammatory cytokines or the absence of PPAR-α itself.

These studies together with the earlier studies suggest that the reduction in apoA-I and PON during the APR is most likely not simply attributable to the displacement of apoA-I particles containing PON by SAA but is an example of the extraordinary molecular complexity of the APR, which includes reciprocal and coordinate changes of many important proteins.

Disclosures
MN, STR, and AMF are principals in Bruin Pharma and AMF is an officer in Bruin Pharma.

References
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