The Complexity of High-Density Lipoproteins

Alan M. Fogelman, MD

In 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 al3 proposed a mechanism of action in which HDL depletes the plasma membrane of TRAM, a key adaptor molecule that activates TRIF in endosomal compartments.

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 Wittum 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.6 A consequence of the influenza A infection in the pneumocytes studied by Van Lenten et al6 was a marked activation of caspases, which was mitigated by treatment with the apoA-I mimetic peptide D-4F.

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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.16

In vivo, oxidized phospholipids were shown to inhibit phagocytosis and worsen outcome in gram-negative sepsis.17 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.18

Suzuki et al2 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 al2 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.1,19,20 Shlomo Eisenberg1 was very prescient when he advised us to think of HDL as more than a “vehicle for lipid transport.”

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Dr Fogelman is a principal and officer in Bruin Pharma.

References

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