HDL and the Inflammatory Response Induced by LDL-Derived Oxidized Phospholipids

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Abstract—Oxidation of low density lipoprotein (LDL) phospholipids containing arachidonic acid at the sn-2 position occurs when a critical concentration of “seeding molecules” derived from the lipoxygenase pathway is reached in LDL. When this critical concentration is reached, the nonenzymatic oxidation of LDL phospholipids produces a series of biologically active, oxidized phospholipids that mediate the cellular events seen in the developing fatty streak. Normal high density lipoprotein (HDL) contains at least 4 enzymes as well as apolipoproteins that can prevent the formation of the LDL-derived oxidized phospholipids or inactivate them after they are formed. In the sense that normal HDL can prevent the formation of or inactivate these inflammatory LDL-derived oxidized phospholipids, normal HDL is anti-inflammatory. HDL from mice that are genetically predisposed to diet-induced atherosclerosis became proinflammatory when the mice are fed an atherogenic diet, injected with LDL-derived oxidized phospholipids, or infected with influenza A virus. Mice that were genetically engineered to be hyperlipidemic on a chow diet and patients with coronary atherosclerosis, despite normal lipid levels, also had proinflammatory HDL. It is proposed that LDL-derived oxidized phospholipids and HDL may be part of a system of nonspecific innate immunity and that the detection of proinflammatory HDL may be a useful marker of susceptibility to atherosclerosis. (Arterioscler Thromb Vasc Biol. 2001;21:481-488.)

Key Words: HDL □ LDL □ atherosclerosis □ oxidized phospholipids

The events involved in fatty streak formation resemble those elicited by mycobacteria. Over the past decade, there has been increasing evidence that this inflammatory response may, in part, be elicited by the oxidation of phospholipids contained in LDL. Several oxidized phospholipids that are able to induce the genes and proteins necessary for the cellular response seen in the fatty streak have been identified in mildly oxidized LDL and in lesions of animal models of atherosclerosis. Two of these oxidized phospholipids, 1-palmitoyl-2-(5-oxovaleroyl)-sn-glycero-3-phosphorylcholine (POVPC) and 1-palmitoyl-2-glutaroyl-sn-glycero-3-phosphorylcholine (PGPC), both induced monocytes to bind to endothelial cells. However, PGPC but not POVPC also induced neutrophils to bind to endothelial cells. Indeed, POVPC strongly inhibited lipopolysaccharide-mediated induction of neutrophil binding and expression of E-selectin protein and mRNA. This inhibition by POVPC was mediated by a protein kinase A–dependent pathway that resulted in downregulation of nuclear factor-κB–dependent transcription. PGPC, on the other hand, induced both E-selectin and vascular cell adhesion molecule-1 (VCAM-1) expression on endothelial cells. On the basis of studies in Xenopus laevis oocytes, Leitinger et al concluded that POVPC and PGPC bind to different receptors. Furthermore, they demonstrated that at concentrations equal to those present in mildly oxidized LDL, POVPC prevented the induction of neutrophil binding and E-selectin expression in endothelial cells despite the presence of PGPC. Thus, we hypothesized that the relative concentrations of POVPC and PGPC will determine whether an acute (neutrophilic) or chronic (monocytic) inflammation would result in any given tissue. A third group of oxidized phospholipids that also induce monocyte binding to endothelial cells was identified as 1-palmitoyl-2(5,6-epoxyisoprostane E2)-sn-glycero-3-phosphorylcholine (PEIPC). Autoantibodies specific for products of oxidized 1-palmitoyl-2-arachidonoyl-sn-glycero-3-phosphorylcholine (Ox-PAPC), including POVPC, have been identified in apolipoprotein-deficient mice and have been shown to inhibit macrophage uptake of oxidized LDL. These antibodies have also been shown to bind to apoptotic cells and inhibit their phagocytosis by macrophages, indicating that these oxidation-specific epitopes mediate macrophage recognition of apoptotic cells. These antibodies, which have been found in atherosclerotic...
lesions, were found to be structurally and functionally identical to classic “natural” T15 anti-phosphorylcholine antibodies that are of B-1 cell origin and that have been reported to provide protection against virulent pneumococcal infection.14

