SORTILIN
Many Headed Hydra

Marit Westerterp, Alan R. Tall

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/EBPα 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 (LDLR)–mediated pathway, thus lowering LDL levels (Figure).4 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

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 (Figure).8 In this study, Patel et al.8 first show that whole body Sort1 deficiency decreases atherosclerosis in a humanized ApoB100/lPAB Tg mouse model without affecting LDL-cholesterol levels. They then show decreased atherosclerosis in Ldlr−/− mice transplanted with Sort1−/−Ldlr−/− bone marrow compared with controls, suggesting that Sort1 deficiency in bone marrow–derived cells decreases atherosclerosis independent of the Ldlr. In both models, Sort1 deficiency reduced macrophage foam cell formation in vivo. In vitro studies showed that SORTILIN promoted LDL uptake and cholesterol accumulation in macrophages independent of the LDLR and macropinocytosis,9 thus revealing a new proatherogenic pathway (Figure). Mortensen et al.10 also showed that Sort1 deficiency decreased atherosclerosis independent of plasma cholesterol levels, using Apoe−/− mice. They attributed these effects to decreased interleukin-6 and interferon-γ; however, these cytokines were not affected in the study by Patel et al.8

Although LDL binding studies were not reported,8 it is plausible that macrophage SORTILIN could act as a receptor for LDL. SORTILIN is a member of the VPS10 (10 bladed β-propeller) family9 and may act as a multiligand receptor with the potential to bind lipoprotein lipase, ApoA V , and other molecules.10,11 Surface plasma resonance binding studies have shown a high-affinity interaction between SORTILIN and ApoB100. Studies in HuH7 cells, a hepatocarcinoma cell line, and in mice have shown that SORTILIN binds LDL at the cell surface and mediates its uptake and lysosomal degradation, and thus contributes to the non–LDLR-mediated uptake and degradation of LDL.4 Additional studies may reveal whether SORTILIN directly binds and mediates uptake of LDL in macrophages, or whether other factors are involved, eg, the nonenzymatic bridging function of lipoprotein lipase.12

Several pathways promoting the uptake of modified forms of LDL by macrophages have been described, such as those mediated by CD36 and scavenger receptor A. CD36 and scavenger receptor A facilitate foam cell formation in vitro; however, their effects on atherosclerosis are modest.13,14 In contrast, the current reports7,8 using several different mouse atherosclerosis models now suggest that macrophage Sort1 deficiency substantially reduces atherosclerosis independent of changes in plasma lipid levels, in a non–LDLR-dependent fashion. Potentially this could represent the long sought mechanism to explain the ability of LDL to promote macrophage foam cell formation independent of the LDLR. Notably, this explanation does not require hypothesizing that LDL must first be oxidized, aggregated, or retained on arterial matrix before promoting foam cell formation.

Interestingly, whereas LDL-uptake decreases the expression of the Ldlr on macrophages,8 and macrophage Ldlr thus has a modest effect on atherogenesis,15 LDL uptake dramatically increases Sort1 levels in macrophages both at the mRNA and protein level.16 This suggests a feed-forward loop in macrophages in atherosclerotic lesions promoting continuous uptake of LDL by SORTILIN. Somewhat perplexingly, the protective allele of human SORT1 has been reported to be associated with a small but significant increase in SORT1 expression in monocytes.16 Expression studies on SORT1 in human macrophages and atherosclerotic lesions could be informative especially if combined with genotyping.

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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 Studies on the role of hepatic SORTILIN in LDL metabolism in several mouse models have yielded complex results. 3,4,17-22 Although 1 study has shown that increased expression of SORT1 seems to decrease VLDL secretion and increase hepatic uptake of LDL, 2 another study showed that SORTILIN facilitates the secretion of PCSK9 and thus reduces LDLR levels, 17 which would suggest the opposite effects of increased hepatic SORT1 expression. However, the finding that increased hepatic SORT1 expression in humans is associated with lower LDL cholesterol levels 4 would suggest that this mechanism is not dominant. Further adding to complexity, 2 independent studies have shown that complete Sort1 deficiency decreases ApoB and VLDL secretion. 4,22

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 in the secretory pathway of VLDL, thus explaining decreased VLDL secretion in complete Sort1 deficiency (Figure). As Sort1 expression levels increase, the capacity of Adam10 is exceeded and thus the cytoplasmic tail of SORTILIN is retained and directs SORTILIN with bound VLDL toward lysosomes for degradation. Thus, at higher levels of SORTILIN, VLDL secretion is also reduced compared with intermediate levels. 18

Although previous studies have indicated that Sort1 overexpression in the liver might lead to reduced LDL levels, 3,4 therapeutic targeting to increase expression may be difficult to achieve. However, the present study showing that SORTILIN 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.

Although hepatic clearance of LDL by SORTILIN might be decreased, this would be offset by reduced VLDL 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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References


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