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News on the molecular regulation and function of hepatic LDLR and LRP1

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Abstract

Purpose of review—Clearing of atherogenic lipoprotein particles by the liver requires hepatic LDLR and LRP1. This review highlights recent studies that have expanded out understanding of the molecular regulation and metabolic functions of LDLR and LRP1 in the liver.

Recent findings—Various proteins orchestrate the intracellular trafficking of LDLR and LRP1. After internalization, the receptors are redirected via recycling endosomes to the cell surface. Several new endocytic proteins that facilitate the endosomal trafficking of LDLR and consequently the clearance of circulating LDL cholesterol have recently been reported. Mutations in some of these proteins cause hypercholesterolemia in human. In addition, LRP1 controls cellular cholesterol efflux by modulating the expression of ABCA1, and ABCG1, and hepatic LRP1 protects against diet-induced hepatic insulin resistance and steatosis through the regulation of insulin receptor trafficking.

Summary—LDLR and LRP1 have prominent roles in cellular and organismal cholesterol homeostasis. Their functioning, including their trafficking in the cell, is controlled by numerous proteins. Comprehensive studies into the molecular regulation of LDLR and LRP1 trafficking have advanced our fundamental understanding of cholesterol homeostasis, and these insights may lead to novel therapeutic strategies for atherosclerosis, hyperlipidemia and insulin resistance in the future.

Keywords

Trafficking; CCC complex; DAB2; hypercholesterolemia; glucose metabolism

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Conflicts of interest

There are no conflicts of interest.

Introduction

The liver plays a crucial role in cholesterol homeostasis through controlling lipid uptake and synthesis. Clearance of plasma lipids via the liver is mediated by the low-density lipoprotein receptor (LDLR) and LDLR-related protein 1 (LRP1) [1–3]. Both receptors are member of the evolutionarily conserved LDLR family [4]. The core of this family is comprised of seven members (LDLR, LRP1, very-low-density lipoprotein receptor [VLDR], LRP8/Apoer2, LRP4/MEGF7, LRP1B, and LRP2/Megalin). These receptors have one transmembrane domain, a large extracellular domain with one or more ligand binding domains, and a cytoplasmic tail, which contains at least one NPxY motif [2]. Numerous adaptor proteins are binding to this particular motif to mediate endocytosis and signal transduction through the receptors. Hepatic LDLR and LRP1 contribute to the clearance of circulating Apolipoprotein E (ApoE) containing particles, such as the triglyceride carrying chylomicrons and VLDL. Intestinal-derived chylomicrons remnants and hepatic VLDL are removed from the circulation by the liver after extensive peripheral metabolism. Part of VLDL is converted to LDL, a cholesterol rich particle that lacks ApoE but contains one apoB100 molecule. In addition to ApoE, also ApoB-containing particles are taken up by hepatocytes through LDLR and LRP1 (Fig. 1, and Fig. 2A).

The role of LDLR in clearing circulating atherogenic lipoprotein particles, such as VLDL and LDL, is well established. A large number of mutations in *LDLR* have been identified that cause familial hypercholesteromia (FH) [5] and predispose to atherosclerosis and cardiovascular disease. Genetic ablation of the LDL receptor in mice also leads to elevation in plasma LDL, and make these animals susceptible to atherosclerosis upon high cholesterol feeding [6,7]. However, the contribution of hepatic LRP1 in preserving cholesterol homeostasis has been ambiguous. In contrast to LDLR deficient mice, mice lacking LRP1 in the germline are not viable, but die at various stages of post-implantation embryonic development, depending upon strain background [8,9]. An initial study with conditional *Lrp1* knockout mice showed that mice deficient for hepatocyte LRP1 are viable but don't have clear alterations in plasma lipid levels [3]. Interestingly, however, the protein levels of hepatocyte LDLR were markedly increased in liver-specific *Lrp1* knockout mice. Hepatic deletion of both *Ldlr* and *Lrp1* resulted in a marked elevation in plasma chylomicron remnants and LDL levels [3]. These data imply that LDLR can partially compensate for the loss of LRP1 in hepatocytes, and demonstrate the importance of both receptors for the clearance of circulating atherogenic lipoprotein particles. Here, we describe recent findings contributing to the understanding of the molecular regulation and function of LDLR and LRP1, with a focus on their function in the liver, and lipid and glucose homeostasis.