The inflammatory response elicited by the oxidized phospholipids (eg, Ox-PAPC) found in mildly oxidized LDL is mediated in part by the induction in endothelial and smooth muscle cells of monocyte chemotactic protein-1 (MCP-1)15; macrophage colony stimulating factor (M-CSF),16 a member of the GRO family of chemokines17; P-selectin18; and interleukin 8 (IL-8).19 Additionally, these oxidized phospholipids induce the accumulation of connecting segment-1 of fibronectin on the apical surface of endothelial cells by activating endothelial β1 integrins, particularly those that associate with α5 integrins.20 Connecting segment-1 serves as the endothelial ligand that binds to α4β1 (very late antigen-4, VLA4) on monocytes, thus promoting adhesion of the monocytes to activated endothelial cells.20 The induction of monocyte binding to endothelial cells exposed to mildly oxidized LDL also involves lipoxygenase (LO) metabolites.21 The mechanism for the induction of MCP-1 and IL-8 in endothelial cells exposed to mildly oxidized LDL, Ox-PAPC, POVPc, or PGPC appears to involve the lipid-dependent transcription factor peroxisome proliferator–activated receptor-α.19

The response of endothelial cells to these oxidized phospholipids appears to be genetically determined.22–25 Using a novel explant technique, Shi et al22 isolated endothelial cells from the aortas of inbred mouse strains with different susceptibilities to diet-induced atherosclerosis. The response of these endothelial cells to mildly oxidized LDL was determined by measuring levels of mRNA for inflammatory genes, including MCP-1, M-CSF, and the oxidative stress gene, heme oxygenase-1.22 Endothelial cells derived from the atherosclerosis-susceptible mouse strain C57BL/6/J (B6) exhibited dramatic inductions of mRNA for MCP-1, M-CSF, and heme oxygenase-1.22 In contrast, endothelial cells derived from the atherosclerosis-resistant strain C3H/HeJ (C3H) showed little or no induction.22 The authors concluded that the genetic difference between the 2 strains for the development of diet-induced atherosclerosis was determined at the level of the vessel wall.22 In other studies, these authors studied a congenic strain of C3H mice carrying an apoE-null allele (apoE−/−).24 Although the C3H apoE−/− mice had higher plasma cholesterol levels, they developed much smaller lesions than did their B6 apoE−/− counterparts on either chow or Western diets.24 Reciprocal bone marrow transplantation between the strains, with congenics carrying the same H-2 haplotype, was performed to determine the role of monocytes.24 Atherosclerosis susceptibility was not altered in the recipient mice, indicating that variations in monocyte function were not involved.24 In a set of recombinant inbred strains derived from the B6 and C3H parental strains, endothelial cell responses to mildly oxidized LDL cosegregated with aortic lesion size, providing strong genetic evidence that the endothelial cells, but not monocytes or plasma lipid levels, accounted for the susceptibility to atherosclerosis between these 2 mouse strains.24 These data do not exclude the possibility that differences in monocytes and lipid levels may be responsible for susceptibility to atherosclerosis in other mouse models.

