A fortunate development in medicine has been the unraveling of the relationship between LDLs and atherosclerosis, as evidenced by the dramatic impact of LDL lowering on cardiovascular events.1-3 Risk reduction by decreasing LDL could also be considered fortuitous; average LDL levels in Western society may well be nearly double “ideal,” even if “normal” or “physiological” cholesterol levels remain difficult to define. Humans typically are born with LDL levels in the 30-μg/dL range; in more agrarian societies, LDL levels average 70 to 100 mg/dL.3 Thus, the cardiovascular benefits documented over the past decade with HMG CoA reductase inhibitors (statins) have occurred through large-scale reductions of LDL by 30% to 70%.4 In contrast, in most cases, halving blood pressure or glucose would not be tolerated. Together, these observations support an “overflow” model in which LDL promotes atherosclerosis at levels that far outstrip any physiological role or survival advantage. Despite this, an asymptote of risk reduction may be reached once LDL levels have been lowered to currently recommended levels, leaving scientists and clinicians to look elsewhere for therapeutic opportunities to reduce the on treatment event rate evident in statin trials, even at LDL levels well below 100 mg/dL.5 In this regard, HDL cholesterol (HDL) has received considerable attention given strong epidemiological data for its protective effects, encouraging clinical data with even modest HDL raising, and a rational scientific mechanism through HDL-mediated reverse cholesterol transport.6

One approach to raising HDL is to activate nuclear hormone nuclear receptors that control transcription of key HDL components like apolipoprotein A1 (apoA1). The identification of peroxisome proliferator-activated receptors (PPARα, γ, and β/δ) and liver X receptors (LXRα and β) as “sensors” of dietary lipids and cholesterol has provided just such an opportunity.7 Like other steroid hormone nuclear receptors, PPARs and LXRs are ligand-activated transcrip-
Key components of reverse cholesterol transport. Cholesterol taken up by tissue macrophages is transferred to HDL through membrane transporters like ABCA1 and ABCG1. HDL can then return to the liver where its cholesterol can be converted to bile acids (BA) through a process mediated in large part by Cyp7a. Finally, bile acids and cholesterol are delivered to intestine where they can be excreted in feces. ABCG5 and ABCG8 appear important to cholesterol absorption/excretion. This simplified schema supports reverse cholesterol transport as a potential target for limiting atherosclerosis by promoting cholesterol removal from macrophages and foam cells at the arterial wall. CE indicates cholesteryl ester; FC, free cholesterol.

by injecting 3H-cholesterol–loaded J774 macrophage-like cells intraperitoneally into 3 mouse models: wild-type C57BL/6, LDLR/apobec-1 double knockout, and human apoB/cholesterol esterase transfer protein (CETP) double-transgenic mice. Each model also received either the LXR synthetic ligand GW3965 by gavage for 10 days before the experiment or vehicle alone. This approach allowed the investigators to separately test the impact of treating the J774 experiment or vehicle alone. This approach allowed the investigators to separately test the impact of treating the J774 macrophages with GW3965 before injection. By analyzing 3H tracer levels in serum, bile acids, and feces, the authors could quantify reverse cholesterol transport in vivo. When these 3H tracer levels were analyzed, systemic GW3965 treatment increased macrophage-derived labeled cholesterol in serum and feces in all 3 models and increased HDL levels in C57BL/6 and apobec/CETP transgenic mice. In so doing, these investigators provide in vivo proof that LXR activation increases (reverses) cholesterol transport from macrophages through to excretion.

The study by Naik et al19 provides an important proof of concept with regard to LXR and reverse cholesterol transport while also offering several other interesting observations. First, pretreating J774 cells with the LXR ligand had no effect on reverse cholesterol transport. This finding may suggest that macrophage cholesterol efflux does not play an important role in LXR actions or that the cellular effects of the LXR agonist were short-lived on injection. Of note, a prior report using bone marrow transplantation demonstrated that macrophages are essential for LXR-mediated atheroprotection.20 Thus, all 3 components of the reverse cholesterol transport may be coordinately regulated and required for efficient cholesterol elimination. Naik et al19 also found unchanged fecal bile acid excretion (except for LDLR/apobec-1–knockout mice) after LXR ligand treatment despite overall increased cholesterol excretion. The authors suggest that this may have been due to rapid turnover. Bile acid synthesis is regulated by a variety of mechanisms, including negative feedback regulation of Cyp7a by bile acids themselves; when this pathway is suppressed, other regulators such as Cyp27a in mice can compensate. This study also supports LXR activation as modulating cholesterol excretion in addition to its known effects on decreasing cholesterol absorption in enterocytes through changes in ABCG5 and ABCG8.14 In this study, GW3965 treatment consistently increased excretion of macrophage-derived cholesterol in all models studied here, indicating that these 2 transporters may also facilitate cholesterol excretion. Because Cyp7a is not regulated by LXR agonists in humans, this study suggests that LXR agonists may still be able to promote cholesterol excretion in the intestine independently of Cyp7a. The relevance of these reverse cholesterol transport assay in peritoneal macrophages to the macrophages in the arterial wall remains to be established but is certainly plausible.

