Expanding functions of lipoprotein receptors

Joachim Herz,[1] Ying Chen, Irene Masiulis, and Li Zhou

Department of Molecular Genetics, University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75390-9046

Abstract Lipoprotein receptors are evolutionarily ancient proteins that are expressed on the surface of many cell types. Beginning with the appearance of the first primitive multicellular organisms, several structurally and functionally distinct families of lipoprotein receptors evolved. Originally, these cell surface proteins were thought to merely mediate the traffic of lipids and nutrients between cells and, in some cases, by functioning as scavenger receptors, remove other kinds of macromolecules, such as proteases and protease inhibitors from the extracellular space and the cell surface. Over the last decade, this picture has fundamentally changed. We now appreciate that many of these receptors are not mere cargo transporters; they are deeply embedded in the machinery by which cells communicate with each other. By physically interacting and coevolving with fundamental signaling pathways, lipoprotein receptors have occupied essential and surprisingly diverse functions that are indispensable for integrating the complex web of cellular signal input during development and in differentiated tissues.—Herz, J., Y. Chen, I. Masiulis, and L. Zhou. **Expanding functions of lipoprotein receptors. *J. Lipid Res.* 2009.** 50: **S287–S292.**

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Lipid transport through the circulation, the extracellular space, and across the plasma membrane involves the concerted action of a wide range of cell surface receptors, lipid carrier and transfer proteins, enzymes, and cellular transporters. As an evolutionarily ancient process, it probably arose to distribute essential nutritional or endogenously synthesized lipids and hormones but also lipid modified signaling proteins and other associated macromolecules between increasingly metabolically specialized tissues. Lipoprotein receptors are among the oldest components of this complex biochemical system. These cell surface receptors fall into two major groups: endocytic receptors that bind their cargo in the form of lipid carrying lipoproteins and mediate their internalization and eventually lysosomal delivery, and a second group that promotes lipid exchange at the plasma membrane without cellular uptake of the protein component of the particle. In addition to their specialized functions as mediators of cellular lipid uptake, lipoprotein receptors have, over the last few years, also been recognized for often unrelated roles as cellular signal transducers or signal modulators. In this review, we will restrict ourselves to only one particularly versatile subgroup of these receptors, the LDL receptor gene family (**Fig. 1**), and its expanding functions in the nervous system.

ROLES OF THE LDL RECEPTOR GENE FAMILY IN THE NERVOUS SYSTEM

Several members of the LDL receptor gene family are involved in a wide range of signaling pathways that control fundamental developmental processes in the embryo, as well as tissue remodeling in the adult organism. Here, the expanding roles of the gene family in the nervous system deserve particular attention. First, a stream of evidence is emerging that several members of the family are directly or indirectly involved in neuronal survival and degeneration, specifically in the incompletely understood mechanisms that underlie the pathogenesis of Alzheimer's disease (1–5). Second, a wealth of insights into the molecular basis for these roles has emerged over the last few years and this now provides us with several additional unique examples for the molecular mechanisms by which LDL receptor family members participate in the control of the most complex human organ, the brain (6).

Abbreviations: Vldlr, very low-density lipoprotein receptor; Apoer2, apolipoprotein E receptor 2; EGF, epidermal growth factor; PI3K, phosphatidylinositol 3-kinase; PKB/Akt, protein kinase B; GSK3β, glycogen synthase kinase-3β; CrkL, Crk-like; CREB, cAMP-response element binding protein; LRP, LDL receptor-related protein; Dab1, Disabled-1; ICD, intracellular domain; JIP, cJun-N-terminal kinase interacting protein; NMDA, N-methyl-D-aspartic acid; NMDAR, NMDA receptor; PSD, postsynaptic density protein 95; SFK, Src family tyrosine kinase; TSP, thrombospondin; APP, amyloid precursor protein; ApoE, apolipoprotein E; APLP2, amyloid precursor-like protein 2; MUSK, muscle-specific kinase; AchR, acetylcholine receptor.