Low-density lipoprotein receptor (LDLR)

In the 1970's, Goldstein and Brown reported for the first time the existence of a specific receptor for LDL [1]. The expression of LDLR at the cell surface is regulated by cellular membrane cholesterol content. Low intracellular cholesterol concentrations result in increased expression of LDLR, which is mediated by the transcription factor sterol regulatory element binding protein 2 (SREBP2) [10]. At the cell surface, LDL binds through ApoB100 to LDLR. LDL and LDLR are endocytosed together (Fig. 1), which is mediated

by several adaptor proteins such as autosomal recessive hypercholesterolemia (ARH) protein, and Disabled homolog 2 (DAB2) protein (reviewed in [11*]) (Fig. 1A). Both adaptor proteins bind to the NPxY motif of LDLR. Mutations in *ARH* have been identified in patients with FH. Like FH patients carrying mutations in *ARH*, mice deficient for ARH show elevated LDL plasma levels. *DAB2* mutations correlated with hypercholesterolemia have not been reported yet, and DAB2 deficient mice are not viable. In mice, DAB2 is likely important for normal development of the placenta as *Dab2* knockout mice with only normal expression of *Dab2* in extra-embryonic tissues are born alive [12]. These mice have a slight increase in circulating plasma cholesterol. Since DAB2 is not expressed in hepatocytes, its contribution to LDLR-mediated cholesterol clearance is likely very restricted, but a recent study has demonstrated that in the liver DAB2 is mainly expressed in sinusoid endothelial cells [13**]. To further investigate the contribution of DAB2 in cholesterol homeostasis the authors of this study depleted both *Dab2* and *Arh* in mice. These mice were fed a high sucrose diet to stimulate the production/secretion of VLDL by the liver. Plasma cholesterol levels were determined and compared with high-sucrose diet fed $Ldlr^{-/-}$ and $Arh^{-/-}$ mice. Plasma cholesterol levels in DAB2 deficient mice were slightly increased, and only *Dab2-Arh* double knockout mice had cholesterol levels comparable to that of $Ldlr^{-/-}$ mice. Furthermore, the degree of HMG-CoA reductase (HMGCR) and cholesterol increase in the liver of *Dab2-Arh* double knockout mice was comparable to that of $Ldlr^{-/-}$ mice. Based on these findings the authors concluded that ARH is mainly required for the endocytosis of LDLR in hepatocytes, whereas DAB2 facilitates the intracellular trafficking of LDLR in liver sinusoid endothelial cells. Since hepatocyte HMGCR levels were only elevated in *Dab2-Arh* double knockout mice and in $Ldlr^{-/-}$ mice, but not in $Arh^{-/-}$ mice, could suggest that LDLR expression in sinusoid endothelial cells has a significant role in the liver uptake and sensing of cholesterol to preserve homeostatic cholesterol levels. Alternatively, a small degree of DAB2 expression by hepatocytes, below the level of detection by conventional methods, might be able to partially compensate for the loss of ARH to allow residual uptake of LDL cholesterol sufficient to suppress full-blown upregulation of *HMGCR* expression.

Internalized LDLR is delivered to the endosomes and sorted either back to the plasma membrane, for reuse, or to the lysosomes where LDLR is degraded [14] (Fig. 1). In an ARH-dependent fashion, proprotein convertase subtilisin/kexin type 9 (PCSK9) directs LDLR via the endocytic pathway to the lysosomes and prevents the recycling of LDLR [15,16*] (Fig. 1). Like PCSK9, ubiquitin ligase inducible degrader of the LDLR (IDOL) stimulates the proteolysis of LDLR in a variety of tissues including the brain (reviewed in [17*]) (Fig. 1). Although the transport of IDOL-mediated LDLR degradation is ARH-independent, it requires the endosomal-sorting complex required for transport machinery (ESCRT) to direct LDLR towards the lysosomes (reviewed in [11*,17*]). Intriguingly, however, for reasons that are not understood, IDOL has no significant effect on the degradation of LDLR in murine livers, but might have a potential role in LDLR proteolysis in human and monkey livers [18*].

