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# Trafficking in Alzheimer's Disease: Modulation of APP Transport and Processing by the Transmembrane Proteins LRP1, SorLA, SorCS1c, Sortilin, and Calsyntenin

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**Abstract** The amyloid precursor protein (APP), one key player in Alzheimer's disease (AD), is extensively processed by different proteases. This leads to the generation of diverging fragments including the amyloid β (Aβ) peptide, which accumulates in brains of AD patients. Subcellular trafficking of APP is an important aspect for its proteolytic conversion, since the various secretases which cleave APP are located in different cellular compartments. As a consequence, altered subcellular targeting of APP is thought to directly affect the degree to which Aβ is generated. The mechanisms underlying intracellular APP transport are critical to understand AD pathogenesis and can serve as a target for future pharmacological interventions. In the recent years, a number of APP interacting proteins were identified which are implicated in sorting of APP, thereby influencing APP processing at different angles of the secretory or endocytic pathway. This review provides an update on the proteolytic processing of APP and the interplay of the transmembrane proteins low-density lipoprotein receptor-related protein 1, sortilin-receptor with A-type repeats, SorCS1c, sortilin, and calsyntenin. We discuss the specific interactions with APP, the capacity to modulate the intracellular itinerary and the proteolytic conversion of APP, a possible involvement in the clearance of Aβ, and the implications of these transmembrane proteins in AD and other neurodegenerative diseases.

**Keywords** APP trafficking · LRP1 · SorLA · Sortilin · SorCS1c · Calsyntenin

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## Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive and memory dysfunction, accompanied by hallmark pathologies such as intraneuronal neurofibrillary tangles and extracellular amyloid plaques. The latter are composed of a heterogenous population of proteolytically cleaved amyloid β peptides (Aβ). According to the amyloid hypothesis, accumulation of Aβ in the brain is a primary cause driving AD pathogenesis and reducing Aβ would ameliorate AD symptoms [1]. Although alternative hypotheses have been formulated, mounting genetic evidence strongly suggests that alterations of sequential proteolytic processing of the amyloid precursor protein (APP) have a significant impact on AD pathology [2]. APP is proteolytically processed at many positions. The respective enzymes reside in different subcellular locations. As a consequence, altered subcellular trafficking of APP is thought to directly affect the degree to which Aβ is generated [3]. Therefore, the mechanisms underlying intracellular APP transport are critical to understand AD pathogenesis and can serve as target for future pharmacological interventions.

APP is a type-I transmembrane protein with a large extracellular/luminal moiety and a short cytoplasmic domain. Intracellular sorting, targeting, and internalization of transmembrane proteins are mediated by signals, usually short linear sequences of amino acids, in the cytoplasmic domain which are recognized by cytosolic adaptor proteins. So far,

only a limited number of proteins have been identified that interact with the APP cytosolic domain and that might direct APP targeting [4]. Notably, specific intracellular targeting events can occur independently of the APP intracellular domain, such as the anterograde axonal transport of APP [5, 6]. A number of type-I transmembrane proteins have been demonstrated to modulate the intracellular itinerary of APP, its proteolytic processing and/or clearance of Aβ. Here, we review the proteolytic processing and intracellular transport of APP and summarize current evidence suggesting that transport and processing of APP is modulated by other transmembrane proteins.

## Processing of APP

APP is processed by sequential proteolytic cleavages. The executing enzymes and their subcellular localization have been described, but the exact modalities and the functional meaning of the different processing steps are still not fully delineated.

