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Sortilin, a novel APOE receptor implicated in Alzheimer disease

Anne-Sophie Carlo
Max-Delbrueck-Center for Molecular Medicine; Berlin, Germany

In the brain, apolipoprotein E (APOE) delivers cholesterol-rich lipoproteins to neurons to support synaptogenesis and maintenance of synaptic connections. Three *APOE* alleles exist in the human population with ε4 being an Alzheimer disease (AD) risk gene and ε2 being protective relative to the common ε3 variant. Many hypotheses have been advanced concerning allele-specific effects of *APOE* on neurodegeneration including effects on Aβ clearance, synaptic transmission, or neurotoxicity. Central to most proposed APOE functions is its interaction with receptors that mediate cellular uptake of this ligand. Several members of the LDL receptor gene family have been implicated as APOE receptors in the (patho)physiology of APOE in the brain, yet their specific modes of action in AD remain controversial. Recently, the pro-neurotrophin receptor sortilin has been identified as a novel APOE receptor in neurons. Ablation of sortilin expression in mice results in accumulation of APOE and Aβ in the brain. Moreover, primary neurons lacking sortilin exhibit significantly impaired uptake of APOE/Aβ complexes. Despite increased brain APOE levels, sortilin-deficient animals recapitulate anomalies in brain lipid homeostasis seen in APOE null mice, indicating functional deficiency in APOE uptake pathways. Taken together, these findings suggest a link between Aβ catabolism and pro-neurotrophin signaling converging on this receptor pathway.

Keywords: apolipoprotein E, sortilin, Alzheimer disease, amyloid β, neurotrophins, LDLR gene family

Correspondence to: Anne-Sophie Carlo; Email: carlo@mdc-berlin.de

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Introduction

APOE is a 299 amino acid glycoprotein that transports cholesterol and other lipids (such as phospholipids and sulfatides) as part of a lipoprotein complex in the periphery as well as in the central nervous system (CNS). APOE is expressed in several organs, with the highest expression in the liver, followed by the brain. In the brain, APOE is synthesized and secreted primarily by glia and to some extent by microglia.[1,2] However, neurons can also produce APOE under excitotoxic injury.[3] Following secretion into the interstitial fluid, APOE associates with disc-like lipid particles, which are composed of phospholipids and cholesterol. Subsequently, this lipid/APOE complex is endocytosed to deliver cholesterol and other lipids to neurons.

In humans, APOE is encoded by a single gene with 3 polymorphic alleles (ε2, ε3, and ε4) that differ from one another by a single amino acid change. The APOE genotype is the major genetic risk factor for developing late-onset Alzheimer disease (LOAD), with the ε4 allele being an AD risk factor and the ε2 allele being protective.[4,5] Several mechanisms have been suggested by which APOE exerts its isoform-specific effect on brain Aβ levels and amyloid plaque burden. Mainly it acts as a binding chaperone of Aβ thereby modulating Aβ clearance, aggregation, and/or deposition. Common to many hypotheses on the involvement of APOE in neuronal function and AD pathogenesis is the central role of APOE receptors as key regulators of APOE biology

In this review, I will discuss recent findings on APOE receptors and their important contributions to amyloid β clearance. In particular, I will focus on the roles of two established APOE receptors in the brain, called low-density lipoprotein receptor (LDLR) and the LDLR-related protein 1 (LRP1) as well as a newly described APOE receptor termed sortilin.

