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Sortilin And Lipoprotein Metabolism: Making Sense Out Of Complexity

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Abstract

Purpose of review—Genome wide associations studies (GWAS) have been used as an unbiased tool to identify novel genes that contribute to variations in LDL-C levels in the hopes of uncovering new biology and new therapeutic targets for the treatment of atherosclerotic cardiovascular disease (ASCVD). The locus identified by GWAS with the strongest association with LDL-C and ASCVD is the 1p13 *SORT1* locus. Here we review the identification and characterization of this locus, the initial physiological studies describing the role of *SORT1* in lipoprotein metabolism, and recent work that has begun to sort out the complexity of this role.

Recent findings—Studies by several groups support an important role for sortilin in lipoprotein metabolism; however, the directionality of the effect of sortilin on plasma cholesterol and its role in the secretion of hepatic lipoproteins remains controversial. Studies by several groups support a role for sortilin in inhibiting lipoprotein export whereas other studies suggest that sortilin facilitates lipoprotein export.

Summary—Understanding the mechanism by which sortilin affects LDL-C will increase our understanding of the regulation of lipoprotein metabolism and hepatic lipoprotein export and may also allow us to harness the power of the 1p13 *SORT1* locus for the treatment of ASCVD.

Keywords

Sort1; genome wide association study; atherosclerotic cardiovascular disease; low-density lipoprotein cholesterol; lipid metabolism

Introduction

Atherosclerotic cardiovascular disease (ASCVD) and its sequela of myocardial infarction (MI) is the leading cause of morbidity and mortality in the developed world[1]. The lifetime risk of developing ASCVD is strongly influenced by environmental factors including smoking, alcohol consumption, obesity, and sedentary lifestyle and also by medical risk factors such as diabetes, hypertension, decreased high density lipoprotein cholesterol (HDL-C) and increased levels of low-density lipoprotein cholesterol (LDL-C). LDL-C is intimately involved in each stage of atherosclerotic lesion development; LDL in plasma can be

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modified and taken up by macrophages, leading to macrophage engorgement and foam cell formation, cytokine release, vascular smooth muscle cell proliferation, and atherosclerotic plaque formation[2].

ASCVD is highly heritable due to the strong influence of genetics on LDL-C and other cardiovascular risk factors as well as directly on the atherosclerotic process. Some of the most dramatic examples of the heritability of LDL-C levels and ASCVD risk come from the study of rare Mendelian disorders of hypercholesterolemia including autosomal dominant hypercholesterolemia, which is caused by mutations in *LDLR*, *PCSK9*, and *APOB*, autosomal recessive hypercholesterolemia, which is caused by loss of function mutations in *LDLRAP1*, and sitosterolemia, which is caused by mutations in *ABCG5* or *ABCG8*. All of these disorders are characterized by markedly increased levels of LDL-C and premature ASCVD development[3].

Though Mendelian disorders provide a dramatic example of the influence of genetics on ASCVD development, they do not explain most of the variability in LDL-C levels and ASCVD risk in the population. Genome wide association studies (GWAS) have identified novel loci associated with LDL-C and ASCVD at the population level[4–9]. One of the most compelling novel loci in the human genome associated with both LDL-C and ASCVD is a locus on chromosome 1p13. The study of this locus has served as a paradigm for moving from locus identification by GWAS to biological mechanism through functional genomics. Here we review the early work of identifying the causal gene at this locus and then discuss the complexity of the physiology that has arisen as a result of these studies.

Identification of the causal gene at 1p13 as *SORT1*

Determination of the causal gene at the 1p13 LDL/MI locus was complicated by the locus structure; seven genes map to the associated region, *SARS*, *CELSR2*, *PSRC1*, *MYBPHL*, *SORT1*, *PSMA5*, and *SYPL2*, the associated SNPs lie in a noncoding region between *CELSR2* and *PSRC1*, and none of the seven genes have a clear role in lipoprotein metabolism[10]. Using expression quantitative trait loci (eQTL) data in human liver, Musunuru et al demonstrated an association between the minor allele haplotype and elevated expression of three genes at the locus, *PSRC1*, *CELSR2* and *SORT1*, with *SORT1* and *PSRC1* expression most strongly affected, increasing 5-6 fold with each copy of the minor allele. Importantly, expression of these genes in omental and subcutaneous adipose was not influenced by genotype, suggesting a liver-specific phenomenon. Linsel-Nitschke et al replicated the association between minor allele homozygosity at 1p13 and reduced LDL-C and protection from ASCVD in an independent population and further found that homozygosity for the minor allele haplotype correlated with increased expression of *SORT1* in peripheral blood with no change in expression of *CELSR2* or *PSRC1* [11].

