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Role of the adaptor protein PDZK1 in controlling the HDL receptor SR-BI

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Abstract

Purpose of the review—Regulation of lipoprotein receptor activity influences lipoprotein metabolism, related physiology and pathophysiology. Adaptor proteins that bind to the LDL or HDL receptors apparently link these receptors to cellular components essential for their normal functioning.

Here we focus on the influence of PDZK1 on the HDL receptor SR-BI, with emphasis on the roles played by its individual PDZ domains, the impact in regulating HDL metabolism and the relevance for cardiovascular disease.

Recent findings—PDZK1 plays an essential role in maintaining hepatic SR-BI levels and controlling HDL metabolism, protects against the development of atherosclerosis in a murine model and also mediates SR-BI-dependent regulation of endothelial cell biology by HDL, suggesting that PDZK1 plays multiple roles in normal physiology and may influence associated pathology. All four PDZ domains of PDZK1 appear necessary to promote normal hepatic expression, function and intracellular localization of SR-BI.

Summary—SR-BI mediates several features of HDL metabolism and function, some of which depend on SR-BI's interaction with PDZK1. Exploration of the structure and function of PDZK1 and the mechanisms by which it controls SR-BI will provide additional insights into HDL metabolism and may provide the basis for new therapeutic modalities for cardiovascular disease.

Keywords

PDZ domains; high-density lipoprotein receptor; atherosclerosis; endothelium

Introduction

The level of plasma high-density lipoprotein (HDL) cholesterol is inversely associated with the risk of developing atherosclerosis [1,2], apparently in part because of its role in promoting reverse cholesterol transport (RCT) [3–6]. In reverse cholesterol transport, cholesterol is removed from peripheral organs and transported to the liver where it or its metabolic products (e.g., bile acids) are excreted into the bile. Reverse cholesterol transport appears to be one of the essential mechanisms by which HDL inhibits the development of atherosclerosis and protects against one of the most common forms of cardiovascular disease. Among the cell

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surface receptors playing major roles in regulating plasma cholesterol levels are members of the low-density lipoprotein (LDL) receptor superfamily (LDL receptor, LRP, etc.), which are regulated by intracellular adaptors, including ARH (autosomal recessive hypercholesterolemia), disabled 1 and disabled 2 [7–11]. The HDL receptor, scavenger receptor class B type I (SR-BI) [12], is one of several cell surface proteins that are regulated by the intracellular adaptor PDZK1 [13–15], previously reviewed in [16]. Here we focus on the regulation of SR-BI's activity by PDZK1.

SR-BI is an HDL receptor

SR-BI is a 509 amino acid, integral membrane glycoprotein [6]. The bulk of the protein comprises a heavily N-glycosylated extracellular loop, the remaining portions of the molecule defining two transmembrane domains and short intracellular amino and carboxy termini. SR-BI is predominantly expressed in the liver, gastro-intestinal tract and steroidogenic organs [12], although it can also be detected in other types of cells (e.g., macrophages, endothelial cells [6]). SR-BI binding to HDL leads to SR-BI-mediated bulk transfer of its core cholesteryl esters to the cell via a distinctive mechanism called selective lipid uptake [12]. In addition, SR-BI mediates bidirectional flux of unesterified cholesterol between cells and lipoproteins ([17], reviewed in [6]).Targeted disruption of the SR-BI gene in mice leads to an ~2.2-fold increase in plasma cholesterol in abnormally large and unesterified cholesterol enriched HDL particles [18,19], accompanied by a decrease in biliary cholesterol secretion [20]. SR-BI's role in reverse cholesterol transport is thought to underlie its potent atheroprotective effects in mice ([21–23], reviewed in [6]). Indeed, increasing the expression of hepatic SR-BI promotes reverse cholesterol transport and reduces atherosclerosis, despite accompanying decreased plasma HDL cholesterol concentration [24–28]. In addition, combined targeted disruptions of the apoE and SR-BI genes results in a novel murine model of coronary heart disease, because it leads not only to severe occlusive coronary arterial atherosclerosis, but also myocardial infarction, cardiac dysfunction and premature death [19,21]. In the liver, and to a lesser extent in the gastro-intestinal tract, the expression of SR-BI is controlled by its adaptor protein PDZK1 [13,14].