A recent study has identified a large number of proteins involved in the removal of plasma cholesterol by coordinating the endosomal trafficking of LDLR [19**]. Here, Bartuzi and colleagues linked the coiled-coil domain-containing protein 22 (CCDC22) to plasma LDL cholesterol clearance. Mutations in *CCDC22* cause X-linked intellectual disability (XLID)

syndrome [20,21]. XLID syndrome is characterized by developmental defects, which includes intellectual disability, cerebellar malformations, cardiac defects and limb abnormalities, but this study reports for the first time that these patients also suffer from hypercholesterolemia. CCDC22 participates in a multiprotein complex, named the CCC complex [19***,22,23*,24]. CCC complex is compromised of 4 proteins, COMMD1, CCDC22, CCDC93 and C16orf62. COMMD1 physically associates with LDLR, through the binding with the NPxY motif of LDLR [19**]. COMMD1 deficiency dramatically decreases the levels of the CCC complex components CCDC22 and CCDC93 in the liver of dogs and mice [19**]. This compromised integrity of the CCC complex coincides with elevated plasma cholesterol levels in these animals, in particularly LDL cholesterol. Studies with primary hepatocytes and mouse embryonic fibroblast (MEFs) cells lacking COMMD1 revealed that the CCC complex is needed for normal trafficking of LDLR. The amount of LDLR localized to endosomes was increased, whereas its level in the plasma membrane was diminished by the loss of COMMD1. Consequently, mislocalization of LDLR in COMMD1 deficient cells impaired LDL uptake. The CCC complex has previously been linked to copper homeostasis by coordinating the trafficking of copper transporting proteins ATP7A and ATP7B [23*,25–29]. CCC complex is physically associated with Wiskott-Aldrich Syndrome Protein and SCAR Homolog (WASH) complex [23*], a multiprotein complex composed of five proteins, WASHC1, WASHC2A, WASHC3, WASHC4, and WASHC5, also known as WASH1, FAM21, CCDC53, KIAA1033 (SWIP), and KIAA0196 (Strumpellin), respectively [30]. WASH facilitates the endosomal trafficking of an array of transmembrane proteins, including ATP7A [23*,30]. The observation that CCC and WASH are physically connected and are both required for the endosomal trafficking of ATP7A suggests that they likely act together. This notion was further supported by the study of Bartuzi and colleagues, in which they showed that LDLR trafficking and its surface expression in MEFs also rely on the WASH complex. A mutation in *WASHC5* has been associated with Ritscher-Schinzel/3C syndrome (RSS), and phenotypically RSS patients resemble XLID patients. This study now shows that both XLID and RSS patients have elevated plasma LDL cholesterol levels, which further implies that the CCC and WASH complexes are both involved in endosomal trafficking of LDLR to direct LDLR back to the cell surface for efficient LDL uptake (Fig. 1).

The importance of the endocytic system for LDL clearance is further supported by other recent studies in which the small GTPase Rab5 was down regulated in adult mouse livers using RNA interference technology [31*,32]. Rab5 has been identified as a crucial hub in a large protein network in endosome biogenesis. Rab5 insufficiency results in a reduced number of early and late endosomes and lysosomes. Interestingly, the total amount of LDLR was increased in Rab5 insufficient livers, but despite these elevated LDLR levels plasma LDL cholesterol levels of these mice were markedly increased. Further analyses revealed that LDL uptake in primary hepatocytes cells with low levels of Rab5 was impaired, supporting the notion that LDLR trafficking highly depends on the endocytic system.

As mentioned previously, both PCSK9 and IDOL-mediated LDLR degradation pathways make use of the endocytic system and it would be therefore informative to assess, whether the CCC and WASH complexes also participate in the sorting of LDLR to lysosomes. Preventing proteolysis of LDLR or increasing endocytosis/recycling of LDLR would be

beneficial to increase LDL uptake. For example, high expression of the endosome-associated protein Sortin nexin 17 (SNX17) enhances LDL uptake due to increased endocytosis of LDLR [33]. SNX17 also facilitates the recycling of LRP1 and ApoER2 [34,35], but whether SNX17 acts in conjunction with the CCC and WASH complexes, and whether these two complexes are also required for endosomal sorting of LRP1 or other members of the LDLR family has yet to be determined.

