PDZK1 Is Required for Maintaining Hepatic Scavenger Receptor, Class B, Type I (SR-BI) Steady State Levels but Not Its Surface Localization or Function*

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PDZK1 is a multi-PDZ domain-containing adaptor protein that binds to the C terminus of the high density lipoprotein receptor, scavenger receptor, class B, type I (SR-BI), and controls the posttranscriptional, tissue-specific expression of this lipoprotein receptor. In the absence of PDZK1 (PDZK1(−/−)/ mice), murine hepatic SR-BI protein levels are very low (<5% of control). As a consequence, abnormal plasma lipoprotein metabolism (−1.5–1.7-fold increased total plasma cholesterol carried in both normal size and abnormally large high density lipoprotein particles) resembles, but is not as severely defective as, that in SR-BI(−/−)/ mice. Here we show that the total plasma cholesterol levels and size distribution of lipoproteins are virtually identical in SR-BI(−/−)/ and SR-BI(−/−)/PDZK1(−/−)/ mice, indicating that most, if not all of the effects of PDZK1 on lipoprotein metabolism are likely because of the effects of PDZK1 on SR-BI. Hepatic overexpression of wild-type SR-BI in PDZK1(−/−)/ mice restored near or greater than normal levels of cell surface-expressed, functional SR-BI protein levels in the livers of SR-BI(−/−)/PDZK1(−/−)/ mice and consequently restored apparently normal lipoprotein metabolism in the absence of PDZK1. Thus, PDZK1 is important for maintaining adequate steady state levels of SR-BI in the liver but is not essential for cell surface expression or function of hepatic SR-BI.

The HDL2 receptor SR-BI plays an important role in lipoprotein-mediated lipid transport and metabolism (1). SR-BI mediates HDL binding to cells and subsequently facilitates the net transfer of cholesterol esters from the particle core but not the protein or most of the lipid components of the outer shell of the lipoprotein, a process called selective lipid uptake (1–4). This receptor also mediates bidirectional movement of unesterified cholesterol between cells and lipoproteins (5–7). SR-BI is most highly expressed in hepatocytes, where it helps control plasma lipoprotein metabolism, and in steroidogenic cells, where it delivers lipoprotein cholesterol for storage and subsequent conversion into steroid hormones (4, 8, 9). Normal expression and moderate transgene-mediated overexpression of hepatic SR-BI have been shown to protect against atherosclerosis in several murine models (10–16), and SR-BI transgene expression in the liver can prevent the female infertility seen in otherwise SR-BI null mice (SR-BI(−/−)/) (12, 17, 18).

SR-BI deficiency in SR-BI(−/−)/ mice causes an ∼2-fold elevation in plasma cholesterol carried in both normal size and abnormally large HDL particles (12, 19), which exhibit an abnormally high ratio of unesterified cholesterol-to-total (unesterified plus esterified) cholesterol (14, 20) as well as a 30–50% decrease in biliary cholesterol secretion rates and concentrations (12, 21, 22). These phenotypes are thought to be consequences of the reduced hepatic uptake of cholesterol from circulating HDL and can be reversed by hepatic SR-BI transgene expression (17, 21, 23, 24).

Tissue SR-BI expression can be regulated by both transcriptional and posttranscriptional mechanisms (25). In the liver, but not in steroidogenic tissues, posttranscriptional control of SR-BI protein expression depends on the presence of an adaptor protein, PDZK1 (26–28). Cytoplasmic adaptor proteins that bind to membrane-associated proteins regulate a variety of biological processes, including signal transduction, adhesion, membrane trafficking, and cellular transport (29). They often comprise combinations of modular protein interaction domains such as Src homology (SH2, SH3), phosphotyrosine-binding (PTB), and PDZ domains that recognize short peptide or phosphopeptide motifs (e.g. PDZ domains usually bind to the C-terminal 3–4 residues of interacting proteins) (30).

