Editorial

Myeloperoxidase-Mediated Dysfunctional High-Density Lipoprotein

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The oxidation of lipoproteins plays an important role in atherogenesis. Most studies have focused on the oxidation of low-density lipoprotein, occurring to a significant extent in the arterial intima leading to the formation of the characteristic foam cell of the atherosclerotic plaque. However, the oxidation of the proteins of high-density lipoprotein (HDL) is thought to substantially attenuate the atheroprotective effects of this lipoprotein. Among the agents that potentially play an important role in oxidizing HDL is myeloperoxidase, an enzyme found in neutrophils, monocytes, and subsets of macrophages. Myeloperoxidase levels in the blood and blood leukocytes have been reported to be elevated in patients with coronary artery disease. Its level may be a valuable risk factor able to predict a major cardiac event in patients with chest pain.

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Apolipoprotein A-I (apoA-I) is thought to have several atheroprotective influences. In this issue of *Arteriosclerosis, Thrombosis, and Vascular Biology*, Hewing et al have reported on the functional attributes of myeloperoxidase-oxidized human apoA-I. To test the relative activity of the native apoA-I and oxidized apoA-I, human plasma apoA-I was oxidized with myeloperoxidase in vitro and the 2 preparations individually injected subcutaneously at relatively high levels into Western diet–fed Apoe−/− mice 4× for 8 days. All 4 tryptophan and 3 methionine residues were oxidized and the 7 tyrosine residues were chlorinated, including tyrosine 192 in the myeloperoxidase-oxidized apoA-I. Although lesion size was not changed, the injection of native apoA-I resulted in reduced lesional lipid and macrophage content, increased polarization of macrophages toward an M2 phenotype, and increased collagen content indicative of more stable lesions. Consistent with decreased lipid content, the expression of 2 sterol-responsive genes in lesional macrophages were increased, including CCR7 that has been shown previously to promote the egress of macrophages from lesions. None of the above modifications of lesion morphology was seen with the oxidized apoA-I. This is not because of the inability of oxidized apoA-I to localize to the lesions. The lack of an effect of oxidized apoA-I may be related to its inability to promote ATP-binding cassette 1 (ABCA1)-mediated cholesterol efflux to nascent HDL particles in vitro. To ascertain the cholesterol efflux capability of the native and oxidized apoproteins in vivo, a macrophage-to-feces reverse cholesterol transport assay was performed. An increase in macrophage-derived cholesterol was noted in the plasma, liver, and feces of animals treated with native apoA-I, whereas no such increment was observed with oxidized apoA-I. Consistent with impaired cholesterol efflux, HDL cholesterol levels were not increased in mice treated with oxidized apoA-I, and the majority of the oxidized apoA-I was found in the lipid-free fractions. As expected from its distribution pattern, the modified apoprotein was removed from the plasma more rapidly than the native apoprotein, and this could contribute to its ineffectiveness.

This elegant study represents a clear demonstration that myeloperoxidase-mediated oxidation of apoA-I greatly impairs its in vivo function, much of which is directly or indirectly attributable to its inability to promote cholesterol efflux. This adds to the ongoing concern about whether HDL function rather than plasma HDL cholesterol levels is a better reflection of the atheroprotective role of HDL. Myeloperoxidase is expressed by cells that participate in atherogenesis and is found in the plasma in a complex with apoA-I in HDL, which may explain why apoA-I is a selective target of myeloperoxidase oxidation.

However, the extent of oxidation of apoA-I is much greater in human atheroma than in the plasma, with apoA-I–containing oxidized tryptophan 72 present in atheroma at ⩾1000x the level found in plasma apoA-I. This modification seems to account for 50% of the impairment of ABCA1-dependent cholesterol efflux.

In addition to furnishing critical data on the functional impairment of oxidized apoA-I in vivo, this study also illustrates a useful model for the structure–function analysis of apoA-I in modifying atherosclerotic lesions. It should be mentioned, however, that it is unlikely that endogenous apoA-I would be as extensively modified as the apoprotein used in this study. Furthermore, in most in vivo contexts, unmodified and myeloperoxidase-modified apoA-I likely coexist. Future investigations can be expected to advance our understanding with regard to the following questions: (1) what proportion of apoA-I modification is compatible with a normal HDL cholesterol and normal HDL function in vivo? (2) What modifications in addition to oxidation of tryptophan 72 must coexist to account for the complete impairment of the cholesterol efflux capability of apoA-I? (3) Is there a good correlation between the apoA-I structural modifications that impair cholesterol efflux capability and the capacity to alter lesion composition in this model? (4) Does native apoA-I induce macrophage migration and lesion stabilization in more complex and advanced lesions than those studied in the article by Hewing et al?

Disclosures

None.
References


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