Oxidized HDL
The Paradox-idation of Lipoproteins
Constanze Bergt, John F. Oram, Jay W. Heinecke

The strong inverse relationship between HDL level and risk for coronary artery disease has been attributed to different mechanisms. More than 30 years ago, Glimset proposed that HDL mediates the transfer of cholesterol from peripheral tissues to the liver, where the sterol and its oxidized products are excreted into the bile. Subsequent studies demonstrated that HDL accepts cholesterol from macrophage foam cells, the cellular hallmark of the atherosclerotic lesion. In this scenario, HDL accepts cholesterol from macrophage foam cells in the artery wall and transports it back to the liver for excretion. Strong evidence for this process, termed reverse cholesterol transport, was provided by the recent identification of the molecular defect in Tangier disease as mutations in ABCA1, a membrane-associated ATP-binding cassette transporter. Patients with Tangier disease have abnormally low levels of HDL cholesterol and suffer from premature coronary artery disease. Importantly, macrophages with genetically engineered overexpression of ABCA1 fail to accumulate cholesterol ester in vivo; in vitro, their ability to donate cholesterol to HDL is markedly increased. Studies of fibroblasts cultured from patients suffering from Tangier disease have shown that the mechanism involves the transfer of membrane-associated cholesterol from cells to poorly lipidated apolipoprotein A-I (apo A-I), the major protein component of HDL.

How Does Tyrosylated HDL Remove Cholesterol From Cells?

The observations raise a number of interesting questions. One key issue is the mechanism that allows tyrosylated HDL to protect hyperlipidemic mice from atherosclerosis more effectively than HDL. Tyrosylated HDL is more potent than native HDL at removing cholesterol from lipid-laden fibroblasts and macrophages in vitro. This process does not appear to involve passive cholesterol desorption from the cells’ plasma membrane, which raises the possibility that tyrosylated HDL promotes reverse cholesterol transport by interacting with ABCA1. Consistent with this possibility, plasma HDL levels were higher in the mice treated with tyrosylated HDL than in those treated with native HDL. This effect was not due to differences in the half-lives of circulating HDL and tyrosylated HDL. Collectively, these observations suggest that tyrosylated HDL promotes cholesterol efflux from macrophages and perhaps other peripheral tissues more effectively than HDL in vivo.

Apoprotein A-I contains multiple amphipathic \( \alpha \)-helices, a structural motif that promotes lipid association. ABCA1 interacts with lipid-free (or poorly lipiddated) forms of apo A-I to remove cholesterol from cells. Synthetic peptides that have \( \alpha \)-helices but differ in primary sequence from apo A-I can also interact with ABCA1 and promote reverse cholesterol transport from cells. However, dimers of such peptides are particularly effective. Moreover, cross-linked heterodimers of apo A-I and apo A-II in tyrosylated HDL appear to be responsible for its enhanced ability to remove cholesterol from lipid-laden cells. These heterodimers act more potently than HDL and apo A-I–apo A-II heterodimers. The observations raise a number of interesting questions. One key issue is the mechanism that allows tyrosylated HDL to protect hyperlipidemic mice from atherosclerosis more effectively than HDL. Tyrosylated HDL is more potent than native HDL at removing cholesterol from lipid-laden fibroblasts and macrophages in vitro. This process does not appear to involve passive cholesterol desorption from the cells’ plasma membrane, which raises the possibility that tyrosylated HDL promotes reverse cholesterol transport by interacting with ABCA1. Consistent with this possibility, plasma HDL levels were higher in the mice treated with tyrosylated HDL than in those treated with native HDL. This effect was not due to differences in the half-lives of circulating HDL and tyrosylated HDL. Collectively, these observations suggest that tyrosylated HDL promotes cholesterol efflux from macrophages and perhaps other peripheral tissues more effectively than HDL in vivo.

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A number of other properties of HDL could also contribute to its cardioprotective effects. Many lines of evidence support the hypothesis that oxidation converts LDL, the major carrier of blood cholesterol, into an atherogenic form. Unmodified HDL protects LDL from oxidative modification by metal ion-dependent and -independent pathways. However, HDL that has been oxidized by copper or hypochlorous acid loses its ability to remove cholesterol from cultured cells. These observations suggest that lipoprotein oxidation is detrimental and should promote cardiovascular disease. However, the physiological significance of lipoprotein oxidation catalyzed by these pathways is not yet established.