PDZK1 is a single chain, four-PDZ domain-containing polypeptide that interacts with the C terminus of several membrane-associated transporter proteins in diverse tissues, including: cMOAT/MRP2 (31), the multidrug-resistance-associated protein, and the type IIa sodium/Pi cotransporter (32); the chloride channel CIC-3B (32), the cystic fibrosis transmembrane conductance regulator (CFTR) (33, 34), the organic cation transporters OCTN1 and OCTN2 (35, 36), and somatosta-
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tin receptor subtype 5 (37); peptide transporter 2 (38), chloride formate exchanger CFEX (39), and SR-BI (26–28) as well as others (40). PDZK1 can influence the abundance, intracellular localization or activity of its binding partners (26–28, 31–36, 38, 40, 41). The multiple PDZ domains in PDZK1 presumably mediate its simultaneous interaction with several target proteins, thus permitting it to orchestrate complex biological functions by acting as a scaffolding protein (42). Arai and colleagues (28) were the first to show that PDZK1, via its most N-terminal PDZ1 domain, binds to the C terminus of SR-BI, and more recently (43) demonstrated that phosphorylation of Ser509 of PDZK1 modulates its ability to regulate SR-BI. Other studies have established the importance of both PDZK1 and the C terminus of SR-BI for the hepatic activity of SR-BI in vivo and its influence on lipoprotein metabolism (26, 27). For example, in PDZK1 knock-out (KO) mice hepatic SR-BI levels are only ~5% of that in wild-type mice, and this is accompanied by a 1.5–1.7-fold increase in plasma total cholesterol carried in abnormally large HDL particles (a phenotype reminiscent of, but not identical to, that in SR-BI(-/-) mice) (26). The precise molecular mechanisms underlying the influence of PDZK1 on SR-BI, including the tissue specificity of this effect, have not yet been elucidated.

In the current study, we have used PDZK1(-/-) and SR-BI(-/-) mice together with hepatic overexpression of stable SR-BI transgenes to explore the mechanism by which PDZK1 influences lipoprotein metabolism and SR-BI activity. We found that essentially all of the consequences of PDZK1 deficiency on lipoprotein metabolism appear to be due to its effects on SR-BI. Hepatic overexpression of wild-type SR-BI could restore near or greater than normal levels of functional, cell surface SR-BI protein levels in the livers of SR-BI(-/-)/PDZK1(-/-) double knock-out mice and consequently could also restore apparently normal lipoprotein metabolism in the absence of PDZK1. Thus, PDZK1 is important for maintaining adequate steady state levels of SR-BI in the liver but is not essential for cell surface expression or function of hepatic SR-BI, provided that sufficient amounts of SR-BI are generated in these cells.

EXPERIMENTAL PROCEDURES

Animals—All mice were fed a regular chow diet (Harlan Teklad (RMH 3000)) with water supplied ad libitum. SR-BI(-/-) mice on a mixed 50:50 C57BL/6:129-S4 background (19) and PDZK1(-/-) mice on a 129SvEv background (26) were obtained as described previously. Two new strains of SR-BI transgenic mice on a SR-BI(-/-) background were generated as described previously (17). Briefly, a 1.5-kilobase fragment spanning the wild-type murine SR-BI cDNA was amplified by PCR from a plasmid (pDT188) that contains the cloned murine SR-BI cDNA (4, 17). The 1.5-kilobase cDNA fragment encoding the gene in its entirety was subcloned between the MunI and XhoI sites in the pLIV-LE6 plasmid (kindly provided by Dr. John M. Taylor, Gladstone Institute of Cardiovascular Disease, University of California, San Francisco). The SR-BI-coding region was confirmed by DNA sequencing using four primers spanning the gene. The pLIV-LE6 plasmid contains the promoter, first exon, first intron, and part of the second exon of the human apoE gene and the polyadenylation sequence and a part of the hepatic expression control region of the apoE/apoC-I gene locus (44). The new constructs harboring the SR-BI gene as well as the above-mentioned apoE/apoC-I control element were linearized by NotI/SpeI digestion, and the resulting 6.5-kilobase fragments were used to generate, by standard procedures (45), two new transgenic mouse lines in a 50:50 mixed C57BL/6 × 129 murine background. These mice stably overexpress hepatic SR-BI transgenes at levels ~6-fold (SR-BI-Tg (med)) and ~60-fold (SR-BI-Tg (hi)) greater than in wild-type mice. As noted previously (17), these transgenes are expressed mainly in the liver. There is very low level expression of the transgene in the kidney on the apical surfaces of the epithelial cells in the proximal tubules facing the tubular lumen rather than the plasma, and thus this minor renal expression of SR-BI does not appear to influence substantially plasma lipoprotein metabolism (17). All of these mice were used to generate the new strains used in this study, all on a mixed 75:25 129C57BL/6 background, with the following genotypes: SR-BI(+/-)/PDZK1(+/-) (wild type); SR-BI(+/-)/PDZK1(-/-); SR-BI(-/-)/PDZK1(+/-); SR-BI(-/-)/PDZK1(-/-); SR-BI(-/-)/PDZK1(-/-)[SR-BI-Tg (med)]; and SR-BI(-/-)/PDZK1(-/-)[SR-BI-Tg (hi)]. Genotypes were determined by PCR as described previously (17, 46). Experiments were performed with 8–12-week-old animals under the supervision of the Massachusetts Institute of Technology Committee on Animal Care.