PDZK1 and PDZ domains

PDZK1 (Figure 1) was first identified in human carcinomas [29]. Initial studies suggested that PDZK1 was exclusively expressed in cells of epithelial origin (proximal tubular cells of the kidney, hepatocytes, intestinal mucosa, adrenal cortical cells among others) [29], however recent studies have demonstrated that it is also expressed in endothelial cells [30,31]. Its name is based on the presence of four PDZ-protein interaction domains in its sequence. PDZ domains (named after three proteins containing such domains: post-synaptic density protein (PSD95), *Drosophila* discs large (Dlg) and the tight junction protein zonula occludens-1 (ZO-1)) [32] are composed of about 80–90 amino acids. The human genome encodes over 250 PDZ domains incorporated into over 100 proteins. They fold into relatively compact structures that characteristically contain six β-strands and two α-helices [33]. Because a significant number of PDZ-domain proteins contain multiple PDZ domains, they are able to promote clustering or scaffolding of groups of proteins, often cell surface and related proteins (e.g., cell surface receptors and ion channels), and are involved in a wide variety of cellular functions. Usually, PDZ domains interact with the five most carboxy terminal amino acids of their binding partners (target, proteins). Some recognize as many as seven carboxy terminal residues [34].

The most C-terminal amino acid (position 0) of the binding target of a PDZ domain is almost always hydrophobic. Early analysis of target sequences suggested three classes of targets: position -2 is either a serine or threonine (Class I), hydrophobic (Class II) or aspartate or glutamate (Class III) [35,36]. However, more recent studies suggest that the PDZ domains

themselves cannot be divided rigorously into simple groups based on these three classes of targets, but rather that their sequences have been optimized to very specifically allow the recognition of their binding partners [37,38]. The C-terminus of mammalian SR-BI (…KG(T/S)VLQEA(R/K)L) (from 10 species, http://blast.ncbi.nlm.nih.gov/Blast.cgi) binds to the first PDZ domain (PDZ1, Figure 1) of PDZK1 [13].

There is a large and growing literature describing PDZK1-dependent control of many other proteins [39], including ion channels and transporters in the kidney and small intestines [15,40,41].

Effects of inactivation of the PDZK1 gene on SR-BI in mice

Targeted disruption of the PDZK1 gene results in an ~1.7-fold increase in plasma cholesterol carried in abnormally large HDL particles that are not abnormally enriched in unesterified cholesterol, a result similar to, but not identical to or as severe as, that observed in SR-BI knockout mice [14,42]. The increase of plasma cholesterol can be attributed primarily to an ~95% decrease in SR-BI protein expression in the liver. There is also an ~50% decreased protein expression in the small intestines, but no change in steroidogenic organs [14]. The differences in lipoprotein metabolism between SR-BI and PDZK1 KO mice are likely due to the residual expression of SR-BI in hepatocytes and intestinal epithelial cells in PDZK1 KO mice and also to the fact that SR-BI expression in steroidogenic organs is PDZK1 independent. In addition, the minor SR-BI variant SR-BII is not regulated by PDZK1 [14]. These findings led to the realization that PDZK1 is a tissue (primarily liver) specific, functionally relevant adaptor protein for SR-BI, reminiscent of the tissue specificity of ARH's effects on LDL receptor activity [7,11].

Hepatic overexpression of SR-BI in SR-BI/PDZK1 double knockout mice restores normal expression of SR-BI on the hepatocyte cell surface, suggesting that PDZK1 is required for maintaining adequate steady state cell-surface levels of SR-BI, but is not essential for its surface localization or function, at least in the case of SR-BI transgene overexpression [43]. In transgenic mice, hepatic protein expression and function of transgenic human SR-BI (also called CLA-1) is increased when a human PDZK1 transgene is co-expressed [44].

