Obesity is associated with a state of chronic, low-grade inflammation that reflects the accumulation of macrophages and other leukocytes in adipose tissue. In obesity, cross-talk between adipocytes and macrophages amplifies the production of inflammatory cytokines and chemokines by macrophages and adipocytes, leading to local and systemic insulin resistance. Macrophage inflammation is also prominent in atherosclerosis, and cholesterol efflux pathways mediated by high-density lipoprotein (HDL), apolipoprotein AI (apoAI), and ATP-binding cassette transporters (ABC) act to suppress inflammation in macrophage foam cells. However, a possible role of cholesterol efflux pathways in the inflammation of obesity has not been previously addressed. In this issue of Circulation Research, Umemoto et al. provide evidence that HDL and apoAI promote cholesterol efflux from adipocytes and reverse the expression of the proinflammatory chemotactic factors induced by saturated fatty acids in adipocytes, suggesting a novel mechanism for anti-inflammatory properties of HDL and the possibility that increasing HDL-mediated cholesterol efflux has beneficial effects on insulin resistance.

In previous work the authors of this study have demonstrated that saturated fatty acids such as palmitate stimulate monocyte chemotactic factor expression and production from 3T3-L1 adipocytes. This effect involves increased NADPH oxidase 4 (NOX4) activity, recruitment of NOX4 to lipid rafts, and enhanced reactive oxygen species (ROS) production. ROS generation has been implicated as an important contributor to insulin resistance in obesity and diabetes mellitus. HDL promotes cholesterol efflux and reduces cholesterol content in lipid rafts, altering the activity of signaling molecules in lipid rafts. Therefore, Umemoto et al. investigated whether HDL-mediated cholesterol efflux from adipocytes affected chemotactic factor expression and whether this involved modulating NOX4 recruitment to lipid rafts and its activity. First, they showed that depletion of membrane cholesterol and disruption of lipid rafts by cyclodextrin, a chemical compound that mimics the effect of HDL and strongly promotes cholesterol efflux, completely blocked palmitate-induced Mcp-1 or Saa3 expression in 3T3-L1 adipocytes. ApoAI or HDL also reduced the palmitate-induced chemotactic factor expression, in association with decreased formation of lipid rafts, reduced membrane cholesterol, and retarded translocation of NOX4 to lipid rafts. Next, the authors investigated the possible involvement of ABCA1, ABCG1, and scavenger receptor class B, type I. ABCA1 and ABCG1 are membrane transporters that actively promote cholesterol efflux to apoAI or HDL whereas scavenger receptor class B, type I is involved in bidirectional transport of cholesterol across the membrane. ApoAI, but not HDL, failed to reduce the formation of lipid rafts, NOX4 translocation, and ROS generation in palmitate-treated adipocytes with downregulated ABCA1 expression by RNA interference, whereas HDL but not apoAI failed to do so in adipocytes with downregulated ABCG1 or scavenger receptor class B, type I expression, findings consistent with previous reports that ABCA1 primarily mediates cholesterol efflux to lipid-poor apoAI and ABCG1 or scavenger receptor class B, type I promotes cholesterol efflux mainly to HDL particles (Figure). Finally, the authors extended their findings to an in vivo model. Human apoAI transgene expression in LDLr<sup>−/−</sup> or Ldlr<sup>−/−</sup> background increased increased apoAI and HDL cholesterol levels. When the mice were fed a high-fat, high-sucrose, cholesterol-containing diet, human apoAI transgenic expression reduced Saa3 and Mcp-1 expression in intra-abdominal adipose tissue, in association with decreased macrophage accumulation and proinflammatory cytokine expression (Tnfα, Il1β, and Il6) in the adipose tissue. Because whole adipose tissue was used in the analysis, the relative contribution of adipocytes versus infiltrated macrophages cannot be determined. Nevertheless, these findings indicate that apoAI and HDL exert an anti-inflammatory effect on adipose tissue in vivo.

These findings also raise interesting questions, that is, how palmitate increases translocation of NOX4 to lipid rafts and how increased NOX4 association with lipid rafts enhances its activity. Previous studies suggest that unlike other NOX family members, NOX4 is constitutively active. Saturated fatty acids can activate Toll-like receptor 4 (TLR4)-mediated pathways. In previous studies, these authors have shown that palmitate-induced ROS generation and Saa3 and Mcp-1 expression in adipocytes are TLR4 dependent, because silencing TLR4 markedly reduces palmitate-induced expression of these genes. Interestingly, direct interaction between TLR4 and NOX4 has been reported, and this interaction seems to be required for lipopolysaccharide-induced ROS generation via TLR4 in other cell types. ABCA1/ABCG1-deficient macrophages display increased formation of lipid rafts, elevated cell-surface TLR4 levels, and enhanced TLR4-mediated signaling, likely because of defective cholesterol efflux. Excess palmitate also increases lipid raft formation in adipocytes, as shown by the current study. Together, these observations suggest the possibility that cell-surface TLR4 levels may be increased and that TLR4–NOX4 interactions are involved in palmitate-induced NOX4 translocation, ROS generation, and chemotactic factor expression.
HDL is known to have antioxidative activities such as prevention of low-density lipoprotein or phospholipid oxidation, and these activities are considered to be responsible in part for the antiatherogenic effects of HDL. However, mechanisms independent of cholesterol efflux and ABCA1 is required for this activity of HDL in the former tissue.28 Interestingly, a post hoc analysis shows that torcetrapib, a cholesterol ester transfer protein inhibitor that markedly increases plasma HDL cholesterol levels in humans, lowers plasma insulin and glucose levels in diabetic subjects.33

This study also has other important therapeutic implications. A recent clinical study indicates that the ability of HDL to efflux cholesterol from macrophages in an ex vivo assay has a strong inverse association with cardiovascular disease risk, independent of the HDL cholesterol level.24 Infusion of rHDL seems to reduce atheroma volume in clinical trials.35–37 rHDL infusion also improves inflammatory profiles in type II diabetic subjects.38 The current study suggests that the anti-inflammatory effects of rHDL infusion could be mediated in part by rHDL to suppress adipose tissue inflammation, offering novel possibilities for prevention of diabetes mellitus, atherosclerosis, and their complications. It also supports the efforts to increase cholesterol efflux and reverse cholesterol transport as potential therapies of atherosclerosis and diabetes mellitus by other means such as increasing ABCA1/ABCG1 expression and apoAI/HDL synthesis.39–41

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Disclosures
None.

References
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