With the eQTL data most strongly implicating *PSRC1* or *SORT1* as the causal gene and the liver as a relevant organ, efforts began to study the effects of overexpression and deficiency of these genes in liver. Adeno-associated viruses (AAV) were used to overexpress *Psrc1* and *Sort1* in hyperlipidemic *Ldlr*−/− mice, and while *Psrc1* overexpression had no effect on plasma cholesterol, *Sort1* overexpression led to a 40% reduction in plasma cholesterol [10,

12](Table One). As a complementary approach, careful phenotyping of *Psrc1*+/− and *Psrc1*−/− mice did not reveal any differences in plasma cholesterol, whereas *Sort1* knockdown in mouse liver using siRNAs was associated with a 20-40% increase in plasma cholesterol [10, 12]. These results strongly implicated *SORT1* as the causal gene at the 1p13 locus whose elevated expression confers reduction in LDL-C.

Early studies of the effect of sortilin on lipoprotein uptake

SORT1 encodes the protein sortilin, a VPS10 multi-ligand sorting receptor involved in Golgi to lysosome trafficking. Like other VPS10 proteins, sortilin consists of an N-terminal propeptide with a furin cleavage site, an extracellular VPS10 domain for ligand binding, a transmembrane domain and a cytoplasmic tail harboring two lysosomal sorting motifs[19, 20]. Sortilin localizes primarily to the Golgi apparatus [20, 21] where it serves as a trafficking receptor to sort lysosomal hydrolases to the lysosome [19, 22, 23], and a small fraction also traffics to the cell surface where it can act as a signaling receptor for pro-neurotrophins [24, 25], serve as an uptake receptor [26–28], or be cleaved by the alpha secretase A Disintegrin And Metalloproteinase domain-containing protein 10 (Adam10) to generate a soluble extracellular domain of yet poorly characterized function [29]. Sortilin has many ligands; however, at the time of its discovery as a GWAS hit for LDL-C, the only known lipid related ligand was lipoprotein lipase (LPL), which is involved principally in triglyceride metabolism, failing to explain the strong association between elevated *SORT1* expression and reduced LDL-C [30].

With the identification of *SORT1* as the causal gene, efforts began to determine the mechanism by which increased hepatic expression of *SORT1* reduced plasma LDL-C. Though initially characterized as an intracellular sorting receptor, a cell surface role for sortilin in ligand uptake is becoming increasingly appreciated; recent studies have found that sortilin acts as a cell surface internalization receptor for progranulin [26], apolipoprotein E [27], and alpha-galactosidase A [28]. Such observations raised the question of whether LDL itself might be a ligand for sortilin. Through a series of *in vitro* LDL uptake studies and *in vivo* kinetic studies, Strong et al showed that increased *Sort1* expression in mouse liver and in multiple different cell lines increased LDL clearance [13]. Conversely, *Sort1* deficiency was found to impair LDL clearance *in vivo*. Importantly, absence of the LDL receptor did not reduce the effect of *Sort1* overexpression or deficiency on LDL uptake, suggesting an LDL receptor independent mechanism. Strong et al further demonstrated that sortilin serves as a bona fide cell surface receptor for LDL and facilitates its cellular uptake and lysosomal degradation. These findings are supported by studies from other laboratories. Linsel-Nitschke et al reported that *SORT1* overexpression in HEK293 cells increased LDL uptake and that this increase is abrogated by co-incubation with known sortilin ligands including RAP and LPL [11]. Tveten et al showed that sortilin overexpression in HeLa-T-REx cells increases LDL surface binding and uptake, and a sortilin trafficking mutant that localizes to the plasma membrane and is deficient in its ability to traffic to the endolysosomal system increases LDL cell surface binding, supporting a direct cell surface interaction between sortilin and LDL [16]. An additional study also demonstrated impaired clearance of VLDL and chylomicrons in the context of reduced *Sort1* expression, also consistent with a role for sortilin in the clearance of apoB-containing lipoproteins [31]. These studies suggest that

hepatic sortilin influences LDL-C levels at least in part through promoting its uptake and degradation (Table One).

