Apolipoprotein A-I and Cholesterol Efflux
The Good, the Bad, and the Modified

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High-density lipoprotein (HDL) cholesterol is strongly and inversely associated with coronary heart disease. However, recent developments have raised major questions about the causal nature of this relationship. Several randomized controlled clinical trials of HDL-raising interventions have failed to demonstrate reduction in risk of major adverse cardiac events.1-4 Furthermore, in 1 Mendelian randomization study, genetic variants associated with increased HDL cholesterol were not associated with protection from coronary heart disease.5 It has been proposed that HDL can be dysfunctional and that this might cloud the relationship between HDL cholesterol and coronary heart disease. In this issue of Circulation Research, Shao et al6 further our understanding of the concept of HDL dysfunction by showing that oxidative modifications of apoA-I, the main protein constituent of HDL, impair its ability to accept cholesterol from macrophages.

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. 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 efflux15 but also exhibit additional proinflammatory properties.16 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,20 whereas 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 cholesteryl ester, an important early step in reverse cholesterol transport.9 Shao et al9 show that the levels of chlorination at Tyr192 and nitrosylation at Met148 show a significant correlation with HDL cholesterol efflux capacity (r2=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 al9 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.6,19

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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 a 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 al6 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 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.

Figure. Post-translational modifications of apolipoprotein A-I at multiple sites lead to decreased cholesterol efflux capacity and lecithin:cholesterol acyltransferase (LCAT) activation. Locations of the LCAT binding site (residues 159–170, shaded) and myeloperoxidase (MPO) binding site (residues 190–203, shaded) are highlighted. ONOO− indicates peroxynitrite.


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