A strong inverse association exists between plasma HDL cholesterol (HDL-C) levels and incidence of coronary artery disease. Although environmental factors play a role, variation in HDL-C levels are at least 50% genetically determined. The genetics of syndromes of very low HDL-C have been extensively studied. Mutations in apoA-I (the major HDL structural protein), ABCA1 (which promotes efflux of cellular lipids to apoA-I forming nascent HDL particles), and LCAT (which converts unesterified cholesterol to cholesteryl ester [CE]) to form the lipid core of mature HDL particles) have all been demonstrated to cause very low levels of HDL-C and apoA-I due to rapid catabolism of apoA-I. However, their relationship to premature atherosclerosis is often uncertain, leading to the concept that the HDL-mediated “flux” of cholesterol from the periphery to the liver, where cholesterol is delivered for excretion into the bile (a process known as reverse cholesterol transport [RCT]), may be more important than the actual plasma concentrations of HDL-C in protecting against atherosclerosis.

Syndromes of inherited high HDL-C also exist, but have been much less studied. The only known monogenic cause of inherited high HDL-C in humans is deficiency of the cholesteryl ester transfer protein (CETP), which transfers HDL CE out of HDL to apoB-containing lipoproteins. CETP deficiency results in markedly reduced rates of turnover of apoA-I. CETP deficiency occurs primarily in Japan, where its relationship to cardiovascular risk is still under debate: some investigators believe it is associated with protection from cardiovascular disease, whereas others contend that it increases cardiovascular risk. This topic is not merely academic, as inhibitors of CETP are under development as novel HDL-raising therapies. Studies with CETP inhibitors will definitively answer whether raising HDL-C through CETP inhibition in humans reduces atherosclerotic vascular disease. The evolution of the CETP story—from the discovery of the deficiency state in humans to the development of therapeutics targeted toward CETP—has been a fascinating example of the ability of human genetic studies to enlighten our understanding of physiological pathways and lead to new therapies.

Outside Japan, most subjects with inherited high HDL-C do not have CETP deficiency, and the genetic etiology of their high HDL-C is unknown. The only other gene in which genetic variation has been associated with elevated HDL-C levels in humans is hepatic lipase (HL). Patients deficient in HL have modestly increased HDL-C levels and a common variant in the HL promoter is associated with higher HDL-C levels. Patients with HL deficiency also have dyslipidemia and may be at increased risk of atherosclerotic vascular disease; thus, HL is not generally considered a viable target for pharmacologic inhibition. Genetic variations of another member of the lipase gene family, endothelial lipase (EL), might be also associated with elevated HDL-C levels. Overexpression of EL markedly reduces HDL-C levels, and antibody inhibition or deletion of EL significantly increases HDL levels in mice. Several potentially functional genetic variants in EL were found in subjects with elevated HDL-C levels, some of which were not found in a large group of control subjects. One of these common EL variants was reported to be associated with slightly higher HDL-C levels. These studies have increased interest in EL as a potential target for pharmacologic intervention, although its relationship to atherosclerosis remains unknown. Further studies will elucidate whether mutations in EL are a monogenic cause of inherited high HDL-C and whether genetic variation in EL contributes to variation in HDL-C levels and atherosclerosis in the general population.

Finally, scavenger receptor class B type I (SR-BI) is another candidate gene in which loss-of-function might be expected to result in high HDL-C levels. SR-BI was initially described by Acton and colleagues as a cell-surface receptor capable of binding HDL and mediating selective uptake of HDL CE into cells. In vivo studies have clearly demonstrated the crucial role of SR-BI in HDL metabolism and atherosclerosis in mice. Hepatic overexpression of SR-BI markedly reduced HDL-C levels and, paradoxically, reduced atherosclerosis in LDLR-deficient mice fed a high-cholesterol diet. Conversely, total or partial deficiency of SR-BI in mice causes increased HDL-C levels and accelerated atherosclerosis. These studies have led to the concept that hepatic SR-BI expression, by promoting the uptake of HDL CE, promotes RCT and therefore reduces atherosclerosis (Figure). However, direct measures of RCT from tissue to bile or feces have not been reported in SR-BI overexpressing or knockout mice and therefore this hypothesis remains to be tested. Furthermore, the effect of SR-BI on atherosclerosis is mediated not only by its hepatic expression, but also by its

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expression in other cell types that are involved in atherosclerosis. SR-BI is present in macrophages, where it mediates cholesterol efflux to mature HDL particles. Indeed, SR-BI deficiency is associated with increased lipid deposition in macrophages in vivo and bone marrow transplantation from SR-BI–deficient mice into LDLR-deficient mice resulted in increased atherosclerosis. Furthermore, endothelial SR-BI is required for the ability of HDL to stimulate endothelial eNOS expression and promote NO production. Tissue-specific SR-BI knockout mice will be required to definitively assess the effects of SR-BI in different tissues on HDL metabolism and especially atherogenesis.