The canonical processing of APP is described by the amyloidogenic and the non-amyloidogenic pathway (Fig. 1a). The latter begins with cleavage of full-length APP by α-secretase activity, which is mainly mediated by ADAM10 (A Disintegrin And Metalloprotease 10) in neurons, but also ADAM17 has been implicated in this cleavage step [7–9]. Cleavage by α-secretase results in the release of the ectodomain of APP—soluble APPα (sAPPα)—and the concomitant generation of a membrane retained C-terminal fragment (CTF) consisting of 83 amino acids (aa) (C83 or α-CTF; reviewed in [10]). C83 is further processed by γ-secretase, a transmembrane multiprotein complex consisting of four subunits: presenilin 1 or 2, nicastrin, APH-1, and PEN-2. γ-Secretase cleaves within the transmembrane domain, a mechanism termed "regulated intramembrane proteolysis" (RIP; reviewed in [11]). APP CTFs are proteolytically processed at three positions: first at the ε-cleavage site, then the ζ-cleavage site, and finally, at the γ-cleavage site [12–15]. This leads to the release of a short peptide termed "p3" and of the APP intracellular domain (AICD) [16]. Instead of α-/γ-secretase processing, APP can also be cleaved in the amyloidogenic pathway (Fig. 1a). Here, it is first cleaved N-terminally of the Aβ sequence by the β-secretase β-site APP cleaving enzyme 1 (BACE1) [17, 18]. This results in shedding of the APP ectodomain—soluble APPβ (sAPPβ)—and the production of a 99 aa CTF (C99 or β-CTF) [19]. C99 is subsequently cleaved by γ-secretase, releasing the Aβ peptide and AICD [13, 14]. Approximately 90% of the secreted Aβ peptides are 40 aa long (Aβ40) [20]. The second most common species of Aβ, Aβ42, is more prone to aggregation than Aβ40 [21]. Aggregation of Aβ to oligomeric forms and finally so-called amyloid plaques has been proposed to be the initial step in the development of AD [22]. Thus, a shift in the ratio of Aβ40 to Aβ42 towards Aβ42 is most likely explained by a decrease of γ-secretase cleavage site specificity [23, 24], which affects the age of onset of AD [25]. ε-Cleavage occurs mainly at the carboxyl side of leucine49 of the Aβ sequence whereas cleavage at threonine48 is not as frequent [26]. Those are the starting points for two main product lines of γ-secretase cleavage. ε-Cleavage producing Aβ49, is followed by proteolytic conversion into Aβ46 (ζ-cleavage) [12] and Aβ43, finally ending in secretion of Aβ40 while ε-Cleavage generating Aβ48 is further cleaved into Aβ45 and finally Aβ42 and Aβ38.

Recently, three different non-canonical processing pathways were described, which start with cleavages N-terminally located to the β-secretase cleavage site (reviewed in [27]).

(I) APP can first be cleaved at the recently identified η (eta)-cleavage site 504/505 by matrix metalloproteinase 5 (MT5), also named matrix metallopeptidase 24 (MMP24) [28–31] (Fig. 1b). Subsequently, β- or α-secretase generate two peptides of 92 or 108 amino acids in length, designated as Aη-β or Aη-α peptides, respectively [28]. MT5 is a zinc-dependent metalloprotease-like ADAM10 [32] and belongs to the group of membrane type MMPs, which are mainly located at the cell surface [33] (Fig. 2). Those type-I transmembrane MMPs are activated after furin cleavage in the *trans*-Golgi network (TGN) and therefore presumably active at the plasma membrane [34]. MT5 is predominantly expressed in brain tissue and might play a role in remodeling extracellular matrices during development [35].

(II) Three different cleavages summarized as δ-cleavage are carried out by asparagine endopeptidase (AEP), a pH-dependent soluble cysteine protease, which is active in lysosomes (Fig. 2). Cleavage of APP at Thr584 was first described in [36]; later, two additional sites were found in the ectodomain at positions N373 and N585 (APP695 numbering) (Fig. 1c) [37].

(III) APP can also be shed by Meprinβ at the cell surface, thereby competing with ADAM10 for the substrate (Fig. 2) [38, 39]. Meprinβ is a zinc-dependent metalloprotease-like [40] ADAM10 and MT5 and cleaves APP at positions 1, 2, or 3 of the Aβ sequence [41, 42]. Three additional Meprinβ cleavage sites have been identified further distal in the ectodomain of APP between Ala124/Asp125, Glu380/Thr381, and Gly383/Asp384 (Fig. 1d) [42].

Canonical and non-canonical processing of APP is mediated by enzymes with proteolytic activities at varying subcellular localizations. Depending on its subunit composition, the subcellular localization of the γ-secretase complex differs. A γ-secretase complex comprising presenilin 1 is distributed in the secretory and endocytic pathway and is concentrated at the cell surface, whereas a complex formed with presenilin 2 predominates in late endosomal and lysosomal compartments

