The role of HDL in innate immunity[1]

Kenneth R. Feingold[2] **and Carl Grunfeld**

Metabolism Section, Department of Veterans Affairs Medical Center, University of California San Francisco, San Francisco, CA 94121

HDL has anti-atherogenic properties that are primarily attributed to its key role in reverse cholesterol transport. The ability of HDL to inhibit the oxidation of LDL, decrease inflammation, inhibit thrombosis, stimulate fibrinolysis, and favorably affect endothelial cell function may also contribute to the anti-atherogenic effects of HDL (1, 2). Not well recognized is the role HDL plays in innate immunity (3).

Numerous studies have shown that lipoproteins bind microorganisms or compounds derived from microorganisms (3). When either endotoxin (LPS), from gram negative bacteria, or lipoteichoic acid (LTA), from gram positive bacteria, are incubated with whole blood from healthy humans, the majority of the LPS and LTA are bound to HDL. This binding to HDL inhibits the ability of LPS and LTA to interact with toll-like receptors (TLR) and activate macrophages (3). TLR activation of macrophages stimulates the production and secretion of cytokines and other signaling molecules, which if produced in excess can lead to septic shock and death (4, 5). In addition to binding LPS, studies have shown that HDL also facilitates the release of LPS that is already bound to macrophages, reducing macrophage activation (6).

Transgenic mice overexpressing apolipoprotein A-I have elevations in serum HDL levels and are protected from death due to LPS and severe bacterial infection (7). Similarly, several studies have shown that infusion of HDL or apolipoprotein A-I mimetic peptides into animals with experimental sepsis improves survival (3, 8, 9). Conversely, reducing serum lipoprotein levels increases the ability of LPS administration to induce death and this increased susceptibility can be reversed by providing exogenous lipoproteins (10). Humans with low HDL levels have a more robust inflammatory response to LPS administration (11). Furthermore, the administration of reconstituted HDL to humans blunts the deleterious effects of LPS administration (12). In addition to binding bacterial products, HDL also binds a wide variety of viruses and neutralizes their activity (3). Moreover, HDL also plays a protective role in parasitic infections (3). The lysis of trypanosomes is mediated by HDL particles that contain apolipoprotein L1 and haptoglobin-related protein (13). Additionally, recent studies have shown that apolipoprotein L1 and hapto-globin-related protein also inhibit infection by Leishmania (14). Finally, low levels of HDL and apolipoprotein A-I are associated with an increase in mortality in patients admitted to intensive care units (15–17). Taken together, these observations indicate that HDL plays a role in protecting the host from the toxic effects of microorganisms and is part of the innate immune system.

The structural basis for the protective effects of HDL has been studied most intensively for LPS. Both the lipid and proteins that comprise HDL contribute to the neutralization of LPS. Apolipoprotein A-I alone can neutralize LPS and this interaction can be altered by changing the structure of apolipoprotein A-I (18). For example, serine substitution of one cysteine (228) in the C-terminal domain dramatically reduces the ability of HDL to neutralize LPS, whereas substitutions of other cysteines (52 or 74) enhance the ability of HDL to neutralize LPS (18). The amino acid substitutions that affect LPS neutralization have minimal effects on the lipid composition of HDL.

However, lipid emulsions devoid of protein can also neutralize LPS, demonstrating that lipids also play a key role (3). The phospholipid content of lipoproteins correlates with the ability of lipoproteins to neutralize LPS, whereas the content of cholesterol or triglycerides does not (3). Additionally, phospholipids alone have been shown to protect animals from LPS-induced toxicity. Thus, both apolipoproteins and phospholipids can play important roles in the ability of HDL to neutralize LPS (3).
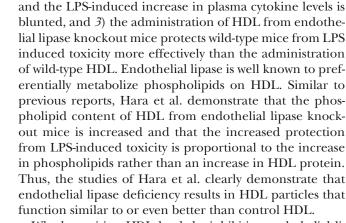
In this issue, Hara et al. (19) explore the effect of endothelial lipase deficiency on the function of HDL particles. They report that HDL isolated from endothelial lipase knockout mice is similar to HDL isolated from wild-type mice in the ability to facilitate cholesterol efflux, protect from oxidation, and inhibit the ability of cytokines to activate endothelial cells. However, they demonstrate that HDL from endothelial lipase knockout mice are more potent in neutralizing LPS than control HDL in vitro and in vivo. Specifically, they show that *1*) HDL from endothelial lipase knockout mice is more effective than control HDL in inhibiting the ability of LPS to stimulate tumor necrosis factor secretion by macrophages in vitro, *2*) Endothelial

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lipase knockout mice are resistent to LPS-induced death and the LPS-induced increase in plasma cytokine levels is blunted, and *3)* the administration of HDL from endothelial lipase knockout mice protects wild-type mice from LPS induced toxicity more effectively than the administration of wild-type HDL. Endothelial lipase is well known to preferentially metabolize phospholipids on HDL. Similar to previous reports, Hara et al. demonstrate that the phospholipid content of HDL from endothelial lipase knockout mice is increased and that the increased protection from LPS-induced toxicity is proportional to the increase in phospholipids rather than an increase in HDL protein. Thus, the studies of Hara et al. clearly demonstrate that endothelial lipase deficiency results in HDL particles that function similar to or even better than control HDL.

Whether raising HDL levels by inhibiting endothelial lipase activity will favorably affect atherosclerosis is unclear. Using endothelial lipase knockout mice, one group has shown a reduction in atherosclerosis in apolipoprotein E deficient/ endothelial lipase double knockout mice, whereas another group has reported no effect in either apolipoprotein E deficient or LDL receptor deficient mice (20, 21).

From the point of view of host defense, it should be noted that inflammation, induced by either LPS or cytokines, has been shown to increase endothelial lipase expression (22–25). The endothelial lipase promoter contains a nuclear factor kB (NFkB) response element and LPS induces an increase in binding to that site (26). Suppression of NFkB activation with inhibitors blocks the increase in endothelial lipase expression induced by LPS (26). Thus, during infection and inflammation, endothelial lipase increases and one could speculate that this would result in a reduction in the ability of HDL to neutralize LPS. In fact, studies have shown that although HDL is the lipoprotein primarily responsible for the binding of LPS in the basal state, during infections and inflammation, the role of HDL decreases and VLDL assumes the major role in LPS neutralization due to both structural changes in VLDL and an increase in VLDL levels (3, 27).

Finally, from a broader perspective, as drugs are developed to raise HDL levels, one will need to determine the effectiveness of these drugs not only on their ability to stimulate reverse cholesterol transport and reduce atherosclerosis, but also on their ability to affect the other protective functions of HDL. It is notable that in the large randomized trial of torcetrapib, there was a marked increase in deaths due to infectious disease in the group treated with the CETP inhibitor (28). Whether this was a chance observation or resulted from alterations in HDL structure and function is unknown, but needs to be addressed in future studies.

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