In epidemiological studies, high plasma levels of high-density lipoproteins (HDLs) protect against the development of atherosclerosis. The precise mechanism is uncertain, although most likely it is the consequence of one or more of the reported actions of HDL. The best known of these relates to the ability of HDL to promote the efflux of cholesterol from cells. This process may minimize the accumulation of foam cells in the artery wall. However, HDL has additional properties that may also be antiatherogenic. For example, HDL is an effective antioxidants. The major proteins of HDL, apoA-I and apoA-II, as well as other proteins such as paraoxonase that cotransport with HDL in plasma, are well-known to have antioxidant properties. As a consequence, HDL has the capacity to inhibit the oxidative modification of low-density lipoprotein (LDL) in a process that reduces the atherogenicity of these lipoproteins. HDL also possesses other antiinflammatory properties. By virtue of their ability to inhibit the expression of adhesion molecules in endothelial cells, they reduce the recruitment of blood monocytes into the artery wall. These antioxidant and antiinflammatory properties of HDL may be as important as its cholesterol efflux function in terms of protecting against the development of atherosclerosis. (Circ Res. 2004;95:764-772.)

Key Words: antiinflammatory • antioxidant • atherosclerosis • high-density lipoprotein

This Review is part of a thematic series on New Pathways in HDL Metabolism, which includes the following articles:

Antiinflammatory Properties of HDL

Regulation of HDL Metabolism and Reverse Cholesterol Transport In Vivo
Endothelial and Antithrombotic Effects of HDL
Genetics of Variation in HDL Cholesterol in Humans and Mice

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DNA synthesis in vascular smooth muscle cells. HDLs are antithrombotic. They modulate endothelial function, probably by stimulating endothelial nitric oxide (NO) production. HDLs also possess antioxidant and antiinflammatory activities. The degree to which any or all of these nonlipid transport functions of HDL contribute to a protection against atherosclerosis is still uncertain, although evidence is mounting that at least some of them may be especially important.

This review focuses on the antioxidant and antiinflammatory properties of HDL (Figure 1). It summarizes the role of oxidation and inflammation in atherogenesis and describes how these processes may be inhibited by HDL. It concludes with an assessment of the potential clinical importance of the antioxidant and antiinflammatory properties of HDL.
Role of Oxidation in Atherogenesis

The two main hypotheses of atherogenesis that have survived decades of research are the reverse cholesterol transport hypothesis and the oxidation hypothesis. Both hypotheses assign a central role to low-density lipoproteins (LDLs) in initiating atherogenesis and to HDL in mitigating the process. As discussed, these two hypotheses may be fundamentally linked.

The central role of LDL in atherogenesis is, in part, the consequence of LDLs entering the subendothelial space, where they bind to the complex matrix beneath the endothelium. As a result, the artery wall concentration of apolipoprotein B (apoB) in normal mammals is approximately double that found in plasma. In contrast, whereas normal HDLs readily enter the subendothelial space, they do not bind to the matrix. Hence, HDLs tend to return to the circulation. This explains why the artery wall concentration of apolipoprotein A-I (apoA-I), the main protein in HDL, is normally only 10% to 20% of that found in plasma.

LDLs provide the main pathway for transporting cholesterol and phospholipids into mammalian cells. Navab et al reported that normal circulating LDL always contains small quantities of lipid hydroperoxides derived from the lipoxygenase pathway. Based on studies using an in vitro artery wall model, it was concluded that the LDLs trapped in the subendothelial space receive additional lipid hydroperoxides produced by the lipoxygenase and myeloperoxidase pathways operating in cells within the artery wall. They hypothesized that when the level of oxidized lipids in the trapped LDL exceeds a critical threshold, the LDL phospholipids that contain arachidonic acid in the \( \text{sn}-2 \) position become oxidized and pro-inflammatory.

Recognition of these oxidized phospholipids by a specific antibody, EO6 (an IgM autoantibody that recognizes the phosphatidylcholine head group in oxidized, but not in unoxidized, phospholipids containing arachidonic acid in the \( \text{sn}-2 \) position), has enabled them to be identified in atherosclerotic lesions in animals and humans.