Sortilin and hepatic lipoprotein export

In addition to a role in the clearance of LDL particles, Musunuru et al also found that AAV-mediated hepatic expression of *Sort1* in the livers of mice reduced the VLDL secretion rate contributing to the reduced plasma cholesterol levels seen in *Sort1*-overexpressing mice [10], consistent with the directionality predicted by the human data. In contrast, Kjolby et al reported that *Sort1* deficient mice also had a reduced VLDL secretion rate with a concomitant reduction in plasma cholesterol levels [18]. These seemingly conflicting reports called into question the physiological role of hepatic sortilin in regulating VLDL secretion and plasma cholesterol levels and at the most basic level left unanswered the fundamental question of the directionality by which hepatic sortilin modulates LDL metabolism (Table One).

Kjolby et al used surface plasmon reasonance (SPR) studies, cell fractionation studies, and pulse chase experiments in loss-of-function models to convincingly suggest a role for sortilin in *facilitating* VLDL export. Strong et al and used surface plasmon reasonance, sortilin trafficking mutants, and lysosome inhibition to demonstrate that sortilin *inhibited* VLDL secretion by directly binding apoB-containing lipoproteins in the Golgi apparatus and promoting their presecretory lysosomal degradation [13]. The general finding that increased hepatic *Sort1* expression reduces VLDL secretion through a lysosomal pathway was supported by other laboratories, as well. Ai et al reported that pharmacological and genetic manipulations that increase *Sort1* expression are associated with reductions in VLDL secretion, whereas pharmacological and genetic manipulations that reduce *Sort1* expression increase VLDL secretion. Ai et al further demonstrated that *Sort1*-specific siRNAs in systems with genetically increased *Sort1* expression restore VLDL secretion, whereas reconstitution of *Sort1* in models with reduced *Sort1* expression normalizes VLDL secretion [14]. Bi et al also reported reductions in VLDL secretion in hepatocytes overexpressing *Sort1* [15]. Chamberlain et al showed that insulin, a known reducer of VLDL secretion, promotes the association of sortilin and apoB-containing lipoproteins and increases their lysosomal localization [32] (Table One). A role for sortilin in the lysosomal degradation of its ligands has become increasingly recognized, and sortilin has been reported to traffic adiponectin [33], TGF-B [34], alpha-1 antitrypsin [35] and the sodium chloride cotransporter [36] to the lysosome for degradation.

A second wave of literature emerged, which used mouse and cell models with reduced hepatic *Sort1* expression to study the role of *Sort1* in cholesterol metabolism. Jun et al reported that *Ins2+/Akita; Apoe−/−* mice that spontaneously develop type I diabetes and hypoleptinemia have reduced hepatic *Sort1* expression accompanied by hypercholesterolemia and increased atherosclerosis [37]. Leptin replacement restored hepatic *Sort1* expression and reduced plasma cholesterol and atherosclerotic disease burden. Klingenberg et al found that depletion of regulatory T-cells reduced hepatic *Sort1* expression and increased plasma cholesterol and atherosclerotic disease burden [31]. Bi et al found that mouse models and humans with reduced hepatic *Sort1* expression have increased

plasma cholesterol and reconstitution of *Sort1* expression using adenovirus rescues the hypercholesterolemia [15]. As a more direct approach, Ding et al used TALENs to functionally delete the *SORT1* locus in HUES cells and reported that HUES cells deficient in *SORT1* expression have increased apoB mass in the media when differentiated into hepatocytes [17]. All of these studies are consistent with the directionality of the human genetic data and suggest that reduced hepatic *SORT1* increases plasma cholesterol (Table One).

A number of reviews were published [12, 38–41] proposing a variety of explanations for the discrepant findings: total body *Sort1* deficiency versus liver-specific manipulations, the genetic background used in each study, adenovirus versus adeno-associated virus, western-type diet versus chow diet, and the nature of the knockout mouse model itself, though no conclusions were reached. Strong et al, in confirmation of Kjolby et al, reported that an independently generated *Sort1*−/− mouse with no residual *Sort1* expression also had reduced VLDL secretion on both a wild-type and *Apobec1*−/−*; hAPOB* Tg background [13]. Thus the fundamental question remained: why do both sortilin deficiency and overexpression reduce VLDL secretion?