[1] To whom correspondence should be addressed.
e-mail: joachim.herz@utsouthwestern.edu

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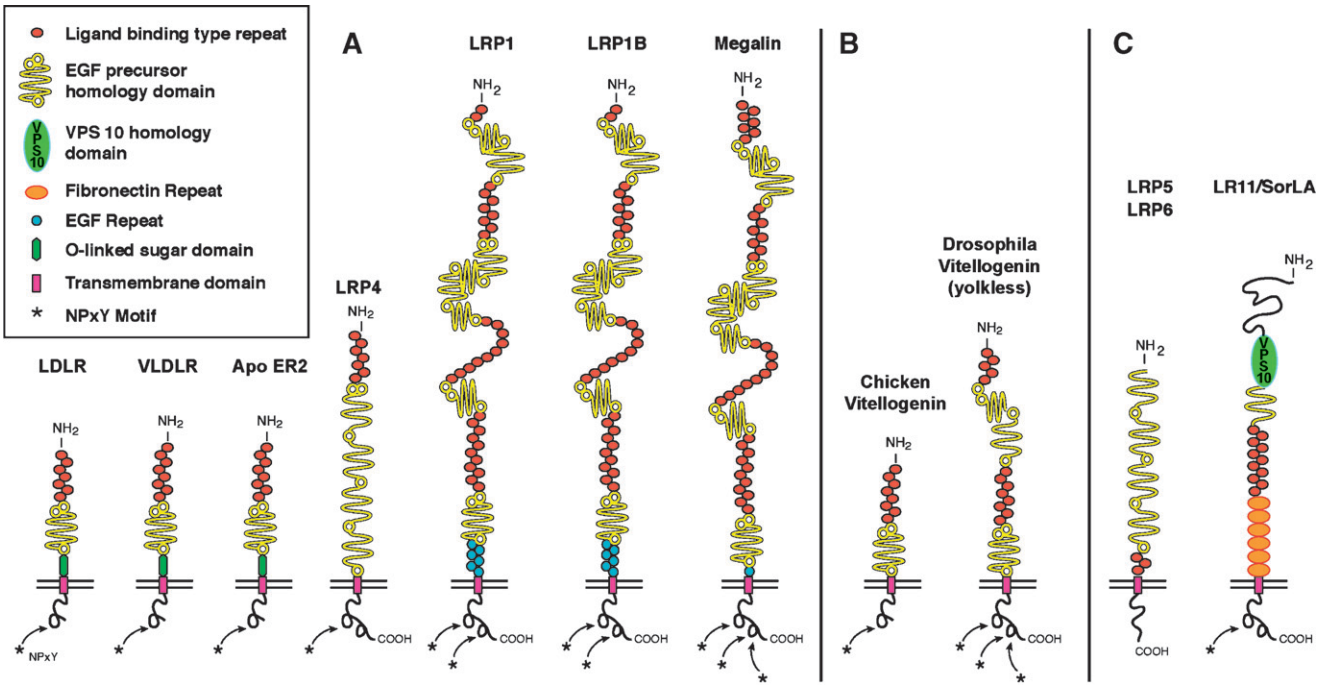

Fig. 1. The LDL receptor gene family. A: The core of the family as it exists in mammalian species. B: Examples for structurally and functionally distinct family members in nonmammalian species. C: Examples for some functionally important, but more distantly related family members that do not fulfill all the structural requirements of the core members. Core family members are characterized by a ligand binding domain of variable repeat length at the N terminus, which is followed by an EGF precursor homology (β-propeller) domain, which is followed by either another ligand binding domain, an *O*-linked sugar domain, or a ligand binding segment, and a cytoplasmic tail containing at least one NPxY tetra-amino acid endocytosis or docking motif.

Apoer2 and Vldlr

The analysis of very low-density lipoprotein receptor (Vldlr) and Apolipoprotein E receptor 2 (Apoer2) knockout mice yielded the first clear example for the deep immersion of LDL receptor family members in the cellular signaling machinery. The molecular mechanisms for this have been reviewed in substantial detail before (7–10). A schematic summary of the signaling pathway that is activated by Apoer2 and Vldlr is also shown in **Fig. 2**.