Low-Density Lipoprotein Receptor (LDLR) Gene Family

The main class of APOE receptors is a group of endocytic receptors called LDLR gene family or LDLR-related proteins (LRPs). These receptors are responsible for cellular uptake of APOE-containing lipoproteins in most cell types in the CNS and in peripheral tissues. Receptor-mediated uptake of APOE-containing lipoproteins serves to deliver cholesterol and other lipids essential for cellular homeostasis such as energy metabolism, membrane biosynthesis, or production of steroid hormones. The LDLR gene family comprises nine closely related surface receptors: LDLR, very-low density lipoprotein receptor (VLDLR), LRP1, LRP1b, LRP2, LRP4, LRP5, LRP6, and LRP8 (**Fig. 1**). The extracellular N terminal domain consists of a conserved arrangement of clusters of complement-type repeats and is the main ligand binding site. The other extracellular domains consist of epidermal growth factor (EGF) homology domains composed of EGF-type repeats and a β-propeller that are involved in the release of ligands in the acidic conditions of the endosomes (for review, see ref. 6). Their cytoplasmic tails contain one to three NPxY motifs, which serve as binding site for adaptors or scaffolding proteins controlling endocytosis and cellular recycling of the receptors. Binding of ligands, such as APOE-containing lipoproteins to the receptor at the cell surface results in internalization of receptor-ligand complexes. Ligands are discharged in lysosomes while the unliganded receptors are recycled to the cell surface to undergo the next endocytic cycle (**Fig. 2A**). The functional relevance of LRPs for the organism is underscored by phenotypes seen in humans and animal models of receptor deficiencies. For instance, the LDLR represents the main pathway for clearance of cholesterol-rich lipoproteins from the circulation. Defects in LDLR function leads to an increase in serum cholesterol levels that correlates with an elevated risk of developing cardiovascular disease in patients.[7] In the nervous system, LRPs involved in the control of brain development and architecture (LRP2, LRP8, VLDLR), in the regulation of synaptic activity (LRP8, LRP1) and as APOE receptors in AD (LDLR, LRP1, VLDLR, LRP8) (for review see ref. 8).

This latter role is supported by the fact that LRPs mediate the clearance of amyloid β (Aβ) bound to APOE. The two main receptors discussed in this context are LDLR and LRP1. Overexpression of the LDL receptor or of the LRP1 mini receptors reduces systemic levels of APOE in the CNS and decreases, in the case of LDLR, amyloid deposition.[9-11] Conversely,