Discussion: Resolving the controversy

One hypothesis put forth to explain the contradictory findings was that the *Sort1* deficiency studies were done in a total body knockout mouse, whereas the GWAS, overexpression and knockdown studies all involved liver-specific manipulations exclusively, so the knockout phenotype could be driven by sortilin deficiency in extra-hepatic tissues. Inconsistent with this hypothesis is the finding reported both by Kjolby et al and Strong et al that primary hepatocytes isolated from *Sort1*−/− mice have reduced VLDL secretion. Studies in a liver specific *Sort1* conditional knockout mouse should definitively address this issue.

Another hypothesis is that there is a fundamental difference between partial reduction and total deficiency of *Sort1* expression. The most likely model to explain this is that sortilin serves as both a chaperone and degrader of apoB-containing lipoproteins in a concentration dependent manner. Specifically, low levels of sortilin may be required for efficient VLDL export; however, at higher sortilin levels, such as those seen in individuals homozygous for the minor allele haplotype at 1p13, sortilin may promote the degradation of pre-secretory VLDL. Consistent with the hypothesis that sortilin can serve as both a chaperone and degrader of its ligands, Evans et al reported that sortilin facilitates the secretion as well as the lysosomal targeting and degradation of proBDNF. Specifically, Evans et al identified Adam10 as the metallopeptidase that cleaves sortilin at the juxtamembrane stalk both intracellularly and at the plasma membrane, separating sortilin's ligand binding domain from its lysosomal sorting motifs. They further suggested that proBDNF bound to full length sortilin that is not cleaved by Adam10 is trafficked with sortilin to the lysosome for degradation, whereas proBDNF bound to cleaved sortilin is secreted from cells [29]. One can envision a similar paradigm for apoB-containing lipoproteins: under physiological conditions the majority of sortilin is cleaved by Adam10 and facilitates VLDL secretion, so loss of sortilin reduces VLDL secretion, whereas in the context of increased *Sort1* expression, Adam10 is limiting, and most sortilin remains full length and facilitates the

endolysosomal degradation of VLDL (Figure 1A). This cleavage pathway may explain the reduction in VLDL secretion seen with both *Sort1* overexpression and deficiency.

Sortilin cleavage alone cannot explain why reductions in *Sort1* expression in different genetic systems can lead to both increased and decreased VLDL secretion. The answer may lie in recent advances in understanding sortilin trafficking and regulation. Generally accepted dogma is that 10% of sortilin localizes to the plasma membrane while 90% is intracellular; however, Kim et al found that this ratio can be altered and that neurotrophin receptor homolog 2 (Nrh2) is a molecular switch that promotes the trafficking of sortilin to the cell surface [42]. This begs the question, what factors affect sortilin trafficking and what effect does sortilin redistribution have on VLDL secretion?

ER stress is emerging as an important modulator atherosclerosis and VLDL secretion [43]. Importantly, the studies by Ai et al, Jun et al and Klingenberg et al which found an association between reductions in *Sort1* expression and increased VLDL secretion were all done in mouse models of ER stress. *Nrh2* and *Adam10* are known ER stress responsive genes [44, 45]. It is possible that on the genetic backgrounds of ER stress used by Ai et al, Jun et al and Klingenberg et al there is increased *Nrh2* and *Adam10* expression, increasing the ratio of cleaved to full length sortilin and diverting sortilin away from the endolysosomal system, thereby driving the sortilin chaperone function (Figure 1B). Conversely, in the absence of ER stress such as the models used by Strong et al and Kjolby et al *Adam10* and *Nrh2* are not upregulated, there is a reduction in cleaved sortilin due to the reduction in total *Sort1* expression, and VLDL secretion becomes compromised. Further studies will have to be done to address these hypotheses.

Perspectives And Future Directions

Clearly, the role of sortilin in cholesterol metabolism is multi-faceted and complex and much work is needed to elucidate the intricacies of the biology (Table One). Recently, a number of new sortilin-interacting partners have been described, most notably PCSK9. Gustafsen et al reported a high affinity interaction between sortilin and PCSK9 and proposed a model in which sortilin binds PCSK9 and facilitates its secretion. Gustafsen et al found that *Sort1*−/− mice have increased intracellular levels of PCSK9, reduced plasma PCSK9 and increased LDL receptor levels [46].

