Human genome-wide association studies have yielded a cornucopia of novel genetic loci that are associated with lipoprotein levels and coronary artery disease. However, a detailed understanding of the underlying mechanisms has for the majority proven elusive. A notable exception may be a widely replicated coronary artery disease locus at the chromosome 1p13 locus: the major alleles at this locus are present in ≈65% to 80% of whites, and homozygosity of the major alleles, as opposed to homozygosity of the minor alleles, is associated with a 20% to 40% increase in the risk of myocardial infarction and ≤16 mg/dL higher low-density lipoprotein (LDL)-cholesterol levels.1-3 The minor allele single nucleotide polymorphism with strongest association creates a functional C/EBPø binding site that increases the expression of SORT1 in human hepatocytes.4 Studies in mice have shown that increased hepatic expression of human SORT1 reduces the secretion of very LDL (VLDL) and increases the uptake of LDL into hepatocytes by a non-LDL receptor (LDL-R)-mediated pathway, thus lowering LDL levels (Figure).4,5 Studies in obese mice have revealed that Sort1 is regulated by endoplasmic reticulum stress, which decreases hepatic Sort1 expression and consequently increases ApoB and VLDL secretion.5,6

Article, see p 789

In a surprising twist, 2 recent studies show that Sort1 expression in macrophages leads to increased atherosclerosis.7,8 One of the studies reported in the current issue of Circulation Research shows that this is likely because of, at least in part, the ability of SORTILIN to mediate the uptake of LDL into macrophages.8 In this study, Patel et al8 first show the ability of SORTILIN to mediate the uptake of LDL into human hepatocytes.9 Studies in mice have shown that increased hepatic expression of human SORT1 reduces the secretion of very LDL (VLDL) and increases the uptake of LDL into hepatocytes by a non-LDL receptor (LDL-R)-mediated pathway, thus lowering LDL levels (Figure).4,5 Studies in obese mice have revealed that Sort1 is regulated by endoplasmic reticulum stress, which decreases hepatic Sort1 expression and consequently increases ApoB and VLDL secretion.5,6

![Figure](http://circres.ahajournals.org/)

SORTILIN
Many Headed Hydra

Marit Westerterp, Alan R. Tall
Although studies in mouse macrophages suggest that Sort1 increases atherosclerosis, \(^{7,8}\) studies in humans have shown that higher hepatic expression of SORT1 is associated with decreased LDL levels, especially highly proatherogenic small LDL particles. \(^3,4\) Studies on the role of hepatic SORTILIN in LDL metabolism in several mouse models have yielded complex results. \(^3,4,6,17,22\) Although 1 study has shown that increased hepatic Sort1 expression decreases ApoB and VLDL secretion, \(^4,22\) SORTILIN also facilitates the uptake of LDL and targets it for lysosomal degradation in the liver. A new study shows SORTILIN facilitates LDL uptake by macrophages in the vessel wall, promoting foam cell formation and atherosclerosis. \(^8\)

In a recent review, Strong et al. \(^18\) offer several explanations as to why hepatic ApoB secretion is decreased in both SORT1 overexpression and Sort1 deficiency models and speculated based on analogy with a related protein that at low levels of Sort1 expression, Adam10 cleaves the membrane domain of SORTILIN allowing the luminal piece to act as a chaperone for VLDL/apoB secretion. At higher levels of expression, the cleavage capacity of the enzymes in the Golgi is exceeded, and SORTILIN transports VLDL/apoB from the Golgi to the lysosome for degradation. In plasma, VLDL is converted into LDL by lipoprotein lipase (LPL). SORTILIN allows the luminal piece to act as a chaperone for VLDL/apoB secretion, thereby increasing LDL uptake by macrophages in the vessel wall. This, in turn, decreases VLDL secretion and increases LDL uptake in the vessel wall, promoting foam cell formation and atherosclerosis. \(^8\)

Figure. SORTILIN regulates ApoB and very low-density lipoprotein (VLDL) secretion by the liver and LDL uptake in the liver and macrophages. In the basal state, hepatic SORTILIN is cleaved in the Golgi and then acts as a chaperone for VLDL/apoB secretion. At higher levels of expression, the cleavage capacity of the enzymes in the Golgi is exceeded, and SORTILIN transports VLDL/apoB from the Golgi to the lysosome for degradation. In plasma, VLDL is converted into LDL by lipoprotein lipase (LPL). SORTILIN also facilitates the uptake of LDL and targets it for lysosomal degradation in the liver. A new study shows SORTILIN facilitates LDL uptake by macrophages in the vessel wall, promoting foam cell formation and atherosclerosis. \(^8\)

is involved in macrophage LDL uptake, along with earlier findings showing that Sort1 \(^{-/-}\) mice have reduced LDL secretion and LDL levels, suggests that complete disruption of the ApoB100-SORTILIN interaction in liver and macrophages might lead to reduced VLDL secretion and LDL levels, as well as reduced uptake of LDL by macrophages in atheroma-ta. Although hepatic clearance of LDL by SORTILIN might be decreased, this would be offset by reduced LDL secretion and could be compensated by concomitant statin therapy. In sum, although much progress has been made toward sorting out the complexities of SORTILIN, additional studies in human macrophages and atherosclerotic plaques will be needed to see whether this translates.

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