The (pro)renin receptor ((P)RR) was discovered by virtue of its role in the activation of the renin–angiotensin–aldosterone system. Clinically, (P)RR is thought to be involved in end-organ damage from diabetes mellitus and hypertension. Yet despite being named for its ability to bind renin and prorenin, (P)RR has remarkably low affinity for these ligands, suggesting extra-renal functions for this receptor, a concept supported by its recently discovered role as a novel regulator of the vacuolar ATPase. In this issue, Lu et al found through an interactome screen and subsequent co-immunoprecipitation experiments that (P)RR directly interacts with SORT1, a multifunctional cellular trafficking protein that was recently discovered through human genetics to be an important regulator of lipid metabolism. Genome-wide association studies identified DNA variants in a locus on chromosome 1p13 to be strongly linked to both blood low-density lipoprotein (LDL) cholesterol levels and risk for coronary artery disease. Initial functional studies in human cells and in mice suggested that a single noncoding DNA variant in the locus, rs12740374, regulates the hepatic expression of the SORT1 gene and that SORT1, out of several candidate proteins expressed from the 1p13 locus, is strongly linked to both blood low-density lipoprotein (LDL) cholesterol levels and risk for coronary artery disease.

In their follow-up experiments after finding an interaction between (P)RR and SORT1, Lu et al observed that RNA interference (RNAi)-mediated knockdown of (P)RR reduces both SORT1 and LDLR protein levels without affecting SORT1 and LDLR mRNA levels. Consistent with the roles of both LDLR and SORT1 in the cellular uptake of LDL particles, knockdown of (P)RR also reduces LDL uptake in multiple cell lines. Lu et al provide evidence that this phenomenon is largely because of the effect on LDLR, with a smaller contribution from the effect on SORT1.

Intriguingly, Lu et al saw a decrease in LDLR protein with SORT1 knockdown independent of (P)RR and an increase in LDLR with SORT1 overexpression. They also found that SORT1 overexpression is unable to rescue LDLR from the effect of (P)RR knockdown and that reduced (P)RR expression increases the lysosomal degradation of LDLR without increasing its rate of removal from the plasma membrane or its degradation by proprotein convertase subtilisin/kexin type 9. To place these findings in context, previous studies have reported conflicting findings with respect to the relationship between SORT1 and LDLR. A couple of studies showed no difference in LDLR protein with RNAi-mediated hepatic Sort1 knockdown in mice as well as in Sort1 knockout mice, and another study reported no difference in LDLR protein with Sort1 deficiency using the same knock-out mouse. In contrast, one study reported increased LDLR protein in CHO-Trex cells with SORT1 overexpression (consistent with the findings of Lu et al), whereas yet another study reported increased LDLR protein in a different Sort1 knockout mouse.

Although this work has important implications for our understanding of (P)RR, it also increases our understanding of the role of SORT1 in lipid metabolism and LDL uptake, which has been a subject of debate for the last 5 years. Overexpression studies in a variety of cultured cell lines as well as in vivo have consistently demonstrated a positive association between SORT1 expression and LDL clearance. Knockdown and knockout studies have been less consistent. One in vivo study reported compromised LDL clearance in Sort1 knockout mice, and another in vivo study reported delayed very-low-density lipoprotein and chylomicron clearance (LDL clearance was not assessed) in mice with reduced Sort1 expression. One in vitro study showed a correlation between reduced cell surface SORT1 and reduced LDL uptake; a second in vitro study reported compromised LDL uptake in Sort1-deficient primary mouse bone marrow macrophages; and a third study found no difference in LDL uptake in primary hepatocytes isolated from Sort1 knockout mice.

In this latest report, Lu et al found that both indirect SORT1 reduction secondary to (P)RR knockdown and direct RNAi-mediated SORT1 knockdown are associated with reductions in LDL uptake.
The findings of Lu et al remind us that we do not completely understand how LDLR and SORT1 are regulated at the post-transcriptional level. The LDLR story seems more straightforward: Lu et al report that RNAi-mediated (P)RR knockdown is associated with increased lysosomal LDLR degradation. One can envision a model in which (P)RR protects LDLR from lysosomal degradation and facilitates its trafficking to the cell surface, and because SORT1 knockdown reduces the (P)RR protein level, it also is associated with a reduction in LDLR protein. This model would explain why SORT1 overexpression does not rescue LDLR levels in the context of (P)RR knockdown. The observation that (P)RR overexpression does not increase LDLR levels suggests that if a (P)RR-SORT1-LDLR pathway exists, it is saturable, which is quite plausible for a Golgi-to-plasma membrane trafficking route (Figure).

The SORT1 story is more difficult to sort out. Lu et al found that RNAi-mediated (P)RR knockdown is associated with reduced SORT1 protein with no change in SORT1 mRNA, and the reduction is not rescued by lysosome, autophagy, or proteasome inhibition. A similar finding was reported by another group when they demonstrated that overexpression of proprotein convertase subtilisin/kexin type 9 reduced intracellular SORT1 levels, and though this inhibition was partially rescued by lysosome inhibition, they could not achieve complete rescue with blockade of any pathway.10 SORT1 is known to be palmitoylated,16 ubiquitinated,17 and phosphorylated18 and has been suggested to undergo degradation via proteasomes19 and lysosomes.16,17 The data presented by the 2 aforementioned studies are consistent with a novel yet uncharacterized pathway of post-transcriptional SORT1 regulation. An initial step would be to determine whether the translational efficacy of the SORT1 mRNA is influenced by proprotein convertase subtilisin/kexin type 9 or (P)RR, but further insight will likely require detailed mechanistic studies to account for the reduced SORT1 protein.

Perhaps the most significant contribution of the work of Lu et al is uncovering a novel link between the renin–angiotensin–aldosterone system and atherosclerotic cardiovascular disease. Renin and prorenin are profoundly elevated in diabetes mellitus and hypertension, and this is believed to contribute to the microvascular damage associated with these 2 disorders.2,3 The notion that the elevations in renin and prorenin may also contribute to hypercholesterolemia via cross-talk through (P)RR and reducing the expression of 2 proteins that mediate cellular LDL uptake, LDLR and SORT1, is intriguing. Lu et al have opened a new avenue of inquiry into the interconnections of the renin–angiotensin–aldosterone system and lipid metabolism, which we expect will be the focus of future investigation and may inform the debate of whether (P)RR would be a good therapeutic target in the treatment of diabetes mellitus and hypertension.

Disclosures

References


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