In this issue of *Arteriosclerosis, Thrombosis, and Vascular Biology*, Macdonald et al provide the first evidence that an oxidatively modified lipoprotein might retard the formation of atherosclerotic lesions. These investigators demonstrate that hypercholesterolemic mice deficient in apo E are protected from atherosclerosis more effectively when they are injected intraperitoneally with tyrosylated mouse HDL than when they are treated similarly with native mouse HDL. Tyrosylated HDL was produced by exposing HDL to tyrosyl radical generated by a peroxidase. These apparently paradoxical findings may be relevant to vascular wall biology because myeloperoxidase, a heme protein expressed by macrophages in human atherosclerotic lesions, produces tyrosyl radical in vitro. The studies of Macdonald et al are also intriguing because they suggest that not all forms of oxidized lipoprotein are atherogenic.

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Apo A-I cross-linked to apo A-II represented a minor fraction (~14%) of the total apolipoproteins in the tyrosylated HDL used in the studies of MacDonald et al. If such heterodimers are responsible for the atheroprotective effects of tyrosylated HDL, relatively low concentrations of such cross-linked apolipoproteins (or synthetic peptides) might be sufficient to exert pronounced effects on atherogenesis, at least in mice. It would then be worth investigating whether other oxidants and reactive intermediates that cross-link HDL-associated apolipoproteins, including carbonyls and hypochlorous acid, would similarly enhance HDL’s ability to inhibit atherosclerosis. Such studies might lead to the development of therapeutic synthetic peptides and other small molecules designed to mimic the antiatherogenic effects of HDL in humans.

Is HDL Tyrosylated in the Human Artery Wall? Another key question is whether tyrosylated HDL or other forms of oxidized apo A-I are formed in vivo. It then would be important to identify the mechanisms, both oxidative and nonoxidative, responsible for their production. One well established pathway for generating tyrosyl radical involves myeloperoxidase, a heme enzyme secreted by phagocytes. In vitro studies have shown that tyrosyl radical produced by myeloperoxidase forms cross-links with tyrosine residues in proteins, creating dityrosine. Furthermore, activated human phagocytes use myeloperoxidase to tyrosylate polypeptides. Also, enzymatically active myeloperoxidase and elevated levels of dityrosine, a marker for protein oxidation by tyrosyl radical, have been detected in human atherosclerotic plaques. However, it is not yet known whether HDL is tyrosylated in vivo. Indeed, remarkably little is known about oxidative modifications of HDL that occur in the human artery wall. It would be of great interest to elucidate the oxidative mechanisms that convert HDL into a cardioprotective particle and to determine whether similarly modified species of HDL exist in vivo.

Does Lipoprotein Oxidation Promote or Retard Atherogenesis? The study of MacDonald et al challenges the dogma that lipoprotein oxidation is necessarily atherogenic. The observations suggest that tyrosylated HDL, an oxidatively modified lipoprotein, reduces atherosclerotic lesion formation more effectively than native HDL, suggesting a yin and a yang for oxidative events in the artery wall. It is noteworthy that clinical trials of vitamin E, a proposed antioxidant, have failed to slow the onset of cardiovascular events in humans with established coronary artery disease. One potential explanation is that some forms of lipoprotein oxidation might be beneficial.

It is also important to note that HDL might affect lipoprotein oxidation and atherogenesis by several other mechanisms. HDL protects LDL from oxidation by metal ions, though, as noted above, the physiological relevance of this reaction pathway is uncertain. Synthetic peptides that contain amphipathic α-helices and are composed of D-amino acids appear to retard atherogenesis in hypercholesterolemic mice without affecting HDL levels. In vitro studies suggest that this effect is mediated in part by inhibition of LDL oxidation, but the possibility that such peptides also promote reverse cholesterol transport has not been investigated. HDL appears to be the major carrier of lipid hydroperoxides in the plasma, and it has been proposed that it also transports oxidized cholesteryl esters to the liver for excretion. Moreover, specific methionine residues in apo A-I appear to mediate the reduction of lipid hydroperoxides to alcohols, which may alter their atherogenic effects. Thus, HDL might also lower the risk for atherosclerosis by altering the structures or metabolic fates of oxidized lipids that would otherwise exert atherogenic effects.

In future studies, it will be important to confirm that tyrosylated HDL is atheroprotective in other animal models, to determine how it removes cholesterol from cells, and crucially to establish whether HDL is tyrosylated or undergoes other oxidative modifications in the human artery wall. The possibility that the atheroprotective activity of HDL actually improves in an oxidative environment adds another intriguing dimension to the potential health benefits of this complex population of lipoprotein particles.

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References


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