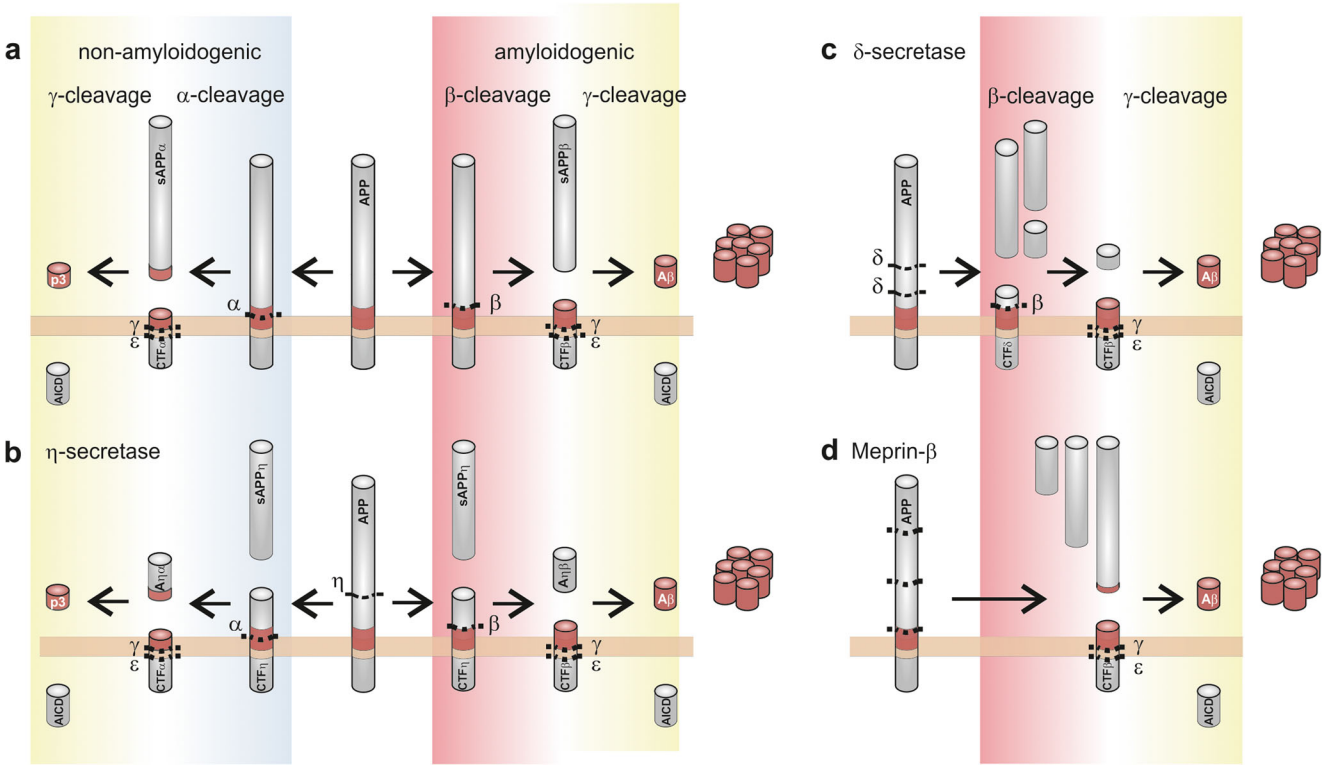


**Fig. 1** Schematic representation of different APP processing pathways. **a** The schematic shows the canonical APP processing pathways and the pictures (**b**–**d**) show the non-canonical pathways. **a** The amyloid precursor protein (APP) is first cleaved by α-secretase in the non-amyloidogenic pathway (gray) within the amyloid-β (Aβ) region (shown in red) to liberate sAPPα. The remaining α-C-terminal fragment (α-CTF) is further cleaved by γ-secretase (yellow) and releases the small 3-kDa peptide p3 and the APP intracellular domain (AICD). The amyloidogenic pathway (pink) starts with β-secretase cleavage, which liberates sAPPβ and concomitantly generates the β-C-terminal fragment (β-CTF). γ-Secretase cleavage (yellow) of the β-CTF releases the Aβ peptide, which can oligomerize and liberates the APP intracellular domain at the ε-cleavage site (AICD). **b** Cleavage by η-secretase gives rise to the 80–95 kDa soluble APPsη and CTFη, which is further processed by α- or β-secretase to generate Aη-α or Aη-β. **c** δ-Secretase generates three soluble APPsδ fragments and C-terminal fragment-δ (CTFδ), which is further cleaved by β-secretase and γ-secretase. **d** Meprinβ cleaves APP at positions 1, 2, or 3 of the Aβ sequence. Three additional Meprinβ cleavage sites have been identified further distal in the ectodomain of APP between Ala124/Asp125, Glu380/Thr381, and Gly383/Asp384. The indicated numbers refer to full-length APP695