Formation of LDL-Derived Oxidized Phospholipids That Induce an Inflammatory Response

LDL is usually thought of as the major source of extravascular cholesterol. However, LDL is also a major source of extravascular phospholipid. As noted above, some of these phospholipids can yield oxidized phospholipids that induce an inflammatory response. Subbanagounder and colleagues11 found that the major structural determinant of the biological activity of oxidized phospholipids was at the sn-2 position. Substituting stearoyl for palmitoyl at the sn-1 position or ethanolamine for choline at the sn-3 position did not alter bioactivity.31 All oxovaleroyl phospholipids studied stimulated monocyte binding and inhibited lipopolysaccharide-induced expression of E-selectin.31 All oxovaleroyl phospholipids but not the glutaroyl phospholipids induced monocyte binding without increasing VCAM-1.11 Glutaroyl phospholipids but not oxovaleroyl phospholipids stimulated E-selectin and VCAM-1.11 However, intact phospholipid molecules were required for bioactivity, since activity was destroyed after treatment of the phospholipids with phospholipase (PL) A2, PLA2, or PLC.31 The levels of POVPc, PGPC, and PEIPC were increased 3- to 6-fold in rabbit atherosclerotic lesions and corresponded to ≈116, 62, and 85 μg/mL POVPc, PGPC, and PEIPC, respectively.31 These levels were ≈10 to 20 times higher than those needed to activate endothelial cells in culture.31

The concept that LDL must be “primed” for oxidation has emerged from the work of many laboratories. Sevanian and colleagues26 described a subpopulation of freshly isolated LDL that was enriched in lipid hydroperoxides, which they named LDL−. Parthasarathy,27,28 Witztum and Steinberg,29 Witztum,30 Chisolm,31 Thomas and Jackson,32 Frei and colleagues (Shwarery et al33 and Polidori et al34), and Thomas et al32 all studied LDL oxidation by metal ions in vitro and, on the basis of their findings, concluded that LDL must be “seeded” with reactive oxygen species before it can be oxidized. Thomas and Jackson32 and Parthasarathy28 speculated that LOs might play a role in this seeding of LDL.

Watson et al44 used defatted albumin to remove the inflammatory lipids from mildly oxidized LDL. Because the lipid-binding properties of apoA-I45–48 are greater than those of defatted albumin, Navab et al49 reasoned that if freshly isolated LDL contained seeding molecules, incubating the LDL with apoA-I and then separating the apoA-I from the LDL might result in a transfer of the seeding molecules from LDL to apoA-I. They hypothesized that this simple strategy could result in the concentration of seeding molecules on apoA-I, from which they could be extracted, identified, and characterized. When freshly isolated LDL was incubated with apoA-I and then separated from apoA-I, the resulting LDL could not be oxidized by human artery wall cells, nor could it induce human artery wall cells to produce monocyte chemoattractant activity. However, when the lipids that transferred from LDL to apoA-I were extracted from the apoA-I and subsequently added back to the treated LDL, the reconstituted LDL was readily oxidized and induced monocyte chemoattractant activity.40 Similar results were obtained with an apoA-I mimetic peptide.40 Analysis revealed that the apoA-I–associated seeding molecules removed from freshly isolated
LDL included hydroperoxyoctadecadienoic acid (HPDOE), hydroperoxyeicosatetraenoic acid (HPETE), and cholesterol linoleate hydroperoxide. These results were not in vitro artifacts, because freshly isolated LDL taken from 7 of 7 normal volunteers were found to contain HPODE and HPETE. The levels of HPODE and HPETE in the LDL remained the same or declined after incubation for 2 hours under conditions identical to those used to transfer the lipids to apoA-I, indicating that HPODE and HPETE were present in the LDL in vivo and were not formed in vitro. Treatment of LDL with apoA-I reduced the levels of seeding molecules in LDL by approximately two thirds. Thus, approximately one third of the seeding molecules remained in the apoA-I–treated LDL. However, as noted above, the apoA-I–treated LDL was resistant to oxidation by human artery wall cells and did not induce monocyte chemotactic activity, and adding back the lipids that had transferred from LDL to apoA-I restored these properties. It was concluded that there must be a threshold concentration of seeding molecules required for LDL oxidation and LDL-induced monocyte chemotactic activity.