Role of individual PDZ domains of PDZK1 in controlling SR-BI

When Ikemoto et al. first reported that PDZK1 binds to SR-BI, they showed that the PDZ1 domain of PDZK1 was responsible for this interaction [13]. Fenske et al. [45,46] have explored the roles of PDZK1's four PDZ domains and the PDZ domain-free C-terminal region (Figure 1) in regulating hepatic SR-BI. They generated wild-type and PDZK1 KO mice with hepatic expression of PDZK1 transgenes encoding proteins with nested C-terminal truncations, including: PDZ1, PDZ1.2, PDZ1.2.3 or PDZ1.2.3.4, which contain only the first one, two, three or four N-terminal PDZ domains, respectively, but not the remaining C-terminal sequences. Hepatic expression of PDZ1 was not able to restore normal expression or function of SR-BI in PDZK1 KO mice. Immunoperoxidase studies showed that small amounts of SR-BI expressed in hepatocytes of these mice were mislocalized in the cytoplasm, instead of being associated with the plasma membrane. Nevertheless, the PDZ1 transgene exhibited a dominant negative effect when expressed in wild-type mice, inducing phenotypes similar to the PDZK1 KO mice expressing the PDZ1 transgene (reduced and mislocalized SR-BI, hypercholesterolemia due to large HDL). These results indicate that the PDZ1 domain can control the abundance and localization, and therefore the function, of hepatic SR-BI and that structural features of PDZK1 in addition to its SR-BI-binding PDZ1 domain are required for normal hepatic SR-BI regulation. PDZK1 KO mice expressing the PDZ1.2 and PDZ1.2.3 transgenes exhibited phenotypes similar to those with the PDZ1 transgene (although there was a low level of hepatocyte cell surface expression and function of SR-BI in PDZ1.2.3 expressing

mice). In contrast, there was restoration of virtually wild-type levels and function of heptatic SR-BI in PDZK1 KO mice expressing hepatic PDZ1.2.3.4. Thus, in this system all four PDZ domains of PDZK1, but not the C-terminal region, are necessary for apparently normal hepatic regulation of SR-BI abundance, localization and function.

Additional studies will be needed to define precisely the roles that PDZ domains 2 to 4 play in normal PDZK1 function. One or more of these domains may 1) facilitate intramolecular PDZK1 folding or act as spacers to maintain the appropriate three dimensional relationship between two or more of the PDZ domains, 2) participate in intermolecular interactions possibly leading to dimerization/oligomerization of PDZK1 essential for SR-BI function, and/or 3) bind to other proteins that promote stable expression of SR-BI at the cell surface. Indeed, Lalonde and Bretscher have recently reported evidence for intramolecular association of PDZK1's C-terminus with its PDZ1 domain and for PDZ3-mediated dimerization of PDZK1 [47]. Future studies, especially those exploring the roles of PDZ2–4 in binding other cellular components (scaffold function), may be facilitated by recently described models designed to predict the target binding sequence of a PDZ domain based on that domain's primary sequence [34,37, 38]

Dietary, genetic, hormonal and pharmacologic regulation of hepatic PDZK1 and SR-BI

Much of the analysis of PDZK1 has focused on its regulation of its target proteins. To date there have only been a relatively limited number of reports focused on the regulation of the expression and activity of PDZK1 itself.

Niemeier et al. [48] have reported that feeding mice an atherogenic diet (high cholesterol, high cholic acid) can reduce hepatic levels of PDZK1 protein as well as SR-BI protein. Several other studies also report coordinate regulation of PDZK1 and SR-BI. Robichaud et al. have reported that the reduced plasma HDL cholesterol level in mice deficient in a key enzyme (phosphatidylethanolamine N-methyltransferase) in one of the two pathways for phosphatidylcholine synthesis is associated with a 1.5-fold increase in the hepatic levels of both PDZK1 and SR-BI protein [49]. Nakamura et al. [50] discovered that the C-terminal region of PDZK1, which does not contain PDZ domains (Figure 1), can be phosphorylated on serine(s) in cultured cells and *in vivo* in rat liver. In cultured cells, such phosphorylation can - at least in some conditions - facilitate the ability of PDZK1 to optimally increase SR-BI protein levels. They also showed that the extent of this phosphorylation, as well as the levels of hepatic PDZK1 and SR-BI and levels of plasma HDL can be increased in rats by glucagon treatment. Thus, PDZK1 levels can be subject to hormonal control.

Maradones et al. [51] showed that treatment of mice with fibrates (ciprofibrate or fenofibrate), peroxisome proliferator-activated receptor alpha (PPARα agonists, dramatically suppresses hepatic levels of PDZK1 and SR-BI proteins (but not mRNAs) and consequently increases plasma levels of abnormally large HDL particles, a phenotype similar to that observed in SR-BI and PDZK1 knockout mice. Fibrate treatment of cultured rat hepatocytes also suppresses SR-BI protein expression. Lan and Silver have shown that at least some of the decrease in murine hepatic SR-BI protein levels by fibrate (fenofibrate) treatment may be due to enhanced, PDZK1-independent, degradation of SR-BI [52].

