Published in final edited form as:

Curr Opin Lipidol. 2015 December ; 26(6): 598–600. doi:10.1097/MOL.0000000000000244.

The enigmatic role of sortilin in lipoprotein metabolism

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Sortilin, a multiple ligand sorting receptor, has emerged as a novel factor strongly associated with LDL cholesterol and atherosclerosis [1, 2]. Since VLDL is the precursor to LDL, hepatic VLDL metabolism becomes an important research focus. Results of manipulation of hepatic sortilin levels have been tabulated [1], and in general, a reciprocal relationship is found between sortilin and VLDL-B100 production. Other studies, however, have reported a direct relationship between sortilin and VLDL-B100 [2]. When sortilin is genetically deleted in mice, VLDL-B100 secretion is unchanged or reduced inconsistent with a reciprocal relationship. Possible reasons for differences have been discussed [1, 2]. A number of new, sometimes conflicting studies, have been reported regarding sortilin function which likely relates to the multiplicity of sortilin ligands and binding partners [2]. This commentary summarizes new information that may adjust our thinking regarding the role of sortilin in lipoprotein metabolism.

Hepatic sortilin can act as an uptake receptor for LDL [3]. A reduction in sortilin would be anticipated to increase circulating LDL, and thereby promote atherogenesis. Sortilin deficiency, however, protects against atherosclerosis by reducing uptake of native LDL by macrophages and foam cell formation [4■]. Sortilin deficiency also attenuates inflammation by influencing interleukin-6 secretion from activated macrophages without changing lipoproteins, macrophage recruitment or foam cell formation [5■]. Atherogenesis in sortilin deficiency could be diminished either by reduced native LDL uptake or dampened inflammatory response. The relative contribution of sortilin as a receptor for LDL versus the LDL receptor (LDLR) in determining LDL concentration is not known.

Conflicts of interest

There are no conflicts of interest.

Sortilin binds proprotein convertase subtilisin/kexin type 9 (PCSK9) with high affinity, and facilitates PCSK9 secretion from hepatocytes [6■]. As summarized [7], the current model of PCSK9 action involves binding to LDLR promoting lysosomal degradation. It follows that sortilin reduction would suppress PCSK9 secretion and increase LDLR expression. The role of sortilin in promoting LDLR degradation has been challenged as sortilin deficiency in human hepatocyte cell lines and mice did not alter LDLR degradation by PCSK9 [8■]. Differences in the role of sortilin in PCSK9 secretion and LDLR degradation may relate to participation with other binding partners. Amyloid precursor-like protein 2 (APLP2) interacts with sortilin, and when complexed, degradation is favored by PCSK9 [8■]. Increases in PCSK9 are induced by insulin [9■] suggesting that metabolic regulation could change the dynamics of binding partner interactions.

Hepatic sortilin expression is reduced in models of obesity [10, 11]. In one study sortilin reduction was due to decreased *Sort1* mRNA, and in *ob/ob* mice, the reduction was associated with mTORC1 activation and ER stress mediated by the early stress gene, *Atf3*, which suppresses *Sort1* transcription [10]. In another study, *Sort1* mRNA was reduced in western diet (WD) fed mice, but in contrast, in *ob/ob* mice mRNA levels were modestly elevated suggesting a post-transcriptional mechanism was responsible for reduced hepatic sortilin [11]. Restoration of sortilin reduced VLDL secretion [10] and decreased serum lipids [11]. Saturated fatty acids (FA) and ERK activation were proposed as a mechanism, and polyubiquitinated sortilin supported that degradation occurred via the proteasome [12]. Fish oil and fenofibrate blocked the destabilization of sortilin independently of PPAR α [12]. Post-translational modifications of the cytoplasmic tail of sortilin are suggested to regulate sortilin degradation [12]. Cellular sortilin levels have also been reported to be stabilized by insulin [13■]. The reduction of sortilin expression observed in models of obesity and insulin resistance represent a balance between transcriptional and post-transcriptional events that may vary depending on genetics or metabolism.

Discovery of compounds that can change specific sortilin-ligand interactions or sortilin stability may allow for modulation of specific functions. Since neurotensin, a known sortilin ligand, does not affect PCSK9 binding to sortilin [6], an additional binding site is suggested [14]. It is not known if the second site binds PCSK9. As multiple binding sites may exist that differentially affect sortilin activity, it may be possible to target a specific site. Results from such studies may provide additional mechanistic information on sortilin action leading to potential new therapies.

Reduction in hepatic sortilin might be beneficial, as sortilin knock-out mice are more insulin sensitive with less hepatic steatosis than control mice on a WD [15■]. Full effects of sortilin on hepatic lipoprotein metabolism may not be appreciated by assessment of fasting animals alone. In humans the presence of the minor allele (rs646776), known to increase hepatic sortilin expression, had a favorable impact on triglyceride metabolism suppressing postprandial lipemia [16■]. The role of sortilin in modulating hepatic VLDL production during the immediate postprandial period is consistent with the enhanced interaction of B100 with sortilin following insulin [17] that leads to B100 degradation through autophagy [18].

Although the current role of sortilin in lipoprotein metabolism is enigmatic, future studies may clarify these controversies revealing information that could make sortilin an important therapeutic target.

Acknowledgments

Financial Support and Sponsorship

This work was supported by a grant from the National Institutes of Health R01 DK100163.

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