The ability of apoA-I to render LDL resistant to oxidation by human artery wall cells was also demonstrated in mice. Injection of apoA-I (but not apoA-II) into mice resulted in LDL that, when isolated, was resistant to oxidation by human artery wall cells. Similar results were seen in humans after infusion of apoA-I/ phosphatidylcholine discs. Pretreatment of artery wall cells with apoA-I or an apoA-I mimetic peptide (but not apoA-II) or with LO inhibitors also prevented LDL oxidation and LDL-induced monocyte chemotactic activity. It was concluded that the artery wall cells needed to provide additional seeding molecules to those already present in circulating LDL to reach the critical threshold concentration necessary for phospholipid oxidation. The human artery wall cells were found to contain 12-LO protein, and transfection with antisense (but not sense) to 12-LO eliminated the 12-LO protein and inhibited LDL-induced monocyte chemotactic activity. In contrast, enriching the human artery wall cells with linoleic acid (but not oleic acid) promoted LDL oxidation by the artery wall cells and promoted LDL-induced monocyte chemotactic activity. HPODE and HPETE were found to dramatically enhance the nonenzymatic formation of POVPc, PGPC, and PEIPC from l-α-1-palmitoyl-1-2-arachidonoyl-sn-glycero-3-phosphorylcholine (ie, PAPC) and to greatly enhance the nonenzymatic formation of cholesterol linoleate hydroperoxide. On a molar basis, HPODE and HPETE were 2 orders of magnitude greater in potency than hydrogen peroxide in causing the nonenzymatic formation of POVPc, PGPC, and PEIPC. A scheme for the formation of these LDL-derived oxidized phospholipids is shown in Figure 1.

The results of the studies by Navab et al. were consistent with those of Cyrus et al., who reported that disruption of the 12/15-LO gene diminished atherosclerosis in apoe- mice. In considering possible mechanisms for their findings, Cyrus et al favored 1 in which “lipoxynegenase-derived hydroperoxides or secondary reactive lipid species may be transferred across the cell membrane to ‘seed’ the extracellular LDL, which would then be more susceptible to a variety of mechanisms that could promote lipid peroxidation.” Navab et al proposed a 3-step model for the mild oxidation of LDL by artery wall cells. In the first step, LDL is seeded. In the second step, the seeded LDL is trapped in the artery wall and receives further seeding molecules derived from the LO pathway(s) of nearby artery wall cells. In the third step, a critical level of seeding molecules relative to phospholipids is reached in the LDL, and a nonenzymatic oxidation process generates POVPc, PGPC, PEIPC, and other similar molecules. Many factors likely determine the critical level of seeding molecules needed relative to the phospholipids in LDL to generate the inflammatory oxidized phospholipids. These include the concentration of antioxidants in LDL, the concentration of phospholipids in LDL with arachidonic acid at the sn-2 position, and the content of platelet-activating factor acetylhydrolase (PAF-AH) in LDL.

The Role of HDL in Modulating the Inflammatory Response Induced by LDL-Derived Oxidized Phospholipids

As noted above, the major apolipoprotein of HDL, apoA-I (but not apoA-II), prevented the formation of LDL-derived oxidized phospholipids by removing seeding molecules from LDL and/or from artery wall cells. However, apoA-I was active only in a preincubation step: adding apoA-I in a coinubation together with LDL did not prevent LDL oxidation or LDL-induced monocyte chemotactic activity. ApoJ is an acute-phase reactant that associates with HDL. In contrast to apoA-I, apol was effective in preventing both LDL oxidation and LDL-induced monocyte chemotactic activity during coincubation with LDL.

