Atherosclerotic vascular disease is a leading cause of morbidity and mortality globally. Evidence suggests that accumulation of activated macrophages, rather than plaque size or luminal stenoses, influences the clinical outcome of cardiovascular diseases such as atherosclerosis and its acute complications, cardiac remodeling after acute myocardial infarction, and arterial and valvular calcification.

Conventional anatomic imaging modalities do not demonstrate the macrophage burden in cardiovascular organs, but recent technologies of molecular imaging can visualize biological processes, including several parameters of macrophage activation (eg, proteolytic activity, phagocytic activity). Such macrophage imaging may offer biomarkers to identify subclinical inflamed lesions as precursors of acute thrombotic events, predict future risk, enable pathophysiological investigations, and assess the effects of therapies such as low-density lipoprotein (LDL) lowering. In experimentally produced atherosclerotic plaques, high-resolution magnetic resonance imaging enhanced with superparamagnetic nanoparticles and activatable near-infrared fluorescence (NIRF) probes can measure macrophage accumulation and monitor changes in inflammatory burden during statin treatment (Figure 1). Recent-ly developed intravascular NIRF imaging platforms may soon visualize dynamic macrophage activity in human arteries. Macrophage imaging with 18F-fluorodeoxyglucose positron emission tomography, already available for human use, can demonstrate the effects of anti-inflammatory therapies. 

Many studies have established that LDL-lowering therapy reduces the macrophage burden and prevents cardiovascular events. However, despite strong epidemiological evidence of the inverse relationship between high-density lipoprotein (HDL) levels and residual cardiovascular risk, the successive failures of large, randomized trials of HDL-raising drugs has understandably lead to significant concern about the role of HDL in cardiovascular disease. It is time to reinterrogate the HDL hypothesis. When HDL metabolism is put under the microscope, it becomes increasingly clear that the “quality” or “function” of HDL matters as much as, if not more than, its “quantity” or “amount.” Total plasma HDL-cholesterol levels do not necessarily capture the diverse atheroprotective functions of the heterogeneous HDL population, and may not be a reliable surrogate for causative biological processes through which HDL protects against atherosclerotic plaque development. Thus, urgent demands have driven the development of in vivo assays that can determine HDL functionality, measure this abstract process to guide HDL drug discovery, and be used to evaluate the effectiveness of existing therapies through preclinical and clinical development.

The ideal functional molecular imaging would directly visualize the interaction between HDL and plaque macrophages. Although HDL may exert protective effects against cardiovascular disease through multiple mechanisms, the main mechanism entails HDL eliciting cholesterol efflux from cholesterol ester-enriched macrophage foam cells, HDL could thus inhibit or even reverse atherosclerotic plaque development, and contribute to plaque stability. Several assays have been developed to trace the RCT process in vivo. Specifically targeting macrophages, Rader and colleagues developed a novel approach for tracing the reverse transport of radiolabeled-cholesterol specifically from injected macrophages to the liver and feces in vivo. But whether injected macrophages with radiolabeled-cholesterol represent atherosclerotic plaque macrophages, the main action site for macrophage-specific RCT, remains unknown.

In this issue of the Journal, Kawachi and colleagues report a novel molecular imaging technique that promises to provide functional HDL imaging at the site of atherosclerotic plaques. Using positron emission tomography imaging, the investigators demonstrated that a tracer, a modified version of a 24-amino acid apolipoprotein A-I (apoA-I) mimetic peptide (96Ga-DOTA-FAMP), could be found in atherosclerotic tissues in the aorta of hypercholesterolemic rabbits. Ex vivo imaging of extracted aorta from these rabbits using a planar positron imaging system found a high correlation between radioactivity and plaque distribution. If properly validated with immunohisto-
In the effects of antiatherogenic therapies in clinical practice or during clinical trials for new drugs. In particular, functional molecular imaging is a major candidate technology that could provide direct, in vivo assessment of macrophage-HDL function, which would be key to guiding HDL drug development and in identifying high-risk patients who need HDL intervention.

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Figure 2. Overview of reverse cholesterol transport (RCT) and high-density lipoprotein (HDL) metabolism. HDL is first secreted by the liver and small intestine as lipid-poor preβ-HDL, which interacts with ABCA1 in peripheral tissues, such as macrophage foam cells in atherosclerotic plaque, to initiate the RCT process. Plasma free cholesterol effluxed from cells and incorporated into preβ-HDL is esterified by the enzyme, lecithin-cholesterol acyltransferase (LCAT), with the formation of spherical α-HDL. Cholesterol ester in plasma α-HDL derived from atherosclerotic plaque and other peripheral tissues is transported to the liver by either direct delivery through scavenger receptor class B member I (SR-BI)-mediated selective cholesterol ester offloading or cholesterol ester transfer protein (CETP)-mediated exchange of HDL-cholesterol ester for apoB lipoprotein-bound triglyceride and then low-density lipoprotein (LDL) receptor-mediated uptake of apoB lipoproteins. Drug development currently focuses on CETP inhibition, which blocks the exchange of cholesterol esters for triglyceride between HDL and apoB lipoproteins. CETP raises HDL-cholesterol primarily through expanding the population of mature, large α-HDL. Other potential interventions under clinical evaluation include administration of HDL or apoA-I mimic peptide, inducers of endogenous apoA-I synthesis, LCAT induction, ATP-binding cassette transporter 1 (ABCA1) activation, and selective liver X receptor (LXR) agonists. (Reproduced from Zheng et al30 with permission from Elsevier.) apoA-I, apolipoprotein A-I.
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