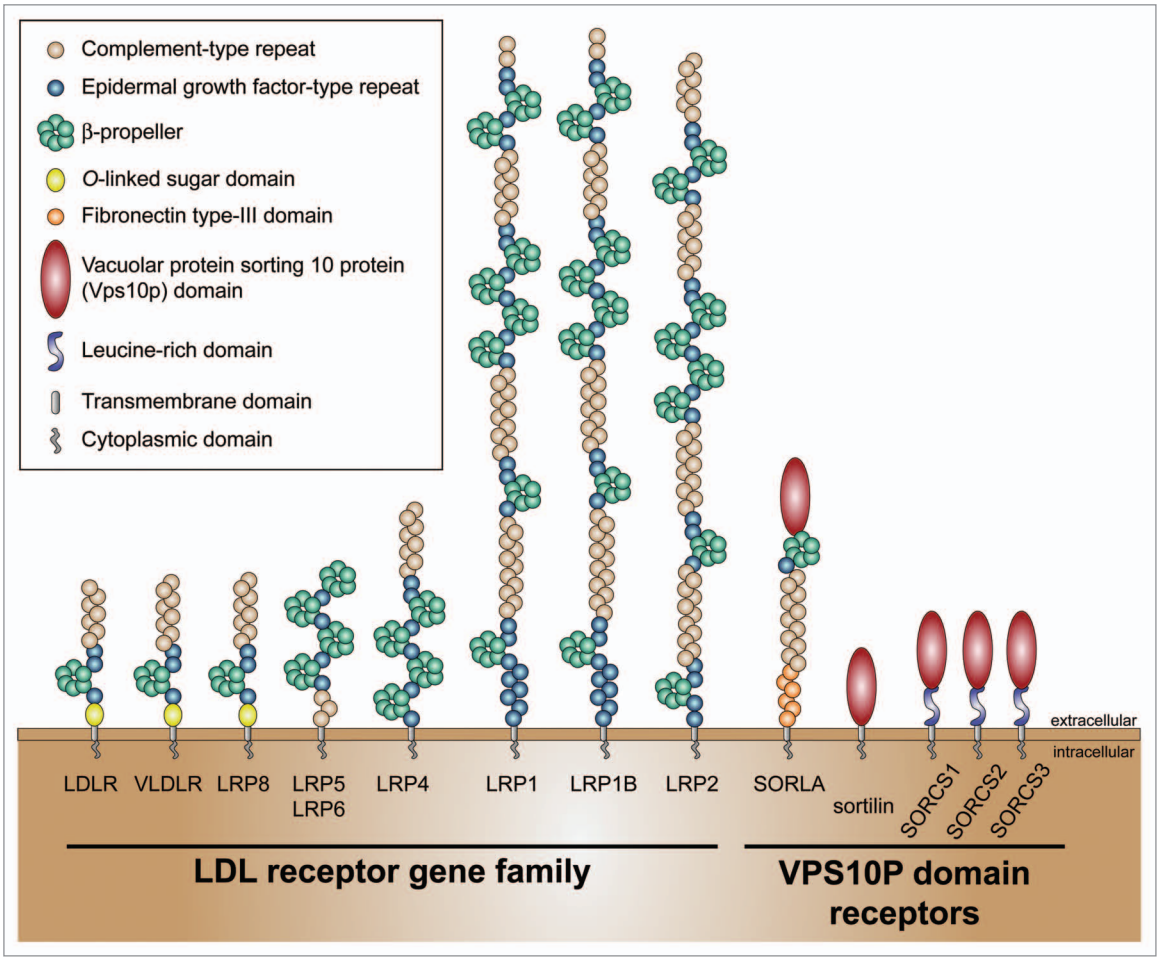

Figure 1. Members of the LDL receptor gene family and VPS10P domain receptors or sortilins. Note that SORLA shares some structural domains with the LDL receptor gene family.

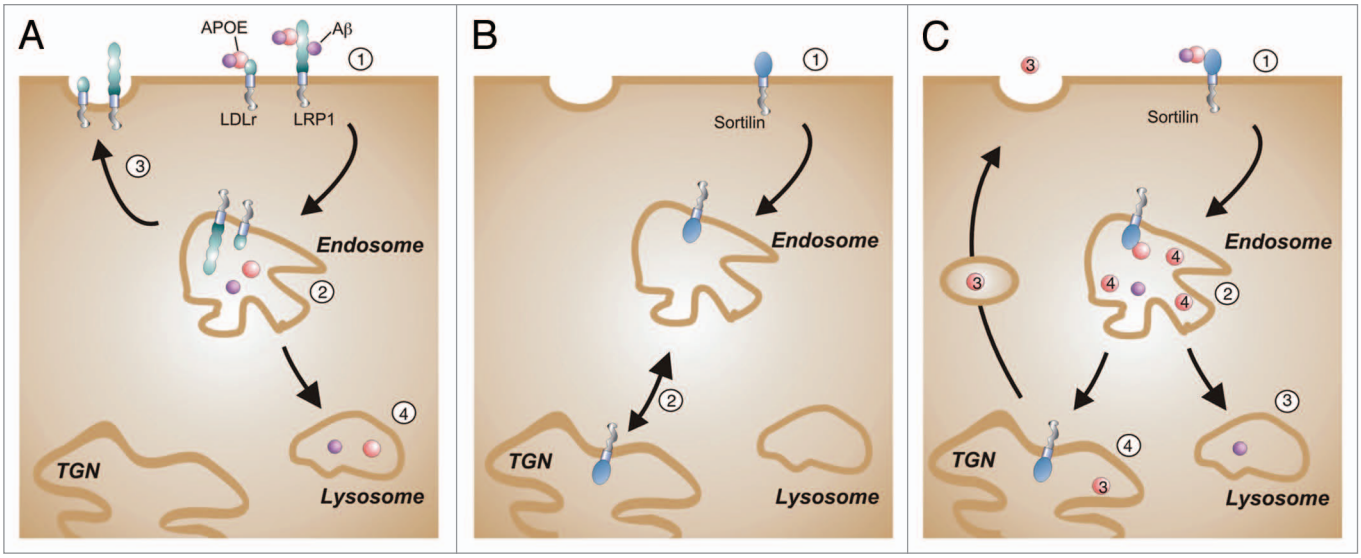

Figure 2. Schematic representation cellular APOE uptake pathways. **(A)** LDLR and LRP1 are classical endocytic receptors. Aβ/APOE complexes associate either with LDLR or LRP1 at the plasma membrane (step 1). Note that Aβ can directly bind to LRP1 while binding to the LDLR is mediated through association of Aβ with APOE. After endocytosis, Aβ and APOE reach the endosomal compartment (step 2), and finally the lysosomes for degradation (step 4) while the receptors are recycled to the cell surface (step 3). **(B)** Sortilin shows a cellular trafficking pathway that is distinct from that of LRPs. Following internalization from the cell surface (step 1) sortilin moves from the endosomal compartment to the trans-Golgi network (TGN), to continue intracellular shuttling between endocytic and secretory organelles (step 2). **(C)** Hypothetical model how sortilin might influence APOE3 and APOE4 trafficking in neurons. After dissociation of the Aβ/APOE complexes in the endosomes (step 2), Aβ and APOE isoforms follow different intracellular routes. Aβ is degraded in the lysosomes (step 3). APOE3 recycles back to cell surface (step 4) but APOE4 is trapped within intracellular compartments, possibly in the endosomes (step 2). Sortilin is a trafficking receptor that has a higher affinity for APOE3 compared with APOE4. Sortilin might thereby release APOE4 already in the endosomal compartment whereas it could traffic APOE3 back to the secretory pathway (step 4)