Paraoxonase (PON) is a component of HDL that has been demonstrated both to prevent the formation of mildly oxidized LDL and to inactivate LDL-derived oxidized phospholipids once they are formed. Mackness et al. first described the role of PON in preventing metal ion oxidation.
of LDL. Aviram and colleagues reported that PON has a peroxidase activity that may explain its ability to render freshly isolated LDL resistant to oxidation by human artery wall cells. PAF-AH, another enzyme associated with some HDL particles, has also been shown to be able to inactivate LDL-derived oxidized phospholipids. A third enzyme associated with HDL that may play a role in preventing the formation of and inactivating LDL-derived oxidized phospholipids is lecithin:cholesterol acyltransferase. A fourth HDL-associated enzyme that reduces organic hydroperoxides and is inhibited by physiological concentrations of homocysteine is plasma reduced glutathione selenoperoxidase. Thus, normal HDL contains several enzymes that can potentially prevent the formation of and inactivate the inflammatory LDL-derived oxidized phospholipids. Except for PAF-AH, the other 3 enzymes are associated exclusively with HDL. Whereas PAF-AH is associated with both LDL and HDL in human plasma, Stafforini and colleagues have suggested that for the prevention of LDL oxidation, PAF-AH transfers to HDL where it functions more efficiently.

Direct proof of a role for 1 of these HDL-associated enzymes in the development of atherosclerosis has been provided in mouse models. Shih et al demonstrated that mice lacking the serum PON gene were susceptible to organophosphate toxicity and diet-induced atherosclerosis. In other studies, these authors demonstrated that combined organophosphate toxicity and diet-induced atherosclerosis. In these reports, they concluded that the acute-phase response, IL-6, was required for this effect. Although the answer to Hajjar’s question may well be yes, the reason that these systems evolved could not have been to accelerate atherosclerosis. More likely they evolved as part of a system of nonspecific innate immunity.

Van Lenten et al sacrificed B6 mice either before or 2, 3, 5, 7, or 9 days after intranasal infection with 10 plaque-forming units of influenza A. Peak infectivity in the lung was reached by 72 hours and returned to baseline by 9 days. No viremia was observed at any time. PON and PAF-AH activities in HDL decreased after infection, reaching their lowest levels 7 days after inoculation. The ability of HDL from infected mice to inhibit LDL oxidation and LDL-induced monocyte chemotactic activity in human artery wall cell cocultures decreased with time after inoculation. As the infection progressed, LDL more readily induced monocyte chemotaxis. Peak IL-6 and serum amyloid A plasma levels were observed 2 and 7 days after inoculation. HDL apoA-I levels did not change, but apoJ and ceruloplasmin levels in HDL peaked 3 days after infection. Ceruloplasmin markedly increased and remained elevated throughout the time course, whereas apoJ levels decreased toward baseline after the third day. It was concluded that alterations in the relative levels of PON, PAF-AH, ceruloplasmin, and apoJ in HDL occurred during acute influenza infection and caused HDL to lose its anti-inflammatory properties.

In other studies, Van Lenten et al found that a key cytokine in the acute-phase response, IL-6, was required for short-term regulation of PON but not of MCP-1 and was not
required for the long-term downregulation of PON by an atherogenic diet in susceptible B6 mice. In short-term feeding experiments (1 to 7 days), Hedrick et al. found that there was a dramatic decrease in HDL cholesterol, apoA-I, and PON in susceptible B6 LDL receptor–knockout mice that was associated with a rapid increase in HDL lipid hydroperoxides and formation of high-molecular-weight forms of apoA-I that contained an epitope recognized by a monoclonal antibody that recognizes POVPC. Measurement of the levels of apoA-I complexes associated with immunoglobulins, together with the time course of events, suggested that preformed antibodies to oxidized lipid–apoA-I complexes were present before the atherogenic diet was administered. It was concluded that on feeding the atherogenic diet, the number of epitopes increased to a critical threshold, and this resulted in the clearance of the immune complexes. Ox-PAPC induced IL-6, a potent acute-phase response mediator, when injected into B6 LDL receptor–knockout mice. HDL from B6 mice on a chow diet inhibited LDL oxidation, whereas HDL from the same mice on an atherogenic diet promoted oxidation. The latter was enriched in apoJ, which is a marker of the acute-phase response. In contrast, HDL from C3H mice that were resistant to diet-induced atherosclerosis protected LDL from oxidation, whether the mice were maintained on a chow or an atherogenic diet, and HDL from C3H mice on the atherogenic diet did not have increased levels of the acute-phase reactant apoJ. These studies suggest a link between proinflammatory HDL and decreased PON activity. HDL from C3H mice on the atherogenic diet was administered. It was concluded that proinflammatory HDL and developed atherosclerosis on a chow diet. Total HDL concentrations in the transgenic mice overexpressing apoA-II were elevated but the PON activity was not, resulting in a concentration of PON in HDL of approximately half normal. Addition of exogenous PON to the HDL of the transgenic mice overexpressing apoA-II converted the HDL from proinflammatory to anti-inflammatory, suggesting that