Tissue Analysis—Plasma and liver samples were collected and processed, and total plasma cholesterol levels, FPLC-fractionated lipoprotein cholesterol profiles from individual mice, and immunoblots with polyclonal anti-SR-BI antipeptide antibodies were obtained as described previously (17). Immunoblotting was performed using either 2.5 or 50 μg of protein samples of liver lysates. The detection of e-COP using a polyclonal antibody was used as a loading control (17).

Immunohistochemical Localization of Hepatic SR-BI—Livers were harvested, fixed, and frozen, and 5-μm sections were prepared and stained with primary anti-SR-BI and secondary biotinylated anti-rabbit IgG antibodies. SR-BI was visualized by immunoperoxidase staining, and the sections were counterstained with Harris modified hematoxylin as described previously (17).

Statistical Analysis—The statistical significance of differences was determined by one-way analysis of variance Tukey’s post hoc test. Differences were considered significant when *p* was <0.05.

RESULTS AND DISCUSSION

Both SR-BI(-/-) and PDZK1(-/-) mice exhibit hypercholesterolemia (total cholesterol ~2.3-fold or ~1.5–1.7-fold above wild-type, respectively) and abnormally large HDL particles (Refs. 19 and 26 and Table 1). Although the dramatic (~95%) reduction in hepatic SR-BI levels in PDZK1(-/-) mice seems likely to have been the principal cause of the dyslipidemia found in PDZK1(-/-) mice, some of the effects of the loss of PDZK1 may be the consequence of SR-BI-independent mechanisms. To examine this issue directly, we compared the plasma cholesterol levels and lipoprotein profiles of single knock-out mice (PDZK1(-/-) or SR-BI(-/-)) with those of double knock-out mice (SR-BI(-/-)/PDZK1(-/-)) generated by
crossing the single KO mice. The plasma cholesterol levels (272 ± 13 mg/dl in SR-BI(−/−) versus 252 ± 13 mg/dl in SR-BI(−/−)/PDZK1(−/−); Table 1, no transgene), plasma unesterified cholesterol levels (results not shown), and plasma lipoprotein size distributions (as determined by FPLC size exclusion chromatography; Fig. 1) showed that the plasma lipoproteins of SR-BI(−/−)/PDZK1(−/−) double KO and SR-BI(−/−) single KO animals were essentially indistinguishable. Given that PDZK1 deficiency does not exert any additional effects on plasma lipoprotein cholesterol in SR-BI(−/−) mice, it appears that the effects of PDZK1 on plasma lipoprotein metabolism are primarily because of its effects on SR-BI.

There are several potential, yet not mutually exclusive, mechanisms by which PDZK1 could influence hepatic SR-BI activity. For example, PDZK1 may be essential for the proper delivery of SR-BI from its site of synthesis in the endoplasmic reticulum to the sinusoidal plasma membranes. In that case, in PDZK1(−/−) mice SR-BI may never reach the plasma membrane of hepatocytes, and its misorting may result in its rapid degradation and thus low steady state levels. Thus, even if the steady state levels of SR-BI in PDZK1(−/−) mice could be raised artificially to wild-type levels, SR-BI would not be functional because it could not be delivered properly to the cell surface. Independently of its effects on the steady state levels of SR-BI or its intracellular transport, PDZK1 might be essential for the normal function of SR-BI molecules that reach the cell surface, including their lipoprotein binding and lipid transport activities. Indeed, there is precedence in cell culture studies for an effect of PDZK1 on the activities of cell surface transporters to which it binds (e.g. see Refs. 28 and 36).