LDLR-related protein 1 (LRP1)

LRP1 is the only other core member of the LDL receptor gene family that is expressed at functionally significant levels in hepatocytes and thus can mediate the bulk transport of ApoE-containing lipoproteins that have entered the Space of Disse, following extensive metabolism by lipolysis or lipid transfer in the periphery and in the circulation (Fig. 2A). Early genetic insights, gathered from the work by Kita, Brown and Goldstein (1982) [36] implied the existence of a hepatic ApoE-binding chylomicron remnant receptor distinct from the LDL receptor. The discovery of LRP1, its structural similarity with the LDL receptor, its expression on the hepatocyte cell surface [2], and its ability to bind ApoE [37,38] and deliver internalized remnant lipoproteins to the lysosome [38] were highly suggestive that LRP1 was the elusive chylomicron remnant receptor. However, the apparent absence of human mutations in *LRP1* causing remnant clearance defects and early embryonic lethality in whole animal mouse knockout models [8,9,39] prevented conclusive genetic proof of this hypothesis. The introduction of tissue-specific gene disruption technologies in mice ultimately showed that LDLR and LRP1 jointly mediate the hepatocellular uptake of chylomicron remnants [3,40].

In these initial studies of the hepatic LRP1 function in lipid metabolism no major effect of an isolated, hepatic-only LRP1 deficiency on plasma lipid levels were reported [3]. This is due to a large extent to an approximately 2-fold increase in the protein expression of hepatic LDLR in the absence of LRP1. However, in another study Basford and colleagues noted reduced levels of plasma HDL in liver-specific LRP1 deficiency consistent with a diminished expression of the ATP-binding cassette, subfamily A member 1 (ABCA1) at the liver cell surface [41*]. A similar, but much more pronounced reduction of ABCA1 had previously been reported in LRP1-deficient vascular smooth muscle cells [42]. ABCA1 acts as an important hepatic cholesterol efflux transporter, and its activity determines plasma HDL levels. Congenital deficiency of ABCA1 causes Tangier Disease (OMIM#205400), a rare genetic disorder characterized by a severe reduction in circulating HDL cholesterol. Translocation of ABCA1 to the plasma membrane has been reported to be dependent on the precursor of the glycosphingholipid-hydrolyzing saposins, Prosaposin (PSAP), which is itself a ligand of LRP1 [43]. Furthermore, Cathepsin D (CtsD) mediates the processing of PSAP. Since LRP1 can also mediate the internalization of CtsD, a possible mechanism by which LRP1 deficiency might adversely affect the translocation of ABCA1 to the plasma membrane is due to impaired PSAP trafficking and CtsD-mediated PSAP activation (Fig. 2B). Moreover, GWAS found an association between the *LRP1* locus and plasma HDL levels [44]. LRP1 might therefore have an additional role in lipid metabolism, independent of its role as a chylomicron clearance receptor, and thus could contribute to cardiovascular events in humans, similar to what has previously been reported for SR-B1 [45**].

In smooth muscle cells (SMCs) LRP1 deficiency results in reduced LXR-mediated *ABCA1* expression that coincides with lipid accumulation [42,46]. Recently, El Asmar and colleagues further investigated the molecular mechanism by which LRP1 controls *ABCA1* expression [47**]. In this study, the second NPXY motif within the cytoplasmic tail of LRP1 was found to be important for LRP1-mediated expression of *ABCA1*. This motif is important for the binding of Erk2 and subsequently for the phosphorylation of Erk1/2 during low intracellular cholesterol conditions. ERK activation leads to phosphorylation and activation of $cPLA_2$ [46]. Activation of $cPLA_2$ results in increased production of arachidonic acid, which inhibits LXR [46,48] and consequently diminishes *ABCA1* expression. Furthermore, the study also reported that activation of the Wnt5a signaling pathway requires LRP1 and that LRP1 deficiency impairs TGFβ-mediated *Wnt5a* expression, which in turn mediates cholesterol export through controlling the expression of the cholesterol efflux transporter *ABCG1*, and by blocking SREBP-2 and cholesterol biosynthesis. Taken together, these data may explain the massive cholesterol accumulation observed in the vascular wall of mice lacking LRP1 in SMCs [42,46]. These intriguing LRP1-dependent mechanisms were observed in either SMCs or in MEFs treated with an adipogenic cocktail, but whether these signaling pathways also occur in other cell types, such as hepatocytes, has yet to be determined.