Proinflammatory HDL as a Potential Marker of Susceptibility to Atherosclerosis

HDL has been previously described as a “chameleon-like” lipoprotein, being anti-inflammatory in the basal state and proinflammatory during an acute-phase response. As noted above, LDL-derived oxidized phospholipids were found to induce IL-6 in hepatocytes and to repress PON mRNA levels. A number of mouse models that exhibit susceptibility to atherosclerosis have been found to have proinflammatory HDL and decreased PON activity. Leitinger et al. found that an atherogenic diet resulted in the formation of oxidized phospholipids in the livers of mice that were genetically susceptible to diet-induced atherosclerosis, and these oxidized phospholipids were increased further in mice transgenic for secretory PLA_2. Presumably, these oxidized phospholipids induced an acute-phase response, which resulted in proinflammatory HDL in mice susceptible to diet-induced atherosclerosis. ApoE–/– mice also had evidence of proinflammatory HDL and low PON activity. HDL from transgenic mice overexpressing apoA-II had proinflammatory HDL and developed atherosclerosis on a chow diet. Total HDL concentrations in the transgenic mice overexpressing apoA-II were elevated but the PON activity was not, resulting in a concentration of PON in HDL of approximately half normal. Addition of exogenous PON to the HDL of the transgenic mice overexpressing apoA-II converted the HDL from proinflammatory to anti-inflammatory, suggesting that

HDL and LDL-Derived Oxidized Phospholipids

Figure 2. The acute-phase (AP) reaction favors the formation of proinflammatory HDL and mildly oxidized LDL. A, In the basal state, HDL contains apoA-I and apoJ as well as 4 enzymes, PON, PAF-AH, lecithin:cholesterol acyltransferase (LCAT), and plasma reduced glutathione selenoperoxidase (GSH peroxidase) that can prevent the formation of or inactivate the inflammatory LDL-derived oxidized phospholipids found in mildly oxidized LDL. As a result, in the basal state, HDL may be considered anti-inflammatory. During the acute-phase reaction, A-I may be displaced by the pro-oxidant acute-phase reactant SAA. Another pro-oxidant acute-phase reactant, ceruloplasmin, associates with HDL as does the anti-oxidant acute phase reactant apoJ. PON, PAF-AH, and LCAT decrease in HDL during the acute-phase reaction, and the lipid hydroperoxides HPETE, HPODE, and cholesteryl linoleate hydroperoxide (CE-OOH) increase in HDL. A-II and GSH peroxidase are shown as unchanged during the acute-phase reaction although there are no data on the latter. The net effect of the changes in HDL during the acute-phase reaction is the production of pro-oxidant, proinflammatory HDL particles (AP-HDL). B, In the basal state, HDL prevents the formation of and inactivates the LDL-derived oxidized phospholipids shown in Figure 1. As a result, HDL favors the maintenance of noninflammatory LDL and the conversion of the proinflammatory, mildly oxidized LDL (MM-LDL) to a noninflammatory state. In contrast, during an acute-phase reaction, AP-HDL favors the conversion of LDL to the proinflammatory MM-LDL. As discussed in the text, the acute-phase reaction can be truly acute, as in the case of a viral infection, or it may become chronic, as in mice that are genetically susceptible to diet-induced atherosclerosis when they are fed an atherogenic diet or in some patients with normal blood lipids and atherosclerosis. 