[43, 44]. While α-secretase, MT5, and Meprinβ activity is mainly localized to the cellular surface [34, 38], β-secretase activity is predominantly found in endosomal compartments and δ-cleavage occurs in lysosomes (Fig. 2) [8, 17, 37, 45, 46]. Therefore, processing of APP into amyloidogenic (Aβ) and non-amyloidogenic fragments is highly dependent on its intracellular itinerary. Consequently, altered subcellular targeting of APP directly affects the degree of Aβ generation. Thus, mistargeting of APP has been realized to cause amyloidogenic processing and a number of factors that are involved in APP subcellular targeting have been identified. Mutations in APP or in components of the γ-secretase complex lead to an increase in Aβ42 production and cause the rare early onset familial form of AD (EOAD). These genetic defects are usually not seen in the late onset form of AD (LOAD) accounting for 95% of all cases [47]. Mutations in factors that partake in APP subcellular targeting may underlie the complex pathology of LOAD. Accordingly, some of these factors discussed in this review have been genetically linked to LOAD.

## Trafficking and Endocytosis of APP

The intracellular itinerary of APP has been extensively studied in undifferentiated cells [48]. After cleavage of its signal peptide in the ER, APP enters the secretory pathway and is translocated through the Golgi apparatus, where it is predominantly localized [49–51], to the plasma membrane (Fig. 2). Here, it can be processed or internalized. Following endocytosis, APP is targeted to early endosomes and then sorted to three different paths: (I) a subset of APP molecules undergoes recycling to the cell surface [48, 52], (II) a different fraction of APP is transported retrogradely from endosomes back to the TGN in a retromer-mediated pathway [53], and (III) some APP molecules are targeted to late endosomes which fuse with lysosomes where APP is degraded [54, 55]. APP is mainly endocytosed via clathrin-coated vesicles into early endosomes [4] and internalization of APP also depends on cholesterol [56, 57], suggesting an overlap of clathrin- and cholesterol-dependent endocytosis [57]. Thus, APP might be first