However, another signaling mechanism that is also regulated by LRP1 and that is central to the functioning of the liver and the regulation of hepatic glucose and fatty acid metabolism involves the insulin receptor. A functional interaction between LRP1 and insulin signaling was first noted over 20 year ago, when Descamps and colleagues reported on the rapid translocation of LRP1 from intracellular compartments to the cell surface in response to insulin stimulation of rat epididymal adipocytes [49]. Similar observations were later made in hepatocytes [50]. Conversely, LRP1 also regulates the surface expression of the insulin receptor in neurons [51] and in the liver [52**]. In LRP1-deficient livers, reduced surface expression of the insulin receptor, and subsequently diminished expression of the glucose transporter GLUT2 (Fig. 2C), creates a latent state of insulin resistance that is unmasked by high fat diet feeding, leading to a full-blown metabolic syndrome with hepatic steatosis, reduced VLDL secretion, hepatic insulin resistance, impaired glucose tolerance, hyperglycemia, hyperinsulinemia and increased gluconeogenesis [52**]. A moderate reduction in HDL cholesterol levels was also seen, consistent with the observations by Basford and colleagues [41]. Taken together, these studies indicate that LRP1 and insulin receptor mutually regulate their intracellular trafficking and surface expression (Fig. 2C).

Conclusions

Although the genetic evidence for a role of LRP1 in lipid metabolism and cardiovascular risk in humans is less clear, likely because of its pleiotropic function, the contribution of LDLR has been well established. By contrast, a clear genetic basis for the importance of *LRP1* in the formation of abdominal aneurysms has emerged [42, 53**]. In recent years novel genes and proteins controlling LDLR function has been identified, resulting in the development of new therapies, such as PCSK9 inhibitors, to lower plasma cholesterol levels. Recent studies identified several novel proteins that are involved in the endosomal trafficking of LDLR. Moreover, from genetic studies in mice a picture emerges that brings

LDLR, LRP1, ABC transporters and the insulin receptor under a common umbrella where cellular glucose and lipid homeostasis are integrated to regulate cellular and systemic energy metabolism. Taking further into account that altering the levels of proteins associated with the endocytic machinery, either by overexpressing [33] or by using pharmacological compounds [54], can improve endosomal sorting point towards novel therapeutic opportunities to treat cardiovascular diseases, diabetes and metabolic syndrome.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

* of special interest

** of outstanding interest

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Key points

- LDLR endocytosis requires DAB2 in liver sinusoid endothelial cells.
- Large group of proteins identified facilitating the endosomal trafficking of LDLR.
- LRP1 mediates cholesterol efflux through ABCA1 and ABCG1
- Hepatocyte LRP1 deficiency increases the susceptibility to diet-induced insulin resistance and steatosis in mice