in this model the PON activity was responsible for the proinflammatory HDL. PON has also been associated with atherosclerosis in humans. James and colleagues reported that smoking was independently associated with significant decreases in serum PON activities and concentrations in patients with coronary artery disease and that cessation of smoking led to an increase
in serum PON within months. This group of patients had mildly elevated LDL cholesterol levels on average and normal HDL cholesterol levels that were lowest in the smokers. The relationship of PON to coronary heart disease is complicated by the polymorphisms present in humans. However, the concentration of PON and its activity were significantly lower in patients immediately after myocardial infarction compared with those in age- and sex-matched controls. Forty-two days after infarction, PON activity had increased but was still lower than in controls. Analysis of PON1 genotypes did not discriminate between patients and controls.

Navab and colleagues found that PON activity in HDL was significantly lower in 24 patients with angiographically documented coronary artery disease who were normolipidemic and who were neither diabetic nor taking hypolipidemic medications. However, there was an overlap between patients and 29 age- and sex-matched controls. As noted above, PON is just 1 of at least 4 enzymes and 2 apolipoproteins associated with HDL that can potentially modulate the formation of or inactivate LDL-derived oxidized phospholipids. Therefore, it was not surprising that there was overlap in PON activities between patients and controls. To focus on whole HDL rather than on PON exclusively, Navab et al studied a subset of the patients to determine whether their HDL was anti-inflammatory or proinflammatory. HDL from 10 of 10 of the patients not only failed to inhibit LDL oxidation by artery wall cells and the biological activity of Ox-PAPC but, on average, also increased LDL oxidation and enhanced the biological activity of Ox-PAPC. These data suggest that some patients with coronary artery disease and normal HDL cholesterol levels have proinflammatory HDL. These data also suggest that proinflammatory HDL may be a marker of susceptibility to atherosclerosis in humans as it appears to be in mice. However, large-scale studies will be required to determine the true predictive value of such tests. Such studies would have to include consideration of the age of the subject. At birth, human HDL cholesterol levels are equal to or greater than adult levels. However, PON activity at term is approximately half of what it is at age 2 years. Low PON activity relative to HDL cholesterol levels at birth may be part of a non-specific innate immune system that protects the infant against sepsis as discussed above. However, the persistence of proinflammatory HDL into adulthood may predispose and predict susceptibility to atherosclerosis.

There is increasing evidence that markers of inflammation and the acute-phase response, including induction of C-reactive protein, predict susceptibility to risk for coronary syndromes. It has been suggested that the acute-phase response can become chronic and that a state of low-grade systemic inflammation is a consequence of being overweight. It may well be that the changes seen in HDL in mice with diet-induced atherosclerosis and in some patients with normal blood lipid levels represent a chronic acute-phase response. This chronic acute-phase response could be perpetuated, in part, by LDL-derived oxidized phospholipids and may be exacerbated by the infections and stresses (eg, surgeries) that humans endure in modern society. Figure 2A summarizes the changes that occur in HDL during an acute-phase response, and Figure 2B indicates what the impact of these changes in HDL would be on the balance between LDL and mildly oxidized LDL in the artery wall. If the concentration of LDL-derived oxidized phospholipids determines the intensity of the inflammatory response in the artery wall, then the balance between noninflammatory LDL (ie, LDL that does not induce artery wall cells to make proinflammatory molecules such as MCP-1) and mildly oxidized LDL, which is proinflammatory, would in part determine plaque vulnerability and hence, susceptibility to heart attack and stroke.

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References

82. Van der Wal AC, Becker AE, van der Loos CM, Das P. Site of intimal rupture or erosion of coronary atherosclerotic plaques is characterized by an inflammatory process irrespective of the dominant plaque morphology. Circulation. 1994;89:36–44.
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