The 12/15-lipoxygenase pathway, the 5-lipoxygenase pathway, the myeloperoxidase pathway, the cyclooxygenase pathways, and the NADPH oxidase pathways have all been implicated in atherogenesis. The work of Blair et al has shown that bifunctional electrophiles (\( \gamma \)/unsaturated aldehyde genotoxins) such as 4-oxo-2-nonenal can be formed from different lipid hydroperoxides by the action of trace metal ions or by vitamin C. The possibility that 4-oxo-2-nonenal acts on LDL to produce biologically active oxidized phospholipids that are recognized by EO6 may explain how the genetic manipulation of multiple pathways producing different lipid hydroperoxides can influence atherogenesis.

Antioxidant Properties of HDL

The main protein in HDL, apoA-I, is capable of removing LDL lipid hydroperoxides in vitro, after injection into mice in vivo, and after infusion into humans in vivo. It has also been reported that HDL CE-O(O)H (cholesteryl ester hy-
droperoxides) are rapidly and selectively removed by liver cells.\textsuperscript{51,52} Thus, one of the main antioxidant/antiinflammatory functions of HDL is mediated by a transport mechanism that binds and carries away oxidant molecules.

HDLs are major carriers of plasma lipid hydroperoxides in animal models of atherosclerosis\textsuperscript{19} and in humans.\textsuperscript{53} HDLs are also carriers of enzymes that destroy the lipid hydroperoxides that oxidize LDL phospholipids.\textsuperscript{18} These enzymes include paraoxonase-1\textsuperscript{54–56} and paraoxonase-3, \textsuperscript{57} and possibly glutathione phospholipid peroxidase.\textsuperscript{18} In addition, it has been shown that HDL phospholipid hydroperoxides are reduced to corresponding hydroxides with a concomitant oxidation of apoA-I methionine residues. This reducing activity of apoA-I is independent of paraoxonase. HDLs also transport enzymes such as platelet-activating factor acetyl hydrolase\textsuperscript{59} and lecithin cholesterol ester acetyltransferase\textsuperscript{60} that are able to remove EO6-positive oxidized phospholipids.

It has been suggested that HDL evolved as part of the innate immune system.\textsuperscript{18} HDLs account for a significant component of the antiviral activity of human plasma.\textsuperscript{61} Van Lenten et al\textsuperscript{62} reported that HDLs lose their antiinflammatory properties during acute influenza infection. HDLs isolated from mice infected with influenza A virus lose their ability to protect LDLs against oxidation by human artery wall cells and are ineffective in preventing the LDL-induced monocyte chemotactic activity in a human artery wall coculture.\textsuperscript{62} In other studies, LDL receptor-null mice were infected with influenza A virus. They were then treated with injections of an apoA-I mimetic peptide, D-4F, or vehicle alone. Those receiving vehicle alone had an increase in macrophage trafficking into the aortic arch and innominate arteries.\textsuperscript{63} In contrast, the mice receiving injections of D-4F had no increase in macrophage trafficking into the aortic arch and innominate arteries.\textsuperscript{63} In vitro, D-4F\textsuperscript{63} was shown to be comparable to apoA-I\textsuperscript{64} in terms of its ability to inhibit macrophage cytokine production induced by T cells.

The mechanism underlying these properties of the apoA-I mimetic peptide, D-4F, was further investigated in cultures of human type II pneumocytes infected with influenza A in the presence or absence of D-4F.\textsuperscript{65} It was concluded that human type II pneumocytes respond to influenza A infection by activating caspases and by secreting cytokines and phospholipids (including oxidized phospholipids that evoke inflammatory responses) into the extracellular environment and that treatment with the apoA-I mimetic D-4F inhibits these events.

**Inflammation**

**Role of Inflammation in Atherogenesis**

It is now well-accepted that atherosclerosis is a chronic inflammatory disorder characterized by an accumulation of macrophages and T lymphocytes in the arterial intima\textsuperscript{66,67} and an increased plasma concentration of several inflammatory markers.\textsuperscript{68–70} The macrophages accumulating in atherosclerotic plaques are derived mainly from blood monocytes that adhere to endothelial cells before migrating into the subendothelial space. Within the artery wall, the monocytes differentiate into macrophages that express a range of scavenger receptors, some of which have the ability to bind and internalize (modified) LDLs. The foam cells that result are considered to be the hallmark cells of atherosclerosis.