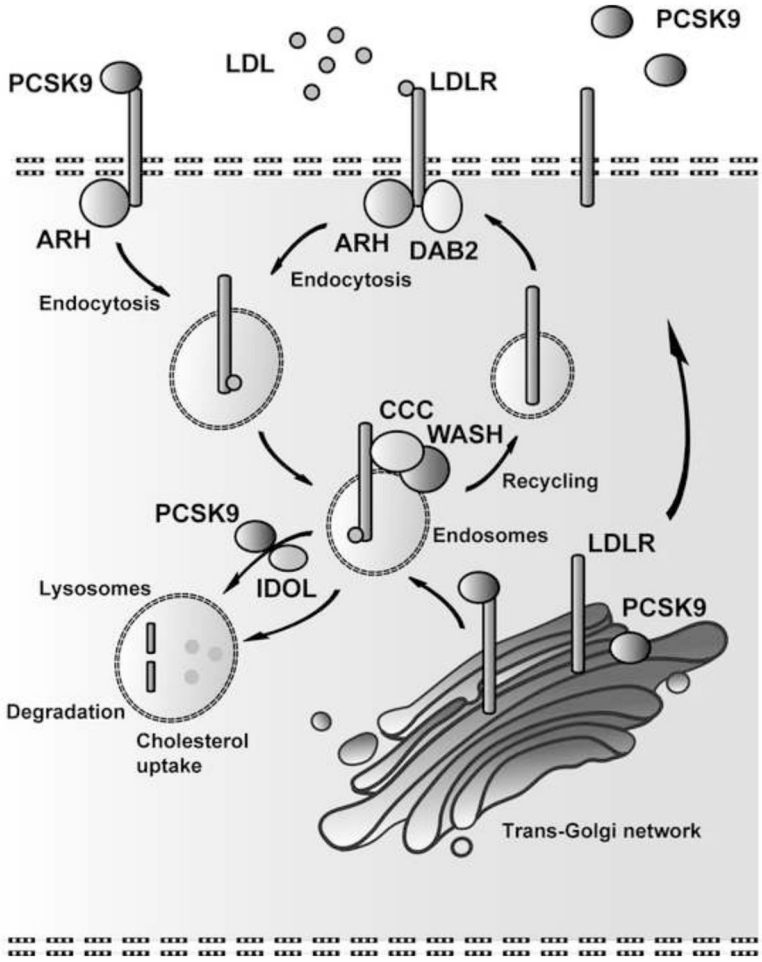

Figure 1. Simplified model of the molecular regulation of cellular LDLR trafficking

Cholesterol-rich ApoE and ApoB containing lipoprotein particles bind to LDLR and are together with LDLR internalized and accordingly directed to the endosomes. Endocytosis is mediated by ARH in hepatocytes and recent data indicate that DAB2 facilitates LDLR internalization in sinusoid endothelial cells [13**]. At the endosomes, the CCC and WASH complexes recognize LDLR, sort and redirect LDLR back to the cell surface [19**]. Alternatively, LDLR is sent to the lysosomes for proteolysis, which is mediated by PCSK9 and/or IDOL. Esterified cholesterol is hydrolyzed by lysosomal acid lipase in the lysosomes, from where free cholesterol is further distributed to the plasma membrane and the endoplasmic reticulum [55*]. ARH: autosomal recessive hypercholesterolemia; CCC: COMMD1, CCDC22, CCDC93, C16orf62; DAB2: Disabled homolog 2; IDOL: Inducible degrader of the LDLR; PCSK9: Proprotein convertase subtilisin/kexin type-9; WASH: WASHC1, WASHC2A, WASHC3, WASHC4, and WASHC5.

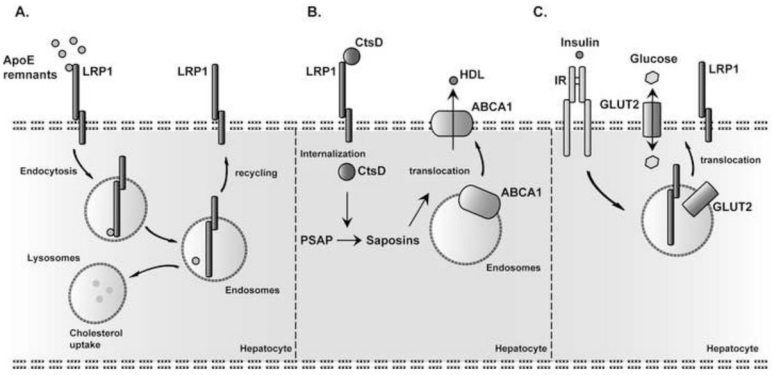

Figure 2. Hepatic LRP1-mediated pathways

A. Like LDLR (Fig. 1), LRP1 clears cholesterol-rich ApoE containing particles from the circulation. **B.** LRP1-mediated Cathepsin D (CtsD) uptake is required for processing of Prosaposin (PSAP) into Saposins. Saposins positively controls the translocation of ABCA1 to the transmembrane. ABCA1 is an important hepatic cholesterol efflux transporter, and controls plasma HDL levels. **C.** Insulin-induced GLUT2 translocation to the plasma membrane depends on LRP1 [52**]. Hepatocyte LRP1 deficiency diminishes surface IR levels and consequently attenuates insulin induced GLUT2 translocation. IR: Insulin receptor.