The role of sortilin in atherosclerotic disease is a subject of intense investigation. Tveten et al sequenced the *SORT1* gene in more than 800 hypercholesterolemic individuals and found no pathological mutations and concluded that *SORT1* mutations are unlikely to cause autosomal dominant hypercholesterolemia [16]. Interestingly, Mendoza-Barberá identified three novel mutations in ApoAV in three individuals with unexplained hypertriglyceridemia, and *in vitro* functional studies show that these mutants are impaired in their ability to interact with sortilin [47]. Finally, the role of sortilin in the blood vessel wall is emerging as an important factor in atherosclerotic disease. Campagnolo et al reported that sortilin is expressed in atherosclerotic lesions and plays a role in vascular smooth muscle cell remodeling and apoptosis [48], Jones et al reported a genetic association between the *SORT1* locus and abdominal aortic aneurysm independent of the lipid and atherosclerotic

association [49, 50], and Aikawa et al has recently described a role for sortilin in vascular calcification. Beyond these novel avenues, further work is still needed to elucidate the precise mechanistic relationship between sortilin and VLDL secretion and the basis of the association between elevated *SORT1* expression and small dense LDL subspecies.

Conclusion

The *SORT1* locus represents a promising target for the treatment of ASCVD; however the disparate findings in *Sort1* overexpression versus deficiency systems calls into question the therapeutic strategy that should be pursued – while overexpression studies suggest that *SORT1* overexpression will reduce LDL-C and ASCVD risk, deficiency studies suggest that *SORT1* inhibition will be of therapeutic benefit. The sortilin field is at its infancy, and hopefully we can look forward to many new discoveries in this intriguing and novel pathway of lipoprotein metabolism.

