Editorial

Myeloperoxidase-Mediated Dysfunctional High-Density Lipoprotein

Godfrey S. Getz, Catherine A. Reardon

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.

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 generate 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, 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 present in atheroma at ≈1000× 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.

From the Department of Pathology, University of Chicago, IL.

Correspondence to Godfrey S. Getz, University of Chicago, Box MC 1089, 5841 S Maryland Ave, Chicago, IL 60637. E-mail getz@bsd.uchicago.edu

(Arterioscler Thromb Vasc Biol. 2014;34:695-696.)

© 2014 American Heart Association, Inc.

Arterioscler Thromb Vasc Biol is available at http://atvb.ahajournals.org

DOI: 10.1161/ATVBAHA.114.303282
References


Key Words: Editorials • atherosclerosis • apoA-I • cholesterol efflux • myeloperoxidase
Myeloperoxidase-Mediated Dysfunctional High-Density Lipoprotein
Godfrey S. Getz and Catherine A. Reardon

Arterioscler Thromb Vasc Biol. 2014;34:695-696
doi: 10.1161/ATVBAHA.114.303282
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2014 American Heart Association, Inc. All rights reserved.
Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://atvb.ahajournals.org/content/34/4/695

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Arteriosclerosis, Thrombosis, and Vascular Biology can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Arteriosclerosis, Thrombosis, and Vascular Biology is online at:
http://atvb.ahajournals.org/subscriptions/