HDL may protect against atherosclerosis via several potential mechanisms. HDL has been shown to inhibit inflammation, regulate nitric oxide production, function in innate immunity, and, in its most extensively studied property, remove excess cholesterol from macrophages in the process of reverse cholesterol transport. During cholesterol efflux, lipid-poor apoA-I and mature HDL interact with integral membrane proteins ATP-binding cassette transporter A1 and ATP-binding cassette transporter G1, respectively, to accept cholesterol from cells. Our group and others have shown that the cholesterol efflux capacity of HDL inversely correlates with atherosclerotic vascular disease. The addition of niacin to statin therapy failed to improve cardiovascular outcomes but also did not improve HDL cholesterol efflux capacity, providing a potential explanation and leaving open the possibility that therapies (such as reconstituted apoA-I mimetic peptides) that do increase efflux may reduce cardiovascular risk and benefit patients.

Further supporting the concept that HDL quality may be more relevant than quantity, several groups have identified modified forms of apoA-I that are poor acceptors for cholesterol efflux. Work from the Hazen and Heinecke laboratories has shown that myeloperoxidase targets apoA-I, leading to chlorination of multiple tyrosine residues, whereas both myeloperoxidase and peroxynitrite may cause HDL nitration. Shao et al now extend these findings by showing that patients with both coronary artery disease and acute coronary syndrome have increased content of 3-chlorotyrosine in their apoA-I isolated from plasma HDL. They show that the tyrosine residue at position 192 (Tyr192) is the major chlorination site in apoA-I, with significantly higher levels in coronary artery disease and acute coronary syndrome groups compared with healthy controls.

In addition, they show that another oxidative modification of apoA-I on methionine 148 (Met(O)148) was significantly higher in patients with coronary artery disease and acute coronary syndrome compared with controls. Oxidation by myeloperoxidase at Met148 had been previously shown to cause decreased activation of lecithin:cholesterol acyltransferase, a plasma enzyme that converts free cholesterol to cholesterol ester, an important early step in reverse cholesterol transport. Shao et al show that the levels of chlorination at Tyr192 and nitrosylation at Met148 show a significant correlation with HDL cholesterol efflux capacity ($r=0.33$) and that levels of Met(O)148 show the highest odds ratio cardiovascular disease status (odds ratio, 7.3; 95% confidence interval, 1.8–30). Although it remains possible that these modifications are themselves a marker of inflammation rather than direct mediators of decreased efflux, Shao et al demonstrate that in vitro oxidation of HDL at Met148 was induced by incubation with hypochlorous acid and associated with decreased efflux capacity, whereas reversal of these oxidative changes significantly improved efflux, suggesting a direct effect. Therefore, increased Met(O)148 levels may inhibit reverse cholesterol transport by 2 mechanisms: decreased ATP-binding cassette transporter A1–dependent cholesterol efflux but also decreased activation of lecithin:cholesterol acyltransferase.

Increased levels of modified apoA-I observed in lesions from plasma and human atheroma are not only poor acceptors of ATP-binding cassette transporter A1–dependent cholesterol efflux but also exhibit additional proinflammatory properties. Modifications at multiple residues of apoA-I, including tryptophan, tyrosine, methionine, and lysine, have been shown to impair properties of apoA-I (Figure) and thus have now been implicated in the generation of dysfunctional apoA-I. Recently, nitration at Tyr166 has also been shown to inhibit lecithin:cholesterol acyltransferase activity, whereas oxidation at tryptophan 66 decreased cholesterol efflux capacity and promoted nuclear factor-$\kappa$B activation. In addition to playing a key role in oxidizing apoA-I, myeloperoxidase also targets the HDL-associated antioxidant enzyme paraoxonase 1, leading to further loss of antioxidant function. The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.
reactive carbonyls including malondialdehyde can form adducts at lysine residues on apoA-I, a process associated with decreased ATP-binding cassette transporter A1–dependent cholesterol efflux and decreased ability of HDL to promote nitric oxide production from endothelial cells.23,24

The molecular details of these post-translational modifications of apoA-I highlight that oxidative changes observed in the plasma may be distinct from processes in the arterial wall. For example, in the present study the level of chlorinated Tyr192 and Met(O)148 observed on apoA-I did not correlate with total plasma myeloperoxidase levels, leading Shao et al6 to conclude that myeloperoxidase likely does not modify apoA-I on HDL in the plasma. Instead, the authors have suggested that these oxidative changes may occur within vessel walls. Consistent with this, nearly 1 in 12 apoA-I molecules isolated from arterial specimens have nitrosylation at Tyr166, whereas this modification is present in only 1 in 1000 circulating apoA-I molecules. The spatial compartmentalization of damaged, lipid-poor apoA-I versus HDL-associated apoA-I and its relevance to HDL function remain an interesting area of scientific inquiry.

Although Tyr192 has been noted by both the Hazen group and Shao et al to be a target for myeloperoxidase-induced oxidative damage, there has been debate on the significance of other residues. Methodological differences in the isolation of apoA-I from human samples likely explain these discrepancies. The former group has developed several antibodies to isolate total apoA-I and HDL and the implications for development toward a better understanding of the functional effects of modified apoA-I and HDL and the implications for development of a new generation of apoA-I–centric therapeutic approaches.

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None.

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Ali Javaheri and Daniel J. Rader

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