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• of special interest

•• outstanding interest

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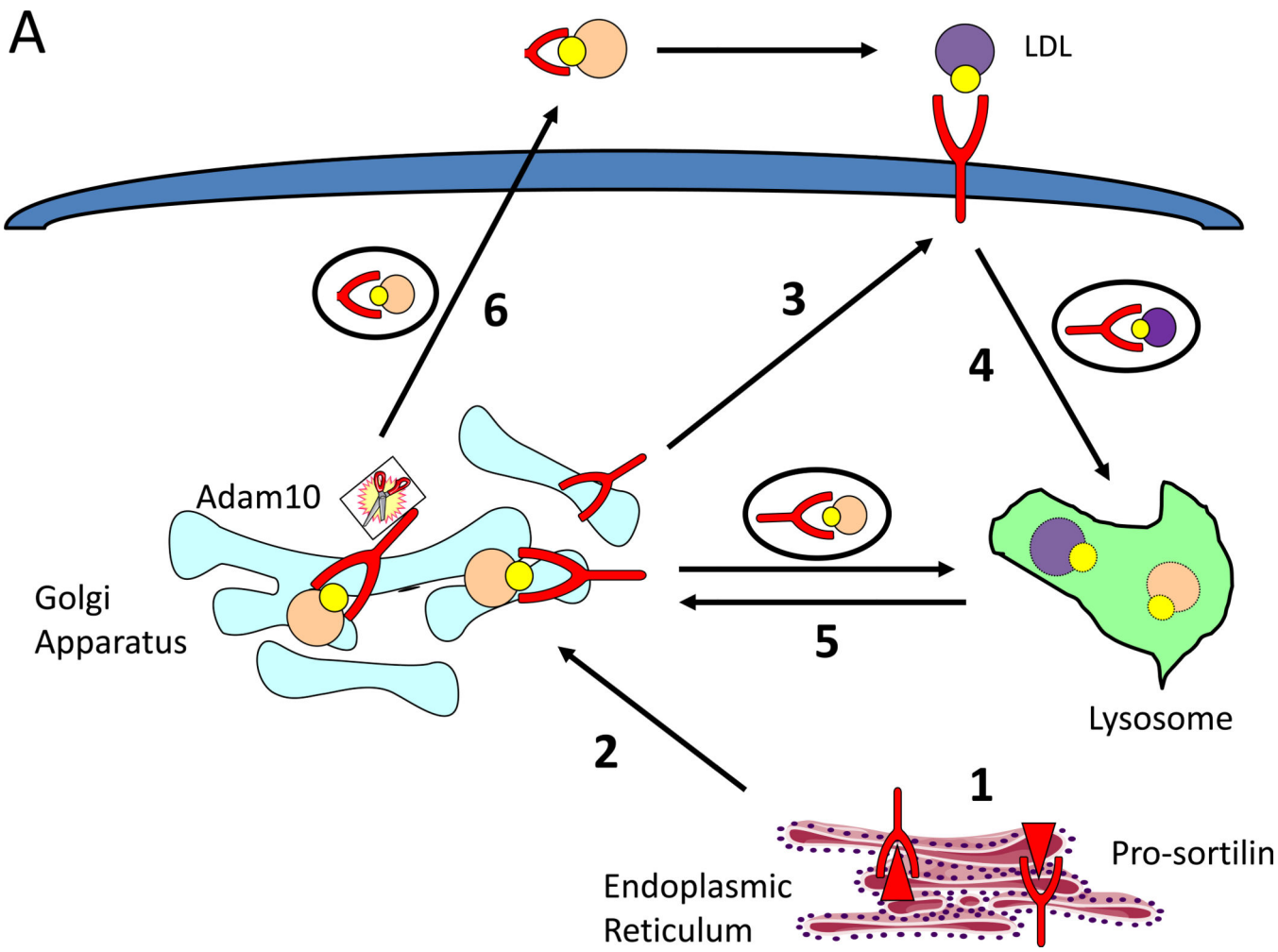
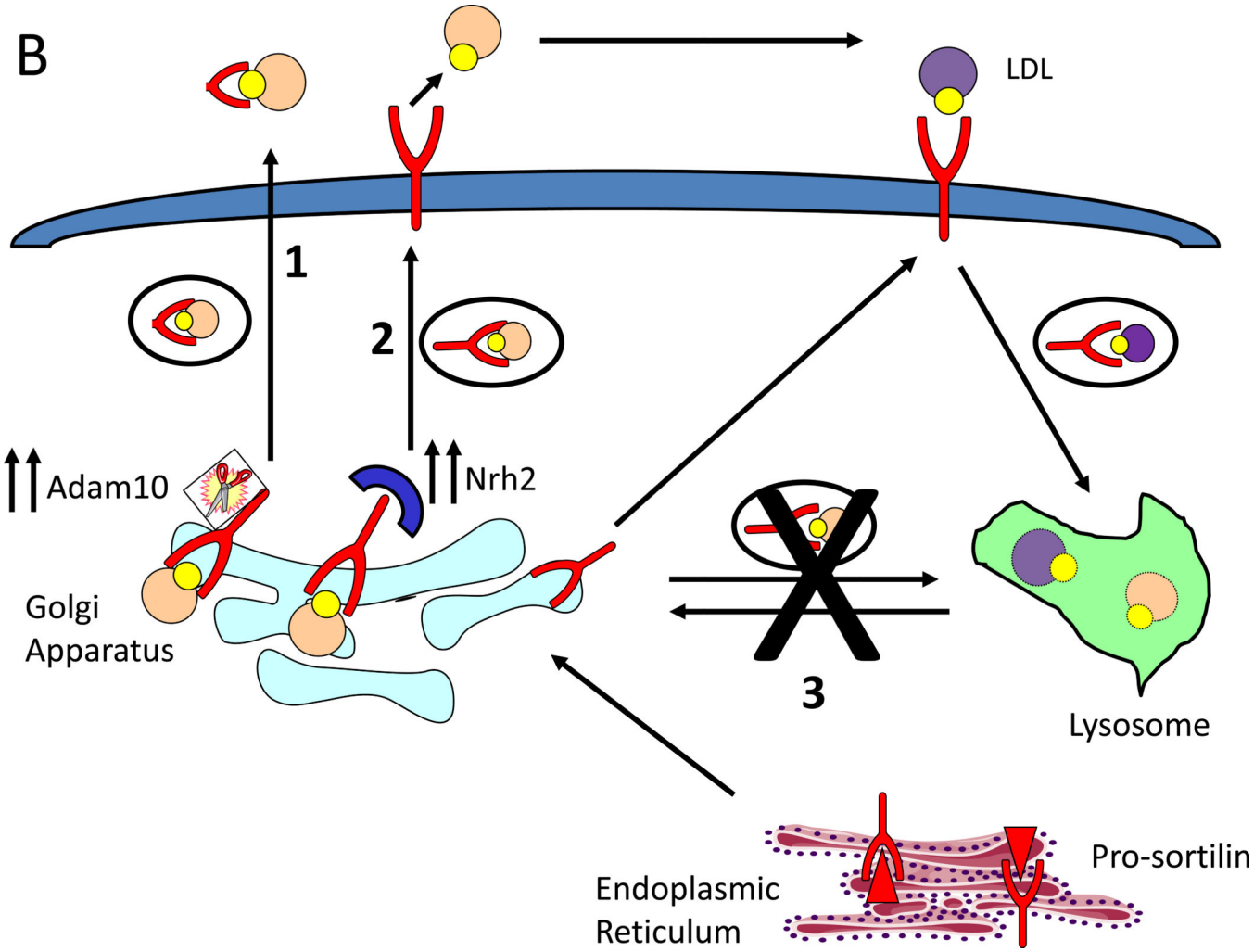
Key Points