Reelin binding to Apoer2 and Vldlr controls neuronal migration and positioning during the development of the embryonic brain (11–13). Disruption of this process results in an easily recognizable disorder of laminated brain structures of the lissencephaly type that primarily affects the cortex and the cerebellum and results in ataxia and severe mental retardation. This precludes conclusions about the functions of this signaling pathway in the normal adult brain.

After the end of neuronal migration, Reelin expression switches to a subpopulation of inhibitory interneurons throughout the cortex and hippocampus [reviewed in (7, 8)]. Although the precise role of Reelin in these cells is not yet sufficiently understood, it is likely that Reelin secretion from these neurons involves autocrine or paracrine control of excitatory synapses in principal neurons and in the interneurons themselves. In this manner, Reelin may play a central role in the coordination of neuronal network activity (14), which is critical for learning and memory (15), neuronal survival (16), and protection from hyperexcitation as it occurs in epilepsy (17).

A primary function of Reelin in the mature brain is the regulation of the N-methyl-D-aspartic acid (NMDA) receptor (NMDAR), an ion channel that is necessary for synaptic plasticity, i.e. the strengthening and weakening of synapses in response to variations in excitation [reviewed in (7, 18)]. NMDAR is regulated by tyrosine phosphorylation of the intracellular domain (ICD) of one of its subunits, following signaling by Reelin through Apoer2 (Fig. 2). Functional coupling of the Reelin/Apoer2 complex to NMDAR, i.e. phosphorylation of NR2 subunits by Reelin-activated Src family tyrosine kinases (SFKs), requires the presence of an alternatively spliced exon encoding 59 amino acids, which contains binding sites for the postsynaptic density protein 95 (PSD95) (19, 20) and for cJun-N-terminal kinase interacting proteins (JIPs) (21, 22), in the ICD of Apoer2 (19). Both interactions are probably necessary to properly present activated Src family kinases (23) to the NR2 ICD and to allow the kinase to phosphorylate the NMDAR subunit, resulting in increased synaptic plasticity. Compound deficiency in JIP1 and JIP2 greatly reduces NMDAR phosphorylation levels (24).

Knockin mice lacking the alternatively spliced exon are learning impaired with prominent fear conditioning defects (19). Apoer2-deficient mice, as well as mice lacking this exon, suffer also from accelerated neuronal loss during aging (16), further underscoring the neuroprotective importance of ApoE receptors. Moreover, defects in any of the components of the Reelin signaling pathway, whether in Reelin, Apoer2, Vldlr, or Disabled-1 (Dab1), significantly