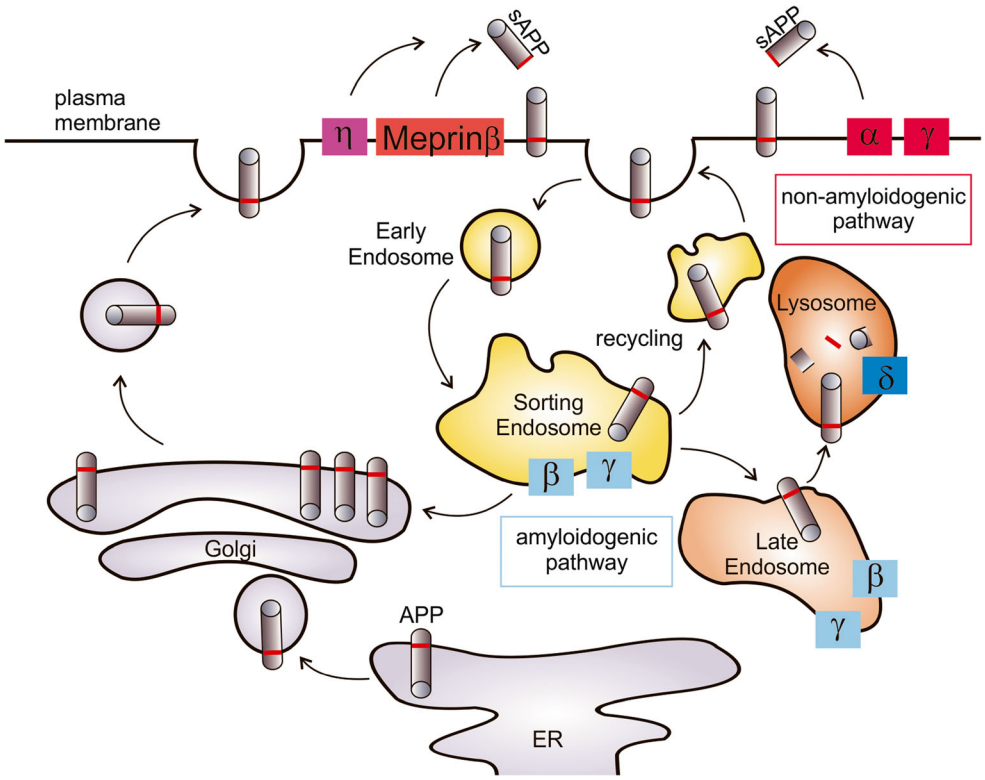


**Fig. 2** APP trafficking and processing. APP is transported in the secretory pathway (gray) from the ER to the plasma membrane via the Golgi apparatus, where it is mainly localized. APP is internalized from the plasma membrane to early endosomes. From there, it can either enter the recycling pathway (yellow) or travel back to the TGN in a retromer-mediated pathway, or can be targeted to late endosomes which fuse to lysosomes where APP is degraded (orange). APP cleavage by η-secretase or Meprinβ mainly takes place at the plasma membrane as well as non-amyloidogenic processing by α- and γ-secretase. Amyloidogenic processing of APP by β- and γ-secretase is predominantly carried out in early and late endosomes and cleavage of δ-secretase in lysosomes

clustered in cholesterol-rich-coated pits and then internalized into a specialized clathrin-dependent endocytic pathway.

Although, it has been shown that the highly conserved YENPTY motif in the C-terminus and possibly also the basolateral sorting signal of APP are essential for this process [58], the molecular machinery involved in clustering and targeting of APP to early endosomes is still unknown.

## Anterograde Axonal Transport of APP

APP trafficking has also been studied in differentiated cells with a focus on neurons and axonal transport. APP moves along axons by fast anterograde transport as shown by nerve ligation [59] and pulse-chase labeling experiments [60, 61].

Live cell imaging studies documented fast axonal transport of vesicular APP distinct in morphology and transport kinetics from synaptophysin-containing vesicles [62]. Consistently, synaptophysin was not found in APP kinesin co-immunoisolations [6]. Gene-silencing experiments indicated that conventional kinesin is the main molecular motor involved in the anterograde transport of APP [59, 63, 64]. Conventional kinesin is a multimeric complex composed of two kinesin heavy chain (KHCs, kinesin-1s) and two kinesin light chain (KLCs) subunits [65]. In mammalian brain, three KHCs (kinesin-1a, b, and c) and two KLC (KLC1 and KLC2) isoforms are expressed, which exist in different combinations of kinesin-1 and KLC homodimers [66]. Kinesin-1C has been identified as the main KHC isoform associated with APP-containing transport vesicles [6]. The mode of interaction between conventional kinesin and APP-containing transport vesicles is still unclear. In general, the alternatively spliced carboxy-terminus of KLCs is assumed to mediate selective binding of conventional kinesin to different membrane-bound organelles [67–69], whereas the tandem repeat containing N-terminus can interact in vitro via hydrophobic patches non-specifically with different target proteins, including APP [70, 71]. So, it was shown that recombinant KLCs produced in bacteria interact non-specifically with proteins as diverse as GFP, Fe65, and PAT1a and the intracellular domain of APP, APLP1, and APLP2 in pull-down assays [71]. Also, indirect associations of APP to kinesin-1 via adaptor proteins, such as JIP1b were reported [72–74]. Current data showed that knockdown of JIP1b either specifically impairs anterograde transport [74], anterograde, and retrograde transport [75] or affects

neither anterograde nor retrograde transport of APP [76]. Further, JIP1b APP binding studies revealed at least two interaction sites in KLC1 and/or KHC. Also, deletion mutants of JIP1b argue for multiple interaction sites for KLC1 [74]. In light of these inconsistencies and the increasing list of candidate protein-binding partners for both KIF5s and KLCs [70], the in vivo significance of JIP1b as an adaptor partner has not yet been rigorously established. Instead, indirect influences of JIP1b on activation of kinases that in turn might modulate kinesin-dependent transport should be taken into account.

Moreover, in contradiction to the model of direct or indirect interaction of the APP C-terminus with KLC1, APP is transported independently of its carboxy-terminus along the axon towards the presynaptic terminal [5, 6, 36, 77]. Thus, APP does not fulfill the criteria expected for a conventional kinesin receptor. Instead, APP most likely represents a cargo protein sorted into transport vesicles associated by a so far barely understood Rab3-dependent mechanism to kinesin-1c [6].