Whether SR-BI has similar role in HDL metabolism and atherogenesis in humans remains to be demonstrated. Surprisingly, SR-BI–deficient humans have not been described to date. Only three common polymorphisms have been reported that may be associated with LDL-C, HDL-C, and anthropometric measures in a sex-specific manner. Importantly, in this issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Hsu et al report that a loss-of-function genetic variant in the human SR-BI gene is associated with increased plasma HDL-C levels. The investigators screened a Taiwanese Chinese population for mutations in the SR-BI promoter region and identified two novel variants. One (a single nucleotide polymorphism) was not associated with variation in HDL-C levels. The other (a promoter deletion of a putative binding site for the transcription factor SP1) was found in 2% of the population and was associated with significantly higher HDL-C levels. Reporter studies indicated that it has 30% less transcriptional activity in HepG2 cells, indicating the functional nature of this variant. Although the apparent effect of this SR-BI variant on HDL-C levels must be confirmed in other populations, this study provides important genetic evidence that SR-BI plays a role in HDL metabolism in humans.

Major questions regarding the genetics of SR-BI and their relationship to atherosclerotic vascular disease in humans remain. For example, why have SR-BI–deficient subjects eluded the grasp of investigators to date? The phenotype of the SR-BI knockout mouse suggests that SR-BI deficiency in humans would be expected to cause elevated HDL-C levels in the setting of premature atherosclerotic disease, a phenotype that has been observed in humans. However, care must be taken when extrapolating from mouse models to humans with regard to HDL metabolism. Mice lack CETP, a state which could accentuate the phenotype of SR-BI deficiency. In the absence of CETP, HDL CE is dependent on the SR-BI pathway for clearance from the plasma, and disruption of the SR-BI pathway may constipate the RCT pathway, leading to accelerated atherosclerosis. Could it be that in humans, who have an intact CETP pathway, deficiency of hepatic SR-BI may have less consequence because HDL CE can be effectively siphoned from HDL and returned to the liver via apoB-containing lipoproteins? If true, the phenotype of SR-BI deficiency in humans may be more subtle than in the mouse. This may have potential therapeutic implications, in that persons with functional SR-BI mutations may not be good candidates for CETP inhibition. Another potential explanation for the failure to find SR-BI–deficient humans could be related to the role of SR-BI in reproduction. SR-BI is highly expressed in the gonads and SR-BI–deficient female mice are infertile. Perhaps loss-of-function mutations in SR-BI impair fertility in humans, markedly diminishing the chances of generating homozygotes with complete SR-BI deficiency.

The most fascinating aspect of the SR-BI–deficient phenotype in mice is the accelerated atherosclerosis. This would seem to be one of the strongest arguments that the RCT pathway is crucial to protection from atherosclerosis, at least in mice. Based on this result, one might predict that genetically reduced SR-BI function in humans would promote atherosclerosis despite the elevated HDL-C levels. Subsequent studies on the association of loss-of-function variants of SR-BI, such as the promoter variant described by Hsu and colleagues, with measures of atherosclerosis are eagerly awaited. If reduced SR-BI function is found to increase atherosclerosis in humans, it stands to reason that upregulation of SR-BI might be a novel anti-atherogenic strategy. The development of such a therapeutic approach, though firmly based in biology, would be complicated by the reduced plasma HDL-C levels.

In summary, while the epidemiology indicates a strong inverse association between HDL-C and cardiovascular risk, at both extremes of the HDL-C distribution, genetic conditions that influence HDL metabolism have a far less predictable relationship to atherosclerosis. Studies of genetic causes of very low HDL-C have provided important insight into the physiology of HDL metabolism and identified new molecular targets for the development of new therapies targeted toward HDL. As in the case of CETP, ongoing studies of genetic causes of very high HDL-C also promise to provide similarly important insights on the complex relationship between HDL and atherosclerosis.
metabolism and atherosclerosis that could lead to new therapies for the treatment of atherosclerotic cardiovascular disease.

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