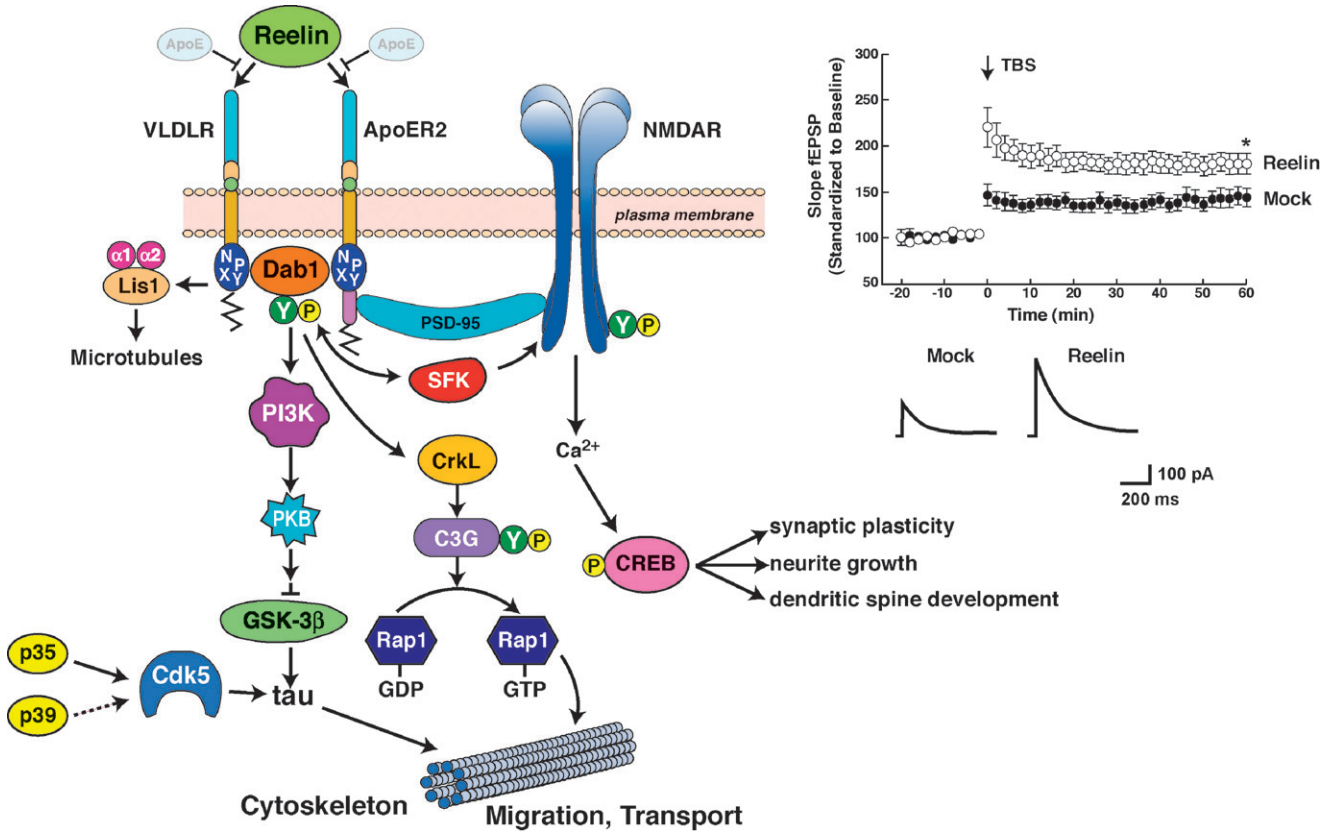

Fig. 2. Reelin signaling through Vldlr and Apoer2 in neurons (modified from Ref. 7). Left panel: Reelin binds to Vldlr and Apoer2 with high affinity at the cell surface and induces phosphorylation and thereby activation of Dab1, an adaptor protein that interacts with NPxY motifs in both receptor tails. Clustering of Dab1 activates SFK, which potentiates tyrosine phosphorylation of Dab1. Phosphorylated Dab1 activates phosphatidylinositol 3-kinase (PI3K) and subsequently protein kinase B (PKB, Akt), which inhibits glycogen synthase kinase-3β (GSK3β) and reduces phosphorylation of τ. Tyrosine-phosphorylated Dab1 can also recruit Crk-like (CrkL), which induces phosphorylation of the guanine nucleotide exchange factor, C3G. Activated C3G promotes the formation of Rap1-GTP, which controls actin cytoskeleton rearrangement. Lis1 can also bind tyrosine-phosphorylated Dab1. It participates in the formation of a Pafah1b complex, which regulates microtubule functions. Cyclin-dependent kinase 5 and its activators p35 and p39 act in parallel with Reelin. Apoer2 associates with the postsynaptic scaffolding protein PSD95 through an alternatively spliced exon. This interaction is critical for the coupling of the Reelin signaling complex to the NMDAR. Reelin-activated SFKs phosphorylate the NMDA receptor on tyrosines in the NR2 subunits, thereby potentiating NMDAR-mediated Ca^{2+} influx. Elevated intracellular Ca^{2+} that has entered the cell through NMDAR activates the transcription and survival factor cAMP-response element binding protein (CREB). This phosphorylation event initiates the expression of genes that are important for synaptic plasticity, neurite growth, and dendritic spine development. Right panel: Reelin potentiates θ burst-induced long-term potentiation (reproduced from Ref. 15). Reelin also enhances NMDAR-mediated whole cell current in wild-type CA1 pyramidal neurons.