## Modulators of Intracellular APP Transport

Intracellular transport and processing of APP can be modulated by other transmembrane proteins, such as low-density lipoprotein receptors (LDLRs), Vps10p-Doamin (Vps10p-D) receptors, and calsyntenins. LDLRs are mainly known as endocytic receptors for a wide variety of ligands, including lipid-carrying lipoproteins and proteases or protease inhibitors, but some family members also play a role in signal transduction and modulation [78–80]. Ligands endocytosed by LDLR family members are directed to endosomes and recycling or lysosomal compartments, while the receptors themselves are transported back to the plasma membrane [81, 82].

In mammals, there are seven core members of the LDLR family which vary in size and structure [80, 83]. All family members are type-I transmembrane proteins with large extracellular moieties and a short cytoplasmic domain. The extracellular domains consist of ligand-binding repeats (also named complement type repeats) and epidermal growth factor (EGF) homology domains (Fig. 3). The intracellular domain harbors at least one NPxY motif. Some family members contain additional structural elements that separate them from the core members. Sortilin-receptor with A-type repeats (SorLA) for example contains in addition a domain homologous to a sorting receptor for yeast vacuolar hydrolases that cycles between the TGN and endocytic compartments (Vps10p) [84]. SorLA is a unique mosaic receptor [85, 86] which combines structural features of the LDLR family by harboring EGF-type and ligand-binding repeats but presents as well the hallmark of the Vps10p-D receptor family, an N-terminal Vps10p-D [87] (Fig. 3). Additionally, SorLA contains a fibronectin type III domain, the exact function of which is still elusive but might be involved in protein-protein interactions [88]. Vps10p-D receptors are also type-I transmembrane proteins. Their large extracellular/luminal moieties contain a Vps10p-D and their short cytoplasmic domains harbor canonical motifs for intracellular sorting. The Vps10p-D makes up the entire extracellular/luminal part of sortilin and is combined with a so-called leucine-rich domain in SorCS1–3 (Fig. 3). Structural features are thought to be shared among all Vps10p-D receptors. The N-terminal part of the sortilin Vps10p-D comprises a ten-bladed β-propeller creating a large tunnel with multiple ligand-binding sites which is followed by the so-called ten conserved cysteines (10CC) domain [87, 89]. This C-terminal segment of 10CC forms five disulfide bonds [89, 90], but the amino acid identity among all Vps10p-Ds is only modest, but high for SorCS1–3 and separates the SorCS subgroup from sortilin and SorLA [87].

The third group of type-I transmembrane proteins modulating APP transport and discussed in this review are calsyntenins (calsyntenin 1–3, Clstn 1–3). These were initially isolated as postsynaptic $Ca^{2+}$-binding proteins [91] and have been also named Alcadeinα, β, and γ. They belong to the Cadherin-related family comprised of atypical Cadherins [92]. Their extracellular moiety is characterized by a repeat of two Cadherin-like domains [91, 93], an LNS domain (laminin, nectin, sex hormone-binding globulin) [94] and kinesin light chain-binding motifs in their cytoplasmic domains [95, 96]. Calsyntenin-1 and -2 contain two KLC1-binding motifs consisting of a WDDS sequence, while calsyntenin-3 is lacking one KLC1-binding motif [93]. Calsyntenin-1 and -2 additionally harbor a c-terminal calcium-binding site via an acidic amino acid stretch, which is shorter in calsyntenin-2 than in calsyntenin-1 [91, 93, 97].

### Low-Density Lipoprotein Receptor-Related Protein 1

Multiple members of the LDLR family have been shown to influence APP physiology with the focus resting on low-density lipoprotein receptor-related protein 1 (LRP1) [83]. LRP1 is one of the largest gene family members with a size of approximately 600 kDa and four extracellular ligand-binding domains [98]. Like APP, LRP1 is transported along the constitutive secretory pathway. Native LRP1 is cleaved in the *trans*-Golgi by furin into a 515 kDa α-subunit and an 85 kDa β-subunit, which stay attached in a non-covalent manner [99, 100]. LRP1 has been shown to bind numerous different ligands to its extracellular domain [101], including APP, apolipoprotein E (apoE), and α2-macroglobulin (α2M), which are all proteins associated with AD [102–104]. Furthermore, LRP1 itself has been identified as a risk factor for AD [105].

LRP1 associates with APP through the N-terminal Kunitz-protease inhibitor (KPI) domain of APP [106, 107] and the