An early step in this inflammatory process is the adhesion of monocytes to endothelial cells that have been injured or stimulated in some other way to express adhesion proteins. Shih et al have reported that this process begins with monocyte adhesion to endothelial connecting segment-1 via activation of β1 integrins.\textsuperscript{71} Activated endothelial cells express several adhesion proteins, including vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), and E-selectin.\textsuperscript{72,73} These adhesion proteins are known to be expressed in arteries in vivo at sites of developing atherosclerosis,\textsuperscript{74} and soluble forms are present at increased concentrations in the plasma of human subjects with coronary heart disease (CHD).\textsuperscript{75} Once they bind to adhesion proteins on the surface of endothelial cells, monocytes are retarded and available for recruitment into the subendothelial space by chemokines such as monocyte chemotactic protein-1 (MCP-1). The discovery that human HDLs inhibit endothelial cell adhesion molecules and MCP-1\textsuperscript{20,21} is thus of potentially great importance.

**Endothelial Cell Adhesion Proteins and Chemokines**

E-selectin is expressed in endothelial cells in response to activation by proinflammatory cytokines via the nuclear transcription factor, nuclear factor kappa B (NF-κB). It mediates the rolling and loose tethering of leukocytes on the luminal surface of endothelial cells before they are more tightly bound by VCAM-1 and ICAM-1, both of which are members of the immunoglobulin superfamily.\textsuperscript{75–77} ICAM-1 is constitutively expressed on endothelial cells and leukocytes, and it interacts with leukocyte-specific integrins. VCAM-1 is expressed on endothelial cells in response to inflammatory cytokines and, like ICAM-1, interacts with integrins on the surface of leukocytes. ICAM-1 and VCAM-1 promote firm adhesion and subsequent arrest of leukocytes on the surface of endothelial cells.\textsuperscript{75–77}

The expression of endothelial cell adhesion proteins is increased in vitro in response to several stimuli, including activation by pro-inflammatory cytokines.\textsuperscript{72,78} In addition, animal studies have demonstrated the increased expression of endothelial cell adhesion proteins in response to cholesterol feeding,\textsuperscript{79} altered shear stress,\textsuperscript{80} and balloon injury.\textsuperscript{81} Their expression after balloon injury parallels the development of abnormal acetylcholine-induced vasodilatation.\textsuperscript{81}

Studies of genetically engineered mice and of mice treated with monoclonal antibody against VCAM-1 support a role of adhesion proteins in atherogenesis.\textsuperscript{82–84} Antibody blockade of the VCAM-1 ligand, VLA-4, has been reported to reduce neointimal formation after carotid injury in primates.\textsuperscript{85} It has been proposed that the atheroprotective effects of antibodies directed against the CD40 ligand are achieved by an inhibition of endothelial cell VCAM-1 expression.\textsuperscript{86} The effects of reduced ICAM-1 expression are inconsistent, with both positive\textsuperscript{87} and negative results reported. Various selectins and members of the immunoglobulin superfamily also exist in a soluble plasma form in concentrations that have been
shown in some studies to correlate with the presence of other cardiovascular risk factors.99,100

Monocyte chemoattractant protein-1 is produced by endothelial cells in response to abnormal shear stress, oxidized LDL, and vascular injury, such as balloon angioplasty.91 Its generation within the arterial wall produces a gradient that promotes migration into the artery wall of any leukocytes that have been retarded by binding to endothelial adhesion proteins.

Effect of HDL on Transmigration of Monocytes

In vitro studies have shown that HDLs inhibit monocyte transmigration in response to oxidized LDL.92 This property appears to be related to paraoxonase and platelet-activating factor acetyl hydrolase on HDL and is reduced in acute inflammatory states as a consequence of the HDL accumulating serum amyloid A.93 This effect of serum amyloid A is rate-limiting serum amyloid A.93 This effect of serum amyloid A is mediated by HDL.94 The explanation for this apparent inconsistency is not known. In another study it was found that HDL isolated from patients with documented CHD (but without low plasma HDL concentrations) did not inhibit monocyte chemotaxis to the same extent as the HDL isolated from control subjects without CHD.95