Alternatively, PDZK1 may not be required for either the delivery of SR-BI to the hepatocellular plasma membrane or the function of SR-BI after it has reached the surface. Rather, PDZK1 may simply stabilize the otherwise functional, surface-expressed receptor. This would permit sufficiently high levels of plasma membrane expression and activity for the otherwise PDZK1-independent function of SR-BI. If this were true, hepatic overexpression of SR-BI in PDZK1(−/−) mice could lead to levels of cell surface SR-BI sufficient to normalize plasma lipoprotein levels. Indeed, SR-BI overexpression in PDZK1(−/−) mice might even result in the hypcholesterolemia that has been shown to accompany SR-BI hepatic overexpression in PDZK1(+/+ ) mice (16, 17, 23, 24).

To differentiate between these mechanisms, we generated mice that stably overexpressed in the liver SR-BI transgenes at levels ~6-fold (SR-BI-Tg (med)) and ~60-fold (SR-BI-Tg (hi)) greater than in wild-type mice. Table 1 shows that SR-BI-Tg (med) expression in SR-BI(−/−)/PDZK1(+/+) mice reduced plasma cholesterol to about half that in wild-type mice (60 ± 7 versus 117 ± 8 mg/dl) and SR-BI-Tg (hi) expression dramatically lowered plasma cholesterol to 3 ± 1 mg/dl. We crossed these transgenic mice into the PDZK1(−/−) background and compared SR-BI expression and its effects on plasma lipoproteins in these transgenic, double KO mice (SR-BI(−/−)/PDZK1(−/−)[SR-BI-Tg (med)] and SR-BI(−/−)/PDZK1(−/−)[SR-BI-Tg (hi)]) and their nontransgenic controls.

Fig. 2 shows immunoblotting analysis of the steady state levels of hepatic SR-BI in these mice. As previously reported, nontransgenic SR-BI(−/−) mice showed no detectable SR-BI either in the presence (+/+ ) or absence (−/−) of PDZK1 (two left columns). Also, in SR-BI(+/+ ) mice the loss of PDZK1 resulted in a dramatic reduction in SR-BI levels (3rd and 4th columns). In SR-BI-Tg (med)-expressing SR-BI(−/−)/PDZK1(+/+) mice (5th column), SR-BI levels were greater than those of the control nontransgenic wild-type mice (SR-BI(+/+ )/PDZK1(+/+ )); nevertheless, the additional loss of

Table 1: Plasma total cholesterol levels in nontransgenic and SR-BI transgenic animals

| Transgene | PDZK1 genotype | SR-BI genotype | Total plasma cholesterol |
|-----------|----------------|----------------|-------------------------|
| None      | +/+            | +/+            | 117 ± 8 (n = 6)*         |
| None      | −/−            | +/+            | 170 ± 9 (n = 10)*        |
| None      | −/−            | −/−            | 272 ± 13 (n = 9)*        |
| None      | −/−            | −/−            | 252 ± 13 (n = 8)*        |
| SR-BI-Tg (med) | +/+    | −/−            | 60 ± 7 (n = 8)           |
| SR-BI-Tg (med) | −/−    | −/−            | 144 ± 10 (n = 10)*       |
| SR-BI-Tg (hi) | +/+    | −/−            | 3 ± 1 (n = 5) c          |
| SR-BI-Tg (hi) | −/−    | −/−            | 4 ± 1 (n = 7) c          |

* Values (mg/dl) are represented as means ± S.E.
** p < 0.0001 by one-way analysis of variance for all values, and p < 0.05 by Tukey’s post hoc test for all pairwise comparisons except those pairs marked as a, b, c, d, e, or f.
† Not statistically significantly different from each other.
‡ Not statistically significantly different from each other.
§ Not statistically significantly different from each other.
¶ Not statistically significantly different from each other.
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PDZK1 (SR-BI(−/−)/PDZK1(−/−))[SR-BI-Tg (med)], 6th column) was characterized by SR-BI levels lower than those of control wild-type mice. Thus, as is the case for the endogenous SR-BI protein, the abundance of the product of the SR-BI-Tg (med) transgene is PDZK1-dependent. Analogous results were observed in SR-BI-Tg (hi)-expressing hepatocytes (Fig. 2, rightmost columns), except that the steady state protein levels were substantially higher (note 20-fold less sample was loaded for the SR-BI-Tg (hi) samples). These data show that hepatic overexpression of SR-BI can permit PDZK1-independent expression of modest levels (SR-BI-Tg (med)) or exceptionally high levels (SR-BI-Tg (hi)) of hepatic SR-BI protein.