increase the pathological phosphorylation of the microtubule stabilizing protein τ at residues that are also abnormally phosphorylated in the brains of Alzheimer's patients (12, 25, 26). Whether abnormal τ phosphorylation contributes to the accelerated neuronal cell death in the Apoer2 mutant mice is currently not known.

In addition to their role in the control of neuronal migration and positioning through Reelin signaling, Apoer2 and Vldlr appear to regulate neuronal chain migration in the rostral migratory stream also through another mechanism involving thrombospondin (TSP)-1. Blake et al. (27) recently reported TSP-1 binding to Apoer2 and Vldlr in the nanomolar range resulting in Dab1 phosphorylation, but, in contrast to activation of the receptors by Reelin, this did not lead to phosphorylation-induced Dab1 degradation or Akt activation. TSP-1 signaling through Apoer2 and Vldlr stabilized neuronal precursor chains in vitro and TSP-1-deficient mice showed abnormalities in their rostral migratory stream. Interaction of TSP-1 and TSP-2 with the Vldlr has also been reported by Oganesian et al. (28), who found a role for these ligands and Vldlr in the growth inhibition of vascular endothelial cells.

LRP1

LDL receptor-related protein 1 (LRP1) modulates signal transduction not only in the vascular wall but also in neurons (29–37). In contrast to Apoer2 and Vldlr, however, the molecular mechanisms by which LRP1 does this are less well understood. One reason for this is that so far, no pathway for LRP1 has been identified that is as clearly genetically and biochemically defined as the Reelin pathway through Apoer2 and Vldlr. Another reason lies in the pleiotropic role of LRP1, which interacts with one of the largest variety of biologically diverse ligands known to date, often resulting in complex phenotypes even in conditional knockout models that can be difficult to inter-

pret. For instance, a neuron-specific knockout of LRP1 using a Synapsin-I-Cre transgenic mouse (33) revealed a striking phenotype characterized by motor defects, hyperactivity, hyperphagia, and increased catabolism with low glucose and low insulin levels. LRP1 was found in the postsynaptic density of excitatory synapses. The role it plays there is not clear but may be related to its ability to interact with the amyloid precursor protein (3). In another forebrain-selective conditional knockout model (32), LRP1 deficiency led to increased amyloid precursor protein (APP) and apolipoprotein E (ApoE) expression. This has been attributed to reduced endocytosis of either ligand by LRP1 (1, 32). Intriguingly, LRP1 levels are increased in APP and amyloid beta precursor-like protein 2 (APLP2) knockout mice, resulting from the loss of transcriptional repression of the LRP1 promoter by the APP cytoplasmic tail (32). The multivalent scaffolding protein FE65 biochemically and genetically interacts with LRP1 and the APP family (2, 38) and is likely involved in this transcriptional repression (32). Moreover, LRP1 and Apoer2, as well as their distant relative, SorL1 (4, 30, 39–41), affect the trafficking of APP, which further emphasizes the intimate involvement of ApoE receptors in the physiological functions and metabolism of APP and, thus, by inference, in the mechanisms that underlie the pathogenesis of Alzheimer's disease.