analysis of mouse models in which Ldlr or Lrp1 have been inactivated showed increased APOE levels in the brain.[6] It is well described that APOE-mediated clearance of Aβ peptides can occur at different locations in the brain. Whereas the LDLR mainly mediates uptake of APOE into microglia and astrocytes, LRP1 constitutes an uptake pathway for APOE in neurons but also at the level of the brain-blood barrier (BBB).[12] Another difference among these two APOE receptors is their specificity to APOE isoforms. In contrast to the LDL receptor, which does not bind APOE2, LRP1 recognizes all APOE isoforms.[13] Also, whereas APOE is the only known ligand for the LDLR in the brain, LRP1 may have a more complex role in brain (patho)physiology since it is able to interact with numerous ligands including amyloid precursor protein (APP; the substrate from which Aβ is derived), free Aβ, as well as Aβ carrier proteins, such as APOE and α_2 macroglobulin (**Fig. 2A**).[6] Contrary to LDLR, LRP1 plays not only a role in Aβ clearance but also in APP internalization, trafficking and processing.[6]

Sortilin, a Novel APOE Receptor with Unique Functions

Sortilin, a novel neuronal receptor pathway

While many studies have focused on the role of LRPs in brain APOE metabolism, recent studies uncovered an unexpected novel type of APOE receptor expressed in neurons, called sortilin.

Sortilin was originally purified from human brain tissue in a quest to identify new lipoprotein receptors.[14] The structural architecture of sortilin was unique among all mammalian surface receptors known but was later classified as part of an entire new class of type 1 receptor expressed in the nervous system called the VPS10P domain receptor family (**Fig. 1**). The structural motif common to all receptors in this family is the VPS10P domain, a 700 amino acid module in the extracellular domain that forms a 10-bladed β propeller, which is conserved from yeast to humans (**Fig. 1**; for review, see ref. 15). This motif represents a site for ligand binding.[16] Surprisingly, despite the different structure of their extracellular domains, sortilin and the LDLR gene family share common ligands including lipoprotein lipase and APOB.[14,17-19]

Although sortilin predominates in neurons of the central and the peripheral nervous systems, it is also expressed in metabolic tissues including liver. Following the association of the human gene locus (SORT1) at 1p13.3 with plasma cholesterol levels and risk of myocardial infarction in several genome-wide association studies (GWASs),[20] sortilin was shown to facilitate hepatic lipoprotein export via binding of APOB100 in the trans-Golgi network.[18] As a result, sortilin ablation leads to disturbances of APOB100 trafficking, to an impaired release of very low-density lipoproteins (VLDL), and ultimately to reduced systemic cholesterol levels.[18] In the CNS, sortilin has a more complex role in neurotrophin signaling: it binds the pro-form of nerve growth factor (NGF; proNGF) and other neurotrophin (NT) precursors (proNTs) that induce cell death in conditions of acute or chronic stress of the nervous system.[21,22] It also has a role in the anterograde trafficking of a class of NT receptors: the tyrosine receptor kinase

(Trk receptors),[23] and sortilin controls the release of proNT (for review see ref. 15). Apart from this involvement in neurotrophin signaling, sortilin is implicated in neurodegenerative disorders. For instance, it mediates the endocytosis of progranulin (PGRN), an etiologic agent in frontotemporal lobar degeneration (FTLD), and delivers it to lysosomes for degradation[24] (**Fig. 2B**). Thus, *Sort1* ablation normalizes PGRN levels in *GRN*$^{+/-}$ mice, a model for FTLD.[24]