To determine whether these transgene-encoded proteins could reach the hepatocyte cell surface, we performed immunohistochemical analysis with anti-SR-BI antibodies (Fig. 3). In wild-type mice, and the indicated transgene (No transgene, SR-BI-Tg (med), SR-BI-Tg (hi)) containing either 50 or 2.5 μg of protein were subjected to immunoblotting, and the abundance of the −82-kDa band corresponding to SR-BI was visualized using chemiluminescence. The low level of SR-BI protein in the liver lysate from the nontransgenic SR-BI(+/+)PDZK1(−/−) mouse was barely visible at the exposure shown. Size markers are indicated on the right. e-COP (−34 kDa) was used as a loading control. The average plasma total cholesterol values from Table 1 are also indicated.

FIGURE 2. Immunoblotting analysis of hepatic SR-BI protein expression in nontransgenic and SR-BI transgenic animals. Lysates of livers harvested from animals with the indicated genotypes (+/+), wild type; −/−, homozygous null) and the indicated transgene (No transgene, SR-BI-Tg (med), SR-BI-Tg (hi)) containing either 50 or 2.5 μg of protein were subjected to immunoblotting (Fig. 2). Thus, PDZK1 is not essential for the transgenic mice (Fig. 3, A and B, respectively), with staining intensities consistent with the levels of protein detected by immunoblotting (Fig. 2). Thus, PDZK1 is not essential for the delivery of SR-BI to the surfaces of hepatocytes.

To determine whether the cell surface SR-BI could function in regulating lipoprotein metabolism in the absence of PDZK1, we measured plasma cholesterol levels and determined the lipoprotein cholesterol profiles. Table 1 shows that expression of SR-BI-Tg (med) or SR-BI-Tg (hi) in SR-BI(−/−)/PDZK1(−/−) mice lowered total plasma cholesterol levels by 43 or 98%, respectively, relative to the nontransgenic controls (252 ± 13 versus 144 ± 10 or 4 ± 1 mg/dl). In SR-BI(−/−)/PDZK1(−/−)[SR-BI-Tg (med)] mice, the total plasma cholesterol level was only 23% greater than that of wild-type (SR-BI(+/+)/PDZK1(+/+)) controls. Indeed, Fig. 4 shows that for these SR-BI(−/−)/PDZK1(−/−)[SR-BI-Tg (med)] mice the plasma lipoprotein size distribution (gray diamonds) was almost identical to that of wild-type mice (open circles), with virtually none of the abnormally large HDL particles observed in nontransgenic SR-BI(−/−), PDZK1(−/−) or SR-BI(−/−)/PDZK1(−/−) mice (black triangles; also see Fig. 1). Furthermore, the levels of hepatic SR-BI protein (Fig. 2) and plasma cholesterol (Table 1) as well as the lipoprotein size distribution in SR-BI(−/−)/PDZK1(−/−)[SR-BI-Tg (med)] mice were
remarkably similar to those reported for heterozygous SR-BI(+/−) mice (19), strongly suggesting that the hepatic SR-BI receptor activity was normal in these mice.

This suggestion was further supported by the finding that the very high hepatic SR-BI levels in SR-BI(−/−)/PDZK1(−/−)[SR-BI-Tg (hi)] mice resulted in very low steady state levels of plasma cholesterol (Table 1) and only trace levels of HDL, with apparently normal particle size (Fig. 4, gray squares). These results are comparable with those previously reported for transgene-mediated hepatic SR-BI overexpression in wild-type (SR-BI(+/+)/PDZK1(+/+)) mice (16, 17, 23, 24).

Taken together, our results show that not only can SR-BI be expressed on the sinusoidal surfaces of hepatocytes in the absence of PDZK1 but also that it apparently can function normally in the liver as an HDL receptor without PDZK1. As a consequence SR-BI can restore to essentially wild-type values the plasma cholesterol levels and lipoprotein size distributions in PDZK1(−/−) mice, provided the extent of overexpression is sufficient to overcome the low levels of hepatic SR-BI that usually accompany PDZK1 deficiency.