Inhibition of Endothelial Cell Adhesion Proteins by HDL

Several groups have shown that HDLs inhibit the expression of cell surface adhesion molecules by activated endothelial cells in vitro.96–98 Both native HDL and reconstituted HDL (rHDL) containing only apoA-I and phosphatidylcholine96,99 inhibit the cytokine-induced expression of VCAM-1, ICAM-1, and E-selectin by human umbilical vein endothelial cells (HUVECs) in a concentration-dependent manner within the range of physiological HDL levels. The inhibition of adhesion molecule expression is associated with a reduction in the mRNA levels of these proteins.96–99 The in vitro inhibition of cytokine-induced expression of endothelial cell VCAM-1 is time-dependent, with the magnitude of inhibition increasing with duration (up to 16 hours) of the preincubation. However, having undergone a period of preincubation, the rHDL can be removed from the cells before adding the TNF-α, without any apparent loss of inhibition of the adhesion molecule expression, indicating that the inhibition is not the consequence of HDL interfering with the binding of TNF-α to its receptor.100 Furthermore, once the inhibitory effect of rHDL on endothelial cells has been achieved by pre-incubation, the inhibition persists for several hours after the rHDLs have been removed.100 These findings imply that exposure to the rHDL modifies the cells in some way to make them resistant to cytokine-induced expression of VCAM-1 in a time-dependent process.

The HDL isolated from the plasma of different human subjects vary in their inhibitory activity (Figure 2);101 the reason for the variation is uncertain. It is well-known that the HDL fraction in human plasma is heterogeneous, consisting of a number of discrete subpopulations that vary in size, density, and composition of lipids and apolipoproteins. It has been reported that the inhibitory activity of the HDL subfraction (in which the particles are smaller and denser) is superior to that of HDL2 (in which the particles are larger and less dense).101 although this did not explain the observed variation in inhibitory activity of the HDL isolated from different subjects. Discoidal and spherical rHDL of defined size and chemical composition have been used to investigate how varying the morphology and composition impacts on the ability of HDL to inhibit the TNF-α–induced expression of VCAM-1 in endothelial cells. Inhibition appears to be unaffected by variations in HDL particle size or in the composition of apolipoproteins, cholesteryl esters, or triglyceride.102 In marked contrast, varying the composition of phospholipids in HDL has major effects on their inhibitory activity.103

Studies were conducted with rHDL to determine the ability of different phosphatidylcholine (PC) species to inhibit cytokine-induced expression of VCAM-1 in HUVECs (Figure 2).103 PC species containing palmitoyl- in the sn-1 position and either palmitoyl- (DPPC), arachidonoyl- (PAPC), linoleoyl- (PLPC), or oleoyl- (POPC) in the sn-2 position were compared. These PC species were studied as components of discoidal rHDL containing apoA-I as the sole protein or as small unilamellar vesicles. The rHDL containing PLPC and PAPC inhibited VCAM-1 expression in activated HUVECs by 95% and 70%, respectively, at an apoA-I concentration of 16 μmol/L. At this concentration of apoA-I, POPC rHDL inhibited by only 16% and DPPC rHDL did not inhibit at all. These differences could not be explained by differential binding of the rHDL to HUVECs.103

The same hierarchy of inhibitory activity was observed when these PC species were presented to the cells as small unilamellar vesicles, but only when the small unilamellar vesicles also contained an antioxidant.103 When the antioxidant was not present, PLPC became oxidized during the vesicle preparation or during the subsequent incubation and was cytotoxic to the cells. The most likely reason why PLPC is not cytotoxic when it is present in discoidal rHDL particles is that apoA-I protects the phospholipid against oxidation, thus enabling it to retain its antiinflammatory properties. The pathophysiological implications of differences in the effects of specific HDL PC species are uncertain. This effect of the
increase in the generation of intracellular reactive oxygen and its nuclear translocation in a process that is linked to an inhibition of NF-kappa B expression. This may therefore also contribute to their inhibition of adhesion molecule expression.

There have been discordant results is unclear. The discrepancy is unclear and will have to await further research. It should be noted that some studies have failed to demonstrate an ability of HDL to inhibit endothelial cell adhesion molecule expression. There have been negative reports of the effects of both native HDL and rHDL on cytokine-induced adhesion molecule expression by arterial and venous endothelial cells. The reason for these discordant results is unclear.