Evidence that sortilin is a major neuronal APOE receptor

While the role of sortilin in lipoprotein metabolism had been documented for the liver, it came as a surprise when a similar function for the receptor in brain APOE metabolism was uncovered.[25] This hypothesis was mainly sparked by the findings that mice genetically deficient for the receptor have a profound increase in APOE levels. Specifically, absence of sortilin resulted in a 2-fold increase in the concentration of APOE in the hippocampus and cortex despite normal secretion of the protein from astrocytes.[25] The underlying molecular mechanism was traced to the ability of sortilin to bind and mediate endocytic uptake of APOE. Interestingly, sortilin interacted with all APOE isoforms but a 2-fold lower K_d for binding of APOE3 (44 nM) vs. APOE4 (114 nM) had been noticed.[25] Also, neurotensin, another ligand for sortilin, blocked receptor interaction with APOE3 much more efficiently than with APOE4 (80% vs. 30% inhibition, respectively). Although not fully elucidated, these findings suggest an isoform-specific interaction of sortilin with human APOE.

Together with increased APOE levels, mouse models lacking sortilin also showed increased levels of amyloid accumulation and senile plaque deposition.[25] The quantitative contribution of sortilin to neuronal APOE/Aβ catabolism showed that APOE-dependent uptake of Aβ was impaired in primary neurons lacking sortilin despite normal levels of LRP1,[25] supporting the idea that sortilin is a major receptor for catabolism of Aβ bound to APOE. In contrast to LRP1 and LDLR, sortilin expression in the CNS is restricted to neurons, arguing for a role of sortilin in neuronal Aβ catabolism.

As discussed earlier, APOE plays a key role in transport of cholesterol, phospholipids and sulfatides in the brain. An intact brain lipid metabolism is all the more relevant since dysregulation in lipid homeostasis is believed to contribute to AD pathology (for review, see ref. 26). One of the major consequences of altered APOE activity in the brain is the alteration of the sulfatide content. Sulfatides are sulfated galactosylceramides produced by oligodendrocytes and incorporated into the myelin sheath of axons. APOE-containing lipoproteins extract sulfatides from the myelin sheath and deliver them to neurons for uptake and catabolism via APOE receptors.[27] Consequently, sulfatide levels in the brain are increased in APOE-deficient but decreased in APOE overexpressing mice.[27] Intriguingly, sortilin-deficient mice display the very same increase in sulfatide concentrations as shown for animals lacking APOE, albeit at higher than normal levels of the apolipoprotein.[25,27] In contrast, LRP1-deficient mice do not shown any accumulation of brain sulfatides.[25] Collectively, these data argue for a functional deficiency of APOE in the brain of sortilin-deficient mice.

Perspectives

Recent data document differences in intra-neuronal trafficking of APOE isoforms to underlie their distinct AD risk profiles. Following endocytic uptake by neuronal APOE receptors, APOE3 is largely re-secreted.[28,29] In contrast, APOE4 remains trapped in endocytic compartments for an extended period of time adversely effecting neuronal functions. For instance, Chen and colleagues have shown that APOE4 (but not APOE3) reduces the neuronal surface expression of LRP8, a protein that acts as receptor both for APOE and for reelin.[28] Because reelin signaling protects NMDA and AMPA receptors from the harmful effects of Aβ, APOE-mediated sequestration of LRP8 in intracellular compartments critically reduces the ability of reelin to enhance synaptic glutamate receptor activity. These findings provide an alternative mechanism by which APOE4 may accelerate onset of dementia and neuronal degeneration by differentially impairing the maintenance of synaptic stability.[28]

Yet, the receptors responsible for APOE intracellular trafficking in neurons remain to be determined. Laatsch and coworkers have shown that LRP1 plays a role in APOE trapping and recycling in a hepatoma cell line[29] while in primary cortical neurons LRP8 surface expression is reduced upon APOE4 stimulation.[28] An exciting yet unexplored hypothesis states that sortilin may play a central role on intracellular trafficking of various APOE isoforms as well (**Fig. 2C**). This hypothesis is based on the fact that, contrary to LRPs that recycle between cell surface and endosomes only, sortilin exhibits a more complex cellular trafficking pathway between plasma membrane, endosomes and the TGN. Intracellular routing of the receptor is governed by sorting motifs in the cytoplasmic tail of sortilin such as binding sites for Golgi-associated, γ-adaptin ear containing, ADP-ribosylation factor (ARF)-binding proteins (GGA) adaptor proteins that are essential for sorting target proteins between intracellular organelles.[30] Whether sortilin differentially affects sorting of APOE3 and APOE4 in neurons is a hypothesis that clearly warrants further investigation.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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