LRP4

Little had been known about LDL receptor-related protein 4 (LRP4) until relatively recently. It is unique in its size, which lies between the small members of the family (LDLR, Apoer2, and Vldlr) and the large receptors represented by LRP1, LRP1b, and LRP2. Several distinct strains of LRP4 mutant mice have been generated by gene targeting (42, 43). LRP4 loss-of-function mutations have also spontaneously and independently arisen in several viable mouse and cattle strains (43–47). In each of these cases, polysyndactyly, i.e. developmental abnormalities of the distal limbs, is a prominent and easily recognizable symptom of the gene defect. By contrast, in some mouse strains, certain LRP4 loss-of-function defects cause perinatal lethality (47), suggesting that those mutations that allow postnatal development in other strains and in cattle are functional hypomorphs. In those strains in which the animals die immediately after birth, the neuromuscular junctions have failed to form (47) due to the complete failure of acetylcholine receptors clustering. The mechanistic cause for this clustering defect has now been identified by the independent work of two groups (48, 49) who found that LRP4 functions as an obligate coreceptor for the muscle-specific tyrosine kinase (MUSK) and is required for the activation of MUSK by the signaling protein Agrin (**Fig. 3**). This mechanism combines two of the previously discussed distinct functional features that characterize the role of LRPs in cellular signal transduction, i.e. their absolute requirement as unique receptors for certain signaling proteins and their ability to directly or indirectly control the activation of cellular tyrosine or serine/threonine kinases in response to ligand binding. Intriguingly, LRP4 was originally identified as an expressed transcript in the brain, where agrins are also expressed. Thus, it is quite possible that we will find yet another ApoE receptor to have a role in the synapses of the central nervous system. If and how LRP4 might be involved in the mechanisms that are at play in neurodegenerative diseases now poses a new and fascinating question.

In conclusion, in this review, we have attempted to summarize and highlight some of the most prominent principles by which one particular class of lipoprotein receptors, the LDL receptor gene family, functions in the control of an expanding range of fundamental signaling pathways in the nervous system that in many cases are not, or only remotely so, related to lipid metabolism. The role of LDL receptor family members as integrators of sometimes two or more cellular signaling pathways on one hand explains why these receptors have not "outed" themselves earlier in the genetic screens that have proven so invaluable in the definition of the classic morphogenetic signaling pathways in which they are now being identified as indispensable participants. On the other hand, the wealth of these emerging findings now also draws a new picture of this ancient

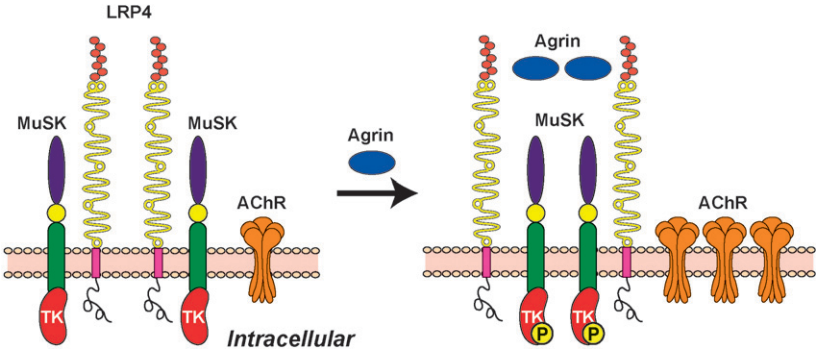

Fig. 3. LRP4 serves as a receptor for agrin and a coreceptor for the tyrosine kinase MUSK in the muscle (48, 49). Activation of the membrane tyrosine kinase MUSK is required for the induction of acetylcholine receptor (AChR) clustering during the formation of neuromuscular junctions (endplates). MUSK forms a complex with LRP4, but does not bind agrin directly. Agrin binding to LRP4 enhances complex formation of MUSK with LRP4 and induces transphosphorylation of MUSK.

gene family that is very different from the traditional one that had been personified by the first member of the family that was discovered and its namesake, the LDL receptor. Understanding the role of these receptors in complex mammalian organisms, and particularly in the brain, will require increasingly sophisticated genetic approaches. Uncovering the perplexing panoply of interdisciplinary roles of this multifunctional gene family and the molecular mechanisms it controls in many highly differentiated and specialized tissues and cell types requires one to isolate them from the essential developmental functions in which they first assert themselves.

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