Antiinflammatory Actions of HDL: A New Insight
Kerry-Anne Rye and Philip J. Barter

doi: 10.1161/ATVBAHA.108.173575
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2008 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/28/11/1890

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/
Antiinflammatory Actions of HDL
A New Insight
Kerry-Anne Rye, Philip J. Barter

Ther arisesclerosis is an inflammatory disorder characterized by the accumulation of macrophages and T-lymphocytes in the arterial intima. The macrophages are derived from blood monocytes that adhere to, and transmigrate across, an activated or injured endothelial surface. The firm adhesion of monocytes to the endothelium requires expression of integrins such as CD11/CD18 on the monocyte surface and endothelial expression of the adhesion molecules vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), and E-selectin. Monocytes that are firmly tethered to the endothelium transmigrate into the subendothelial space in a process that is dependent on endothelial expression of chemokines such as monocyte chemotactic protein-1 (MCP-1).1

The results of numerous epidemiological studies have established that high density lipoprotein (HDL) levels correlate inversely with the risk of developing cardiovascular disease.2 This relationship reflects several functions of HDL, the most extensively studied of which is their ability to remove excess cholesterol from cells, such as macrophages in the artery wall, in the first step of the reverse cholesterol transport pathway.4 In addition to their lipid transporting properties, HDL have antioxidant and antithrombotic properties.5,6 They are also important for maintaining normal endothelium-dependent vasoreactivity, inhibiting endothelial cell apoptosis, and contributing to the repair of damaged endothelium.5,7

In recent years it has become increasingly apparent that HDL also have potent antiinflammatory properties. This has been demonstrated in vitro as well as in vivo. For example, the cytokine-induced expression of VCAM-1, ICAM-1, and E-selectin in cultured human umbilical vein endothelial cells (HUVECs) is inhibited by HDL in a concentration-dependent manner.8 HDL also reduce the binding of monocytes to the surface of tumor-necrosis factor-α-activated HUVECs,9 and their lysosphingolipid cargo has recently been shown to inhibit aortic MCP-1 expression.10 The article by Murphy et al in the current issue of Arteriosclerosis, Thrombosis, and Vascular Biology now reveals that HDL can also prevent inflammatory responses by acting directly on monocytes.11

In this study Murphy et al show that HDL isolated from normal subjects, lipid-free apoA-I (the main apolipoprotein of HDL), and reconstituted HDL (rHDL) containing apoA-I complexed with phosphatidylcholine all potently inhibit expression of the integrin CD11b (also known as Mac-1) on the monocyte surface. The specificity of this observation was confirmed by showing that neither phosphatidylcholine liposomes nor BSA can inhibit monocyte CD11b expression. The physiological relevance of the observation was strengthened by demonstrating that the HDL-mediated inhibition of CD11b expression prevented the monocytes from binding to cultured human coronary artery endothelial cells, although it is difficult to determine to what extent this reflects an HDL-mediated reduction in endothelial expression of ICAM-1, which is a key ligand for CD11b.12 It is equally relevant that the present studies do not allow us to differentiate between the potential antiinflammatory effects of HDL on specific monocyte subpopulations and their ultimate impact on atherogenesis.13

Murphy et al also established that the inhibition of CD11b expression by apoA-I, but not HDL, was most likely secondary to cholesterol efflux. This conclusion was reached by depleting the monocytes of cholesterol with β-cyclodextrin, or by blocking activity of the ATP binding cassette transporter ABCA1 with a neutralizing antibody that specifically prevents cholesterol efflux. The finding that HDL did not inhibit monocyte activation by a mechanism that involves cholesterol efflux suggests that other, as yet unidentified, receptors or transporters are also involved.

These results differ in some respects from what has been reported for the inhibition of inflammatory responses in endothelial cells by HDL. In the present study Murphy et al established that lipid-free apoA-I, but not phospholipid liposomes, inhibit monocyte activation in vitro. Earlier reports from our group have, by contrast, shown that rHDL and small unilamellar phosphatidylcholine vesicles, but not lipid-free apoA-I, inhibit inflammation in activated HUVECs in vitro.14 Although the finding that infusion of lipid-free apoA-I inhibits endothelial inflammation to the same extent as rHDL...
in vivo appears to be at odds with our in vitro observation, this most likely reflects no more than the rapid lipidation of the injected apoA-I to form new HDL particles.15

Considering that Murphy et al found that lipid-free apoA-I but not phospholipid liposomes inhibit monocyte CD11b expression, whereas our earlier observations demonstrated that phospholipid vesicles, but not lipid-free apoA-I, inhibit endothelial cell adhesion molecule expression, the possibility that HDL prevent monocyte and endothelial cell activation by different mechanisms needs to be considered. Although this has obvious implications for the design of antiinflammatory apoA-I mimetic peptides, there is preliminary evidence suggesting that it may not necessarily be a cause for concern as the apoA-I mimetic peptide L37pA has been shown to reduce CD11b expression in monocytes11 as well as in cultured endothelial cells.16

In conclusion, this study by Murphy et al adds to a growing body of evidence that HDL and apoA-I protect against cardiovascular disease by mechanisms that extend well beyond their involvement in cholesterol transport. It remains to be seen whether the ability of HDL to inhibit monocyte activation proves to be important for reducing the debilitating symptoms and economic cost associated with acute coronary syndromes and other inflammatory diseases.

Disclosures
None.

References