It seems that one of two mechanisms is likely to account for the PDZK1 dependence of SR-BI function. The simplest of these is that PDZK1 normally does not play a key role either in the intracellular sorting of SR-BI or in maintaining its intrinsic receptor activity in hepatocytes but, rather, that its primary effect on SR-BI is to stabilize the otherwise functional protein. This might simply be because PDZK1 sterically blocks the access of cellular degradation factors to the SR-BI C terminus or because of more complex mechanisms (e.g. assembly into a complex due to the scaffolding activity of the PDZK1 multiple PDZ domains; or possibly because of the influence of PDZK1 on the rates of SR-BI endocytosis). Alternatively, it is possible that PDZK1 normally plays an important role in controlling the intracellular trafficking of SR-BI in hepatocytes. Thus, in PDZK1(−/−) hepatocytes most of the newly synthesized SR-BI molecules (the majority in nontransgenic animals) may be mis-sorted before or after reaching the cell membrane and consequently rapidly degraded. Were that the case, overexpression of SR-BI in the transgenic mice may have resulted in some molecules abnormally "leaking" past the PDZK1-dependent barrier to surface expression. There are several examples in the literature where overexpression of a protein bypasses an otherwise normal barrier to intracellular transport and cell surface expression or secretion (49–51).

In this regard, it is important to consider our findings in the light of a previous study of the role of PDZK1 binding to the C terminus of SR-BI (27). Silver (27) studied in hepatocytes in vivo the expression of a truncated form of SR-BI (SR-BI-del509) that cannot bind to PDZK1 because it lacks its C-terminal residue (Leu509), which is usually essential for PDZ domain binding to target proteins (27, 30). When expressed in cultured cells in which PDZK1 expression does not appear to be required for normal SR-BI surface expression and function (27, 28), SR-BI-del509 behaves similarly to wild-type SR-BI. However, stable hepatic overexpression of the SR-BI-del509 in transgenic wild-type mice had no apparent effect on plasma lipoprotein metabolism, even though immunoblotting indicated that hepatic levels of SR-BI protein were 6-fold higher than in nontransgenic wild-type controls. Analysis of isolated hepatocytes from the transgenic animals suggested that essentially none of the excess SR-BI-del509 protein was expressed on the cell surfaces, and thus it could not directly participate in plasma lipoprotein metabolism.

These findings clearly established that the C-terminal Leu509 was critical for cell surface expression of SR-BI, and Silver (27) sensibly proposed that PDZK1 is critically important for hepatic cell surface expression, and thus function, of SR-BI. In unpublished studies using adenovirus-mediated hepatic overexpression of SR-BI-del509 in wild-type mice, we have confirmed by immunofluorescence microscopy that most of the SR-BI-del509 protein is intracellularly retained and does not reach the cell surface of the hepatocytes. However, because of the very high SR-BI overexpression generated by the adenovirus, some surface expression was detected, which resulted in the expected decrease in plasma lipoprotein cholesterol and increase in biliary cholesterol. Nevertheless, in contrast to the findings with SR-BI-del509, in the current study we found that in the livers of PDZK1(−/−) mice in vivo most of the full-length SR-BI produced by the transgenes was located primarily on the hepatocyte cell surfaces and apparently functioned normally, even though its steady state levels were lower than that of endogenous SR-BI in nontransgenic wild-type mice and were much lower than the 6-fold elevation of SR-BI-del509 in Silver’s stable transgenic animals. We suggest that these results are not incompatible, because, in addition to preventing the interaction of PDZK1 with SR-BI, the loss of Leu509 at the C terminus of SR-BI may lead to PDZK1-independent interference with the intracellular transport of SR-BI-del509 and consequently to the intracellular accumulation of the protein. The absence of Leu509 may protect the protein directly from the apparent rapid degradation of wild-type SR-BI in the absence of PDZK1 or perhaps protect it indirectly because of the inability of SR-BI-del509 to be transported to intracellular sites required for that rapid degradation.

In summary, it seems likely that the primary mechanism by which PDZK1 controls hepatic SR-BI activity is by controlling its stability and that SR-BI does not need to bind to PDZK1 to be transported to the cell surface of hepatocytes in vivo or to function as an HDL receptor. As described previously (26) the dependence of SR-BI on PDZK1 is tissue-specific. Future studies will be required to identify the molecular basis of this tissue specificity and to determine whether other adaptor/scaffold proteins play similar roles to that of PDZK1 in controlling, in a tissue-specific fashion, the stability of other cell surface receptors.

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