When HDL Gets Fat . . .

Robert J. Brown, Daniel J. Rader

Because low levels of plasma high density lipoprotein cholesterol (HDL-C) are a major independent risk factor for atherosclerotic cardiovascular disease, the mechanisms leading to low HDL-C are of substantial biological and clinical importance. Low HDL-C is most commonly seen in persons who have other components of the “metabolic syndrome,” particularly increased waist circumference, elevated triglycerides (TG), and elevated fasting glucose, which along with low HDL-C are indicators of insulin resistance. Kinetic studies in humans have indicated that the turnover of the major HDL protein apolipoprotein A-I (apoA-I) is increased in patients with the characteristics of metabolic syndrome and insulin resistance. The mechanisms of hypercatabolism of HDL in this setting have been the subject of substantial investigation.

The insulin resistant state is associated with elevated plasma levels of TG-rich lipoproteins (TRL), derived from the liver and the intestine, as well as with elevated levels of the cholesteryl ester transfer protein (CETP). CETP transfers TG from TRL to HDL in exchange for cholesteryl esters. Accelerated CETP-mediated lipid exchange siphons cholesterol out of and transfers TG into HDL, resulting in a cholesterol-depleted and TG-enriched HDL. Enrichment of HDL with TG makes it a much better substrate for hepatic lipase (HL), which is also clearly elevated in insulin resistant states. Lewis and colleagues have previously shown through a series of elegant studies in rabbits and humans that TG-enriched HDL is more rapidly catabolized than “native” HDL and that this requires the action of HL on the TG-enriched HDL, with hydrolysis of the TG to create “remnant HDL” particles. However, the molecular mechanisms of the accelerated clearance of remnant HDL have remained poorly understood.

In the current issue of Circulation Research, Xiao et al ruled-out major roles for the low-density lipoprotein receptor, the scavenger receptor class B type I (SR-BI), and proteoglycans in mediating the increased binding and internalization of remnant HDL particles. Whereas the liver is a major site of catabolism of HDL, the hepatocytic receptors and pathways leading to HDL binding, uptake, and degradation remain unknown. The results of these studies suggest that a critical pathway of uptake and degradation of remnant HDL particles remains undiscovered. Although native HDL has been used in the past, using remnant HDL may be a better way to “fish” for cell surface molecules that bind and internalize HDL.

Although HL is of clear importance in promoting the catabolism of HDL, other lipases also likely play key roles, particularly in the setting of insulin resistance. Endothelial lipase (EL), a close relative of HL, is a key modulator of HDL metabolism in mice and increasingly appears to be important in humans as well. In contrast to HL, EL is predominantly a phospholipase with minor TG hydrolase activity, and is especially tropic for HDL, with a preference for metabolizing small HDL particles. EL is also elevated in insulin resistance and EL positively correlates with factors that are associated with metabolic syndrome, as well as with markers of inflammation. The fact that HL and EL are both upregulated in insulin resistance suggests cooperativity, but the manner in which HL and EL cooperate to modify HDL and influence its metabolism is unknown. It may be possible that HL and EL act in tandem in insulin resistance: HL primarily hydrolyzes TG from TG-rich HDL to generate remnant HDL, whereas EL hydrolyzes phospholipids from remnant HDL particles, which further enhances their catabolism.

Recently, it has been appreciated that plasma HDL-C levels, while an important predictor of cardiovascular risk, do not tell the whole story. The issue of HDL functionality has assumed major importance. It is of interest to wonder whether the TG-enrichment of HDL, and its subsequent hydrolysis by HL, impacts on HDL function. The classic HDL functional property is the promotion of cellular cholesterol efflux and reverse cholesterol transport (RCT). Although plasma from insulin-resistant patients was shown not to exhibit any dysfunction of efflux capacity, to our knowledge the ability of TG-enriched HDL, before or after exposure to HL, to promote cellular cholesterol efflux has never been directly experimentally tested. Furthermore, the effect of HL expression on the overall rate of RCT in vivo, which also includes uptake of HDL-C by the liver and excretion into the bile, has never been tested. The delivery of peripheral cholesterol to the liver via SR-BI might be expected to be enhanced in the presence of HL-modified TG-rich HDL. Collet al have shown that remnant HDL particles have

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From the Department of Medicine and Institute for Translational Medicine and Therapeutics, University of Pennsylvania School of Medicine, Philadelphia.

Correspondence to Daniel J. Rader, 654 BRB II/III, University of Pennsylvania School of Medicine, 421 Curie Blvd, Philadelphia, PA 19104. E-mail rader@mail.med.upenn.edu

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enhanced selective uptake of cholesteryl ester using a cell culture model overexpressing SR-BI. Xiao et al.\(^1\) show that remnant HDL binding is significantly enhanced in the presence of SR-BI, but remnant HDL binding is also enhanced independently of SR-BI. The impact of HL modification of TG-rich HDL on its ability to promote cholesterol efflux, donate its cholesterol to the liver, and overall modulate RCT in vivo should be determined.

More studies are necessary to identify and understand the mechanisms behind how remnant HDL particles are rapidly cleared from the circulation. Future cell culture and animal research should involve additional putative HDL receptors which may have a key impact on remnant HDL catabolism. In addition, animal studies using models of insulin resistance in the absence or presence of CETP would be important to understand whether the generation and clearance of remnant HDL affect RCT in vivo. Although low HDL-C remains a robust marker of insulin resistance and increased cardiovascular risk, questions remain regarding the causal role it plays in atherogenesis and cardiovascular events.

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**Disclosures**

None.

**References**


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