As a consequence, results from one of the first reports examining the promoter of PDZK1 were somewhat unexpected. Tachibana et al. reported that the human PDZK1 gene is a positively regulated target of PPARα [53]). They identified consensus sequences for the peroxisome proliferator responsive element (PPRE) and the estrogen receptor responsive element in the promoter region of the human PDZK1 gene. Earlier, Walker et al. reported that estradiol

induces PDZK1 expression in an estrogen receptor positive ovarian cancer cell line [54]. Tachibana et al. showed that this PPRE in cultured cells mediates fibrate (PPARα agonist) induction of reporter gene expression [53]. They also showed that a different PPARα agonist (GW7647) could induce an approximately 2.3-fold increase in PDZK1 protein expression in a human hepatoma cell line. The apparently inconsistent results for PPARα agonists in the human and murine systems remain to be explained.

Role of PDZK1 and SR-BI in endothelial cells

Lipoproteins can significantly influence endothelial cell biology [55]. For example, HDL leads to inhibition of adhesion of inflammatory cells to the endothelium, decreased endothelial cell apoptosis and anti-inflammatory effects on endothelial cells [56]. HDL has been shown to induce multiple signaling systems and downstream consequences (e.g., activation of eNOS and cell migration) in endothelial cells via SR-BI, which is expressed on their surfaces [30, 57–61]. PDZK1 is required for several HDL-mediated effects on endothelial cells, including activation of src, endothelial NO synthase and cell migration, and for carotid artery reendothelialization following perivascular electric injury [30,62–64]. Thus, HDL/SR-BI/PDZK1 interaction seems to be essential in maintaining integrity of the endothelial monolayer [30].

PDZK1's role in preventing the development of atherosclerosis

Because PDZK1 controls hepatic SR-BI abundance and function and SR-BI is atheroprotective in murine models of atherosclerosis (LDL receptor or apoE KO mice [21,22,65], reviewed in [6]), it seemed likely that PDZK1 would also be atheroprotective. This has been confirmed using apoE/PDZK1 double KO and control apoE single KO mice fed with a high cholesterol, Western diet for three months [31]. Aortic root atherosclerotic plaque was 157% greater in double than control single KO mice. The PDZK1 deficiency did not lower SR-BI protein expression on the surfaces of endothelial or monocyte/macrophage cells. Disease in the apoE/PDZK1 double KO mice was not as severe as that in SR-BI/apoE double KO mice [21]. It seems likely that the effects of PDZK1 deficiency on hepatic SR-BI and HDL metabolism play an important role in the atheroprotective effect of PDZK1. It is also possible that the influence of PDZK1 on SR-BI-mediated signaling in endothelial cells (see above) may also contribute to its atheroprotective activity.

Summary

Considerable progress has been made in analyzing the control of SR-BI abundance, localization and function mediated by PDZK1. However many questions remain to be answered. We don't yet understand the precise molecular and cellular mechanisms by which PDZK1 mediates the tissue specific regulation of SR-BI. For example, it is possible that PDZK1 serves as a scaffold protein in the liver to link SR-BI to other, critically important, as yet unidentified, cellular components. The relative importance of hepatic vs. endothelial PDZK1 in atheroprotection has not been established, nor do we know if naturally occurring variation in PDZK1 structure and function influence human SR-BI and have clinical consequences (e.g., influence risk for atherosclerotic or other cardiovascular diseases). With the continued development of powerful experimental tools to study PDZK1, we can expect substantial progress in addressing these questions in the near future.

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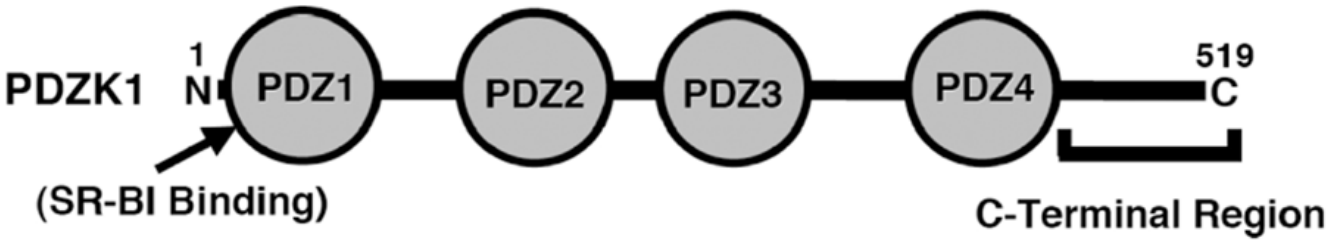

Figure 1.
Model of the primary sequence of PDZK1 [45]