- The locus identified by GWAS with the strongest association with LDL-C and ASCVD is the novel 1p13 *SORT1* locus
- Sortilin reduces LDL-C by serving as an LDL receptor independent pathway for LDL clearance and by promoting the presecretory lysosomal degradation of VLDL
- The *Sort1*−/− mouse has a paradoxical reduction in VLDL secretion
- The effect of reductions in *Sort1* expression on VLDL secretion remains controversial with disparate findings in different animal models





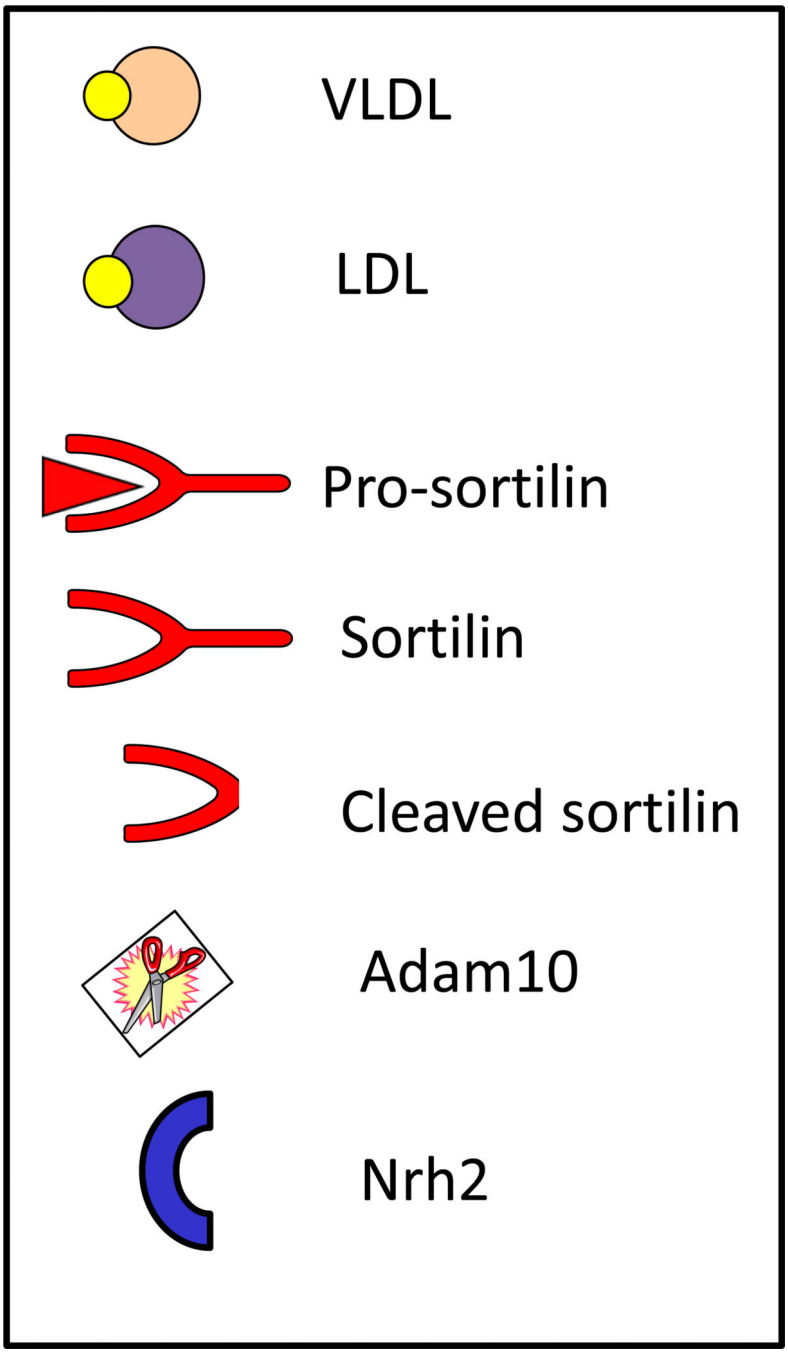


Figure One.
Potential models to reconcile the overexpression and deficiency data

Table One

Summary Of The Effects Of *Sort1* Manipulation On Lipoprotein Metabolism In Cells And Mice

Directionality	Model System	Mechanism Of Manipulation	Plasma Cholesterol	ApoB Secretion	LDL Clearance	Reference
Overexpression	*Apobec1−/−; Ldlr−/−* Mice	AAV	Decreased	-----	-----	Musunuru et al[10]
	*Apobec1−/−; hAPOB*Tg Mice	AAV	Decreased	Decreased	-----	Musunuru et al [10]
	*Apobec1−/−; Ldlr+/−; hAPOB*Tg Mice	AAV	Decreased	Decreased	-----	Musunuru et al [10] and Strong et al [13]
	*Apobec1−/−; Ldlr−/−; hAPOB*Tg Mice	AAV	Decreased	-----	-----	Musunuru et al [10]
	Ob/ob Mice	AAV	-----	Decreased	-----	Ai et al [14]
	DIO Mice	AAV	-----	Decreased	-----	Ai et al [14]
	Wild-type Mice	AAV	Decreased	Decreased	Increased	Strong et al [13]
	Ldlr−/− Mice	AAV	Decreased	Decreased	Increased	Strong et al [13]
	Wild Type Mice	Adeno	Decreased	-----	-----	Bi et al [15]
	Ob/ob Mice	Adeno	Decreased	-----	-----	Bi et al [15]
	HEK293 Cells	Transfection	-----	-----	Increased	Linsel-Nitschke et al [11] and Strong et al [13]
	HuH7 Cells	Transduction	-----	Decreased	Increased	Strong et al [13]
	McA Cells	Transduction	-----	Decreased	-----	Strong et al [13]
	CHO Cells	Transfection	-----	-----	Increased	Strong et al [13]
	ldlD Cells	Transfection	-----	-----	Increased	Strong et al [13]
	HELA-TREx Cells	Transfection	-----	-----	Increased	Tveten et al [16]
	Primary Mouse Hepatocytes	Transduction	-----	Decreased	-----	Bi et al [15]
	HepG2 Cells	Transduction	-----	Decreased	-----	Bi et al [15]
Knockdown	HUES Cells	TALEN mediated Gene Deletion	Increased apoB	-----	-----	Ding et al [17]
	Apobec1−/−; Ldlr−/− Mice	siRNA	Increased	-----	-----	Musunuru et al [10]
	*Apobec1−/−; hAPOB*Tg Mice	siRNA	Increased	-----	-----	Musunuru et al [10]
	*Apobec1−/−; Ldlr+/−; hAPOB*Tg Mice	siRNA	Increased	-----	-----	Musunuru et al [10]
	Sort1−/− Mouse	Knockout	Decreased	Decreased	No Difference	Kjolby et al [18]
	Sort1−/−; Ldlr−/− Mouse	Knockout	Decreased	-----	-----	Kjolby et al [18]
	Sort1−/− Mouse	Knockout	No Difference	Decreased	Decreased	Strong et al [13]

Directionality	Model System	Mechanism Of Manipulation	Plasma Cholesterol	ApoB Secretion	LDL Clearance	Reference
	Sort1−/−; *Ldlr*−/− Mouse	Knockout	Decreased	-----	Decreased	Strong et al [13]
	Apobec1−/−; *Sort1*−/−; *hAPOB*Tg Mouse	Knockout	No Difference	Decreased	-----	Strong et al [13]