**Mechanism by Which HDLs Inhibit Adhesion Molecule Expression**

HDLs inhibit endothelial cell sphingosine kinase, an enzyme that catalyzes a key step in the pathway by which TNF-alpha stimulates the expression of endothelial cell adhesion molecules (Figure 3). This inhibition of sphingosine kinase has a downstream effect by inhibiting the nuclear translocation of NF-kappa B. The ability of HDL to inhibit the nuclear translocation of NF-kappa B has been confirmed by one group, although another report concluded that an HDL-mediated inhibition of E-selectin is independent of NK-kappa B. The explanation for this discrepancy is unclear and will have to await further research.

Oxidized forms of HDL may activate NF-kappa B and promote its nuclear translocation in a process that is linked to an increase in the generation of intracellular reactive oxygen species. A reduction in the activation of NF-kappa B may be secondary to a reduction in oxidative stress. NF-kappa B is activated by reactive oxygen species and maintained in an inactive state by low levels of NO. The ability of HDL to inhibit reactive oxygen species generation and promote the synthesis of NO, and thus to inhibit the activation of NF-kappa B, may therefore also contribute to their inhibition of adhesion molecule expression.

**Inhibition of Chemokines by HDL**

HDLs inhibit the expression of MCP-1 in response to oxidized LDL in a process linked to the antioxidant properties of HDL. Furthermore, the expression of apoA-I in apoE knockout mice results in a reduced plaque expression of MCP-1 after transplantation of atherosclerotic aorta.

**HDL, C-Reactive Protein, and Atherosclerosis**

The plasma concentration of C-reactive protein (CRP), an acute-phase reactant, is a predictor of cardiovascular events. There is emerging evidence that CRP may itself contribute to the inflammatory process. In studies of vascular cells incubated in vitro, CRP has been reported to increase secretion of MCP-1, reduce endothelial NO synthase bioactivity, and induce VCAM-1, ICAM-1, and E-selectin. In a recent study by Wadham et al, it was shown that HDLs inhibit the CRP-induced expression of endothelial cell adhesion proteins. The mechanism by which HDLs inhibit the pro-inflammatory effects of CRP appears to be different from that responsible for inhibiting the effects induced by cytokines. Whereas the HDL-mediated inhibition of TNF-alpha-induced expression of endothelial cell adhesion proteins persists for several hours after the HDLs have been removed, inhibition of the CRP-induced expression requires the physical presence of HDL during the induction. Furthermore, whereas oxidation of HDL reduces the HDL-mediated inhibition of TNF-alpha-induced adhesion protein expression, it enhances the ability of HDL to inhibit the CRP-induced adhesion protein expression. It was concluded that the oxidized phospholipids in HDL are more effective than nonoxidized phospholipids in binding and neutralizing the effects of the CRP.

**Relationship Between the Cholesterol Efflux, the Antioxidant, and the Adhesion Molecule Inhibitory Properties of HDL**

Both the antioxidant and antiinflammatory properties of HDLs appear to be independent of the cholesterol efflux function of these lipoproteins. The acceptor of the ABCA1-mediated efflux of cholesterol is lipid-free or lipid-poor apoA-I, whereas most of the antioxidant potential of HDL is the consequence of activity of factors, such as paraoxonase that are cotransported with HDL, although there is evidence that both apoA-I and apoA-II also possess at least some intrinsic antioxidant properties. The ability of HDL to inhibit the cytokine-induced expression of endothelial cell adhesion molecule (at least in vitro) is achieved as readily (or even more readily) by reconstituted HDL containing only apoA-I and phosphatidylcholine, as by native HDL. Furthermore, whereas lipid-free apoA-I is an effective acceptor of the cholesterol released by the ABCA1-mediated pathway, lipid-free apoA-I does not inhibit endothelial cell adhesion molecule expression. It is likely, therefore, that the cholesterol efflux, the antioxidant, and the antiinflammatory properties of HDL are at least partly independent of each other.

