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

Ali Javaheri, Daniel J. Rader

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. Furthermore, in Mendelian randomization study, genetic variants associated with increased HDL cholesterol were not associated with protection from coronary heart disease. 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 al 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.

HDL may protect against atherogenesis 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, lipopoor 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) 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.
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 al.8 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.8 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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Disclosures

None.

References


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