LXR activation may have benefits beyond cholesterol homeostasis because these receptors also modulate innate immunity.21 LXR ligands inhibit the expression of inflammatory mediators, including interleukin-6, inducible nitric oxide, and cyclooxygenase-2, all of which have been implicated in atherosclerosis.2 This coordinated regulation of cholesterol homeostasis and inflammation by LXRs further supports these receptors as promising antiatherosclerotic targets. There are, however, several important issues to be resolved. First, mouse and human lipid metabolism differs, an ongoing challenge in translating mouse data to humans. Furthermore, mouse and human LXRs appear to direct distinct transcriptional activities. For example, human LXRα activity can be amplified through positive autoregulation.22 In addition, CETP expression in humans is induced by LXRs, but Cyp7a is not.14 It is unclear how upregulation of CETP by LXRs affects levels of HDL and atherogenesis. Most importantly, activation of LXRs increases sterol regulatory element-binding protein-1c expression in liver, raising concern about hepatic steatosis.14 Indeed, animal studies have demonstrated that LXR ligand treatment can significantly increase circulating triglyceride levels, although that did not occur here with GW3965.18 This LXR/triglyceride effect is mediated predominantly through hepatic LXRα. One attractive strategy for avoiding hypertriglyceridemia is to develop LXRβ-specific agonists or tissue-specific LXR modulators. It is interesting to note that LXRα is transcriptionally controlled by PPARγ in the macrophage but not in the liver.23 The development of modulators of PPARs and LXRs that amplify the PPARγ-
LXRα transcriptional activity locally in the macrophage could also be a useful approach.

LXR agonists can be placed in the context of other drugs being developed that focus on HDL. CETP inhibitors potently increase HDL levels. CETP mediates the exchange of cholesteryl ester in HDL for triglyceride in VLDL, thus decreasing levels of HDL and increasing proatherogenic VLDL and LDL. CETP inhibitors maintain HDL levels by blocking this process. Torcetrapib and JTT-705 are 2 CETP inhibitors that increase HDL in humans. Although the impact of such drugs on human atherosclerosis remains under study, the effect of JTT-705 on atherosclerotic lesion development in cholesterol-fed rabbits has been variable. One study showed a 70% reduction in the total atherosclerotic lesion area after 6 months of treatment; a second found no difference between control and JTT-705-treated groups after 3 months despite similar increases in HDL levels (≈2 fold) in both reports. PPARG ligands also increase HDL levels ≈40% in primates, although no PPARG agonist has yet been approved for clinical use.

The present study establishes that LXR agonists promote cholesterol efflux from macrophages to HDL and ultimately intestinal excretion. Interestingly, in the LDLR backbone, the LXR ligand GW3965 did not raise HDL but lowered total cholesterol and reduced the lesion size by 50%, indicating that the rate of cholesterol excretion exceeds or equals that of efflux. Perhaps the ability of HDL to promote cholesterol throughput and the absolute level of HDL represent separate and not always parallel parameters. Interestingly, although individuals with the apoA1 Milano genotype have low HDL levels, they have no increased risk of atherosclerosis. The implications of throughput capacity in terms of the clinical responses to CETP inhibition remain to be determined.

No doubt, insights into nuclear receptor biology will continue to be applied to treating human disorders. Indeed, in 2005, the first large-scale clinical cardiovascular thiazolidinedione trial was reported, a study in which HDL may have contributed to the results seen; findings from a large fibrate/PPARα agonist trial were released; and a dual PPARG/γ agonist was submitted to the Food and Drug Administration for approval. Each of these steps generated controversy, but it is likely that progress will continue, extending to ongoing attempts to harness LXR activation, including its effects on cholesterol transport and excretion that Naik and colleagues have proved occur in vivo with LXR agonists. Ultimately, clinical end points will be needed if we are to move beyond limiting cholesterol overflow and toward understanding if increased reverse cholesterol “throughput,” by LXR activation or any other approach, is truly a reversal of fortune for patients at risk for atherosclerotic and its complications.

Disclosures

None.

References


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