**Importance of the Antiinflammatory Effects of HDL In Vivo**

The ability of HDL to modify endothelial cell adhesion protein expression has also been demonstrated in vivo. Alternate daily infusions of rHDL containing apoA-I and phosphatidylcholine to apoE knockout mice with carotid peri-arterial...
collars resulted in 40% reductions in VCAM-1 expression and monocyte infiltration within 1 week and a substantial reduction in the development of neointimal hyperplasia at 3 weeks.\textsuperscript{116} In another study, a single infusion of rHDL inhibited E-selectin expression in intradermal vessels after subcutaneous administration of IL-1 in a normocholesterolemic porcine model.\textsuperscript{117} In another study, however, the transgenic expression of human apoA-I on a background of apoE knockout mice had no apparent effect on endothelial VCAM-1 expression, monocyte adherence, or lipid infiltration when studied at an early age.\textsuperscript{118}

There are several reports of the effects of infusing rHDL into humans. In subjects with hypercholesterolemia, a single infusion of rHDL increased flow-mediated dilatation at 4 hours.\textsuperscript{119} In addition, forearm blood flow measured by venous plethysmography, shown to be impaired in ABCA1 heterozygotes with low plasma HDL, was restored to that of normal controls 4 hours after an infusion of rHDL.\textsuperscript{120} These studies highlight the ability of a single infusion of rHDL to raise plasma HDL and improve vascular reactivity. These studies, combined with the rapidity of antiatherosclerotic effects of infusing rHDL containing apoA-I\textsubscript{Mawe} (an apoA-I variant that may have enhanced antiatherogenic properties)\textsuperscript{22} into rabbits\textsuperscript{121} and humans,\textsuperscript{122} raise the possibility that some of the noncholesterol transport functions of HDL may be of pathophysiological importance.

**Clinical Implications of Antioxidant/Antiinflammatory Properties of HDL**

To the extent that atherosclerosis is an inflammatory disease that is initiated in part by the presence of oxidized LDL in the artery wall, it is logical to conclude that the antioxidant and antiinflammatory properties of HDL may account for at least part of the antiatherogenic potential of these lipoproteins. To date, however, the evidence, although mounting, is still rather sparse.

There are two reports suggesting that the inflammatory/antiinflammatory properties of HDL are superior to HDL cholesterol concentration in terms of discriminating between those with and without CHD.\textsuperscript{17,95} It should be emphasized, however, that the group sizes in these studies were small, and the results should be interpreted with caution until confirmed in larger studies.

In more direct studies, it has been shown that infusion of human apoA-I into mice and humans results in LDL becoming resistant to oxidation and less effective in inducing monocyte chemotactic activity in a human artery wall coculture.\textsuperscript{13} On the basis of other studies in which the oral apoA-I mimetic peptide (D-4F) was administered to apoE-null mice,\textsuperscript{123,124} it was concluded that the beneficial properties of apoA-I and the apoA-I mimetic peptide are linked both by their ability to reduce lipoprotein lipid oxidation and to enhance reverse cholesterol transport.

A relationship between plasma concentrations of HDL cholesterol and soluble cell adhesion molecules has been reported in humans. In a study of subjects with a wide range of HDL cholesterol concentrations, it was found that the plasma levels of soluble ICAM-1 and soluble E-selectin (but not soluble VCAM-1) were significantly higher in subjects with low HDL levels compared with those with average or high HDL levels.\textsuperscript{125} Furthermore, the concentration of HDL cholesterol correlated inversely with both soluble ICAM-1 (sICAM-1) and soluble E-selectin (sE-selectin) in the low-HDL subjects but not in those with normal or elevated HDL levels.\textsuperscript{125} It was also found that the increase in HDL levels induced by treatment with fenofibrate was associated with a significant reduction in the plasma concentrations of sICAM-1 and sE-selectin.\textsuperscript{125} It is unclear, however, whether the reduction in sICAM and sE-selectin was the consequence of the increase in HDL or a direct antiinflammatory effect of the fibrate on the artery wall.

**Conclusion**

There is no doubt that HDLs have multiple functions beyond their ability to promote the efflux of cholesterol from cells. These noncholesterol transport properties have the clear potential to contribute to the antiatherogenic effects of HDL, although the magnitude and clinical importance of such effects remain to be determined. It will be important to determine how newer therapies designed to raise HDL cholesterol levels impact on the antioxidant and antiinflammatory properties of these lipoproteins. It is highly likely that further research directed at understanding these basic processes will yield new strategies for the prevention and treatment of atherosclerosis.

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