I n a 1984 review, Shlomo Eisenberg1 wrote, “In spite of their large number in plasma, it is difficult to define HDL as a vehicle for lipid transport ... other considerations must apply to this lipoprotein.” In this issue of Circulation, Suzuki et al2 report that high-density lipoprotein (HDL) suppresses the type I interferon response in macrophages challenged with lipopolysaccharide. They found that HDL specifically promoted the translocation of TRIF-related adapter molecule (TRAM) into intracellular compartments, leading to impaired signaling by toll receptor 4 (TLR4) and TRIF (Toll/interleukin-1 receptor-domain-containing adapter protein inducing interferon). In mice lacking apolipoprotein A-I (apoA-I), administration of Salmonella typhimurium (which expresses lipopolysaccharide) resulted in 6-fold higher plasma levels of interferon-β, which is a key regulator of the type I interferon response. These actions of HDL were independent of the interaction of HDL with ATP-binding cassette transporter ABCA1 or ABCG1. These effects of HDL were also independent of the cholesterol content of macrophages and were independent of HDL inhibiting the binding of lipopolysaccharide to CD14 or TLR4 on the cell surface. Therefore, Suzuki et al2 proposed a mechanism of action in which HDL depletes the plasma membrane of TRAM, a key adaptor molecule that activates TRIF in endosomal compartments.

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Kagan et al3 demonstrated that TRAM has a bipartite motif. One portion is the site of myristate attachment, and the other is a polybasic domain that is necessary for binding to acidic phospholipids; both the site of myristate attachment and the polybasic domain are required for TRAM to bind to the plasma membrane. Thus, TRAM is recruited to the plasma membrane primarily via lipid binding. The type I interferon response is a critical part of the cellular reaction to viral infection.4 Suzuki et al2 note that a feed-forward loop that amplifies the initial response to the invading virus is a key component to the response, but under some circumstances positive feedback can be deleterious when the response is excessive.5

Van Lenten et al6 reported that infection of human type II pneumocytes with influenza A virus led to a marked increase in the phospholipid content of the cells and also a marked increase in the secretion of phospholipids into the medium in which the cells were grown. There also was a marked increase in the cellular content of oxidized phospholipids such as 1-palmitoyl-2-[(5,6-epoxyisoprostane E2)-sn-glycero-3-phosphorylcholine (PEIPC) and a marked increase in the secretion of these oxidized phospholipids into the medium. Treatment of the pneumocytes with an apoA-I mimic peptide, D-4F, significantly decreased the cellular content and secretion of oxidized phospholipids but did not alter the cellular content or secretion of the parent nonoxidized phospholipids. D-4F treatment also reduced viral titers and significantly decreased the production of interferon-α and interferon-β by the cells in response to the viral infection.6 In vivo, D-4F treatment significantly reduced the severity of influenza A viral pneumonia in mice and resulted in decreased viral titers in lung tissue.7 The mechanism of action of D-4F is thought to be related to its remarkable ability to bind oxidized lipids of the kind that were identified in the influenza A–infected pneumocytes. The D-4F peptide bound PEIPC with a $K_d$ of 0.06 nmol/L, indicating an extraordinary affinity of the lipid for the peptide.8

Some of these oxidized lipids have been implicated in modulating lipopolysaccharide signaling. For example, the 5-keto-6-octendioic acid ester of 2-phosphatidylcholine (KodiA-PC) was found to be especially potent in inhibiting the ability of lipopolysaccharide to induce interleukin-8 in endothelial cells by a mechanism that appears to involve a lipid raft/caveolar fraction of the plasma cell membrane.9,10 Smythies et al11 reported that treatment of human monocytes with the 4F peptide or apoA-I decreased lipopolysaccharide-induced interleukin-6 production and increased interleukin-10 expression, resulting in a more anti-inflammatory state, by a mechanism that may involve alterations in lipid rafts. Gharavi et al12 reported that HDL reduced the induction of inflammatory genes in endothelial cells in response to oxidized phospholipids such as PEIPC by a mechanism that did not inhibit the induction of heme oxygenase-1, which is known to induce the anti-inflammatory cytokine interleukin-10. Berliner and Witzum and colleagues13,14 demonstrated that oxidized phospholipids such as PEIPC are formed during the process of cellular apoptosis, which may explain the presence of these oxidized lipids in the virally infected cells studied by Van Lenten et al. A consequence of the influenza A infection in the pneumocytes studied by Van Lenten et al16 was a marked activation of caspases, which was mitigated by treatment with the apoA-I mimic peptide D-4F. These oxidized lipids have also been reported to form in response to a bacterial infection. Cruz et al15 demonstrated that lesions from patients with the disseminated form of
leprosy contained the oxidized phospholipid PEIPC. Moreover, on infection of human macrophages with live mycobacteria, PEIPC was formed. Mycobacterial infection and host-derived oxidized phospholipids such as PEIPC both inhibited innate immune responses, and this inhibition was reversed by normal HDL but not by HDL taken from patients with leprosy. PEIPC and other similar oxidized phospholipids have been found in atherosclerotic lesions from animals and humans.

In vivo, oxidized phospholipids were shown to inhibit phagocytosis and worsen outcome in gram-negative sepsis. Also in vivo, administration of the apoA-I mimetic peptide 4F in lipopolysaccharide-treated rats promoted the transfer of lipopolysaccharide to HDL and improved survival.

Suzuki et al did not determine whether oxidized lipids were present or were formed during the course of their experiments. Thus, their findings may not be related to the action of HDL on oxidized lipids. However, as noted above, the localization of TRAM to the plasma membrane depends on its ability to bind to plasma membrane lipids, and thus it is likely that the actions of HDL reported by Suzuki et al relate to some component of HDL that binds or modifies lipids in the cell membrane.

Our understanding of the complexity of HDL has been significantly advanced by the work from Heinecke et al. Shlomo Eisenberg was very prescient when he advised us to think of HDL as more than a “vehicle for lipid transport.”

Sources of Funding
This work was supported in part by US Public Health Service grant HL-50568.

Disclosures
Dr Fogelman is a principal and officer in Bruin Pharma.

References

Key Words: Editorials || apolipoproteins || atherosclerosis || HDL cholesterol || infection || inflammation
The Complexity of High-Density Lipoproteins
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Circulation. 2010;122:1900-1901; originally published online October 25, 2010;
doi: 10.1161/CIRCULATIONAHA.110.984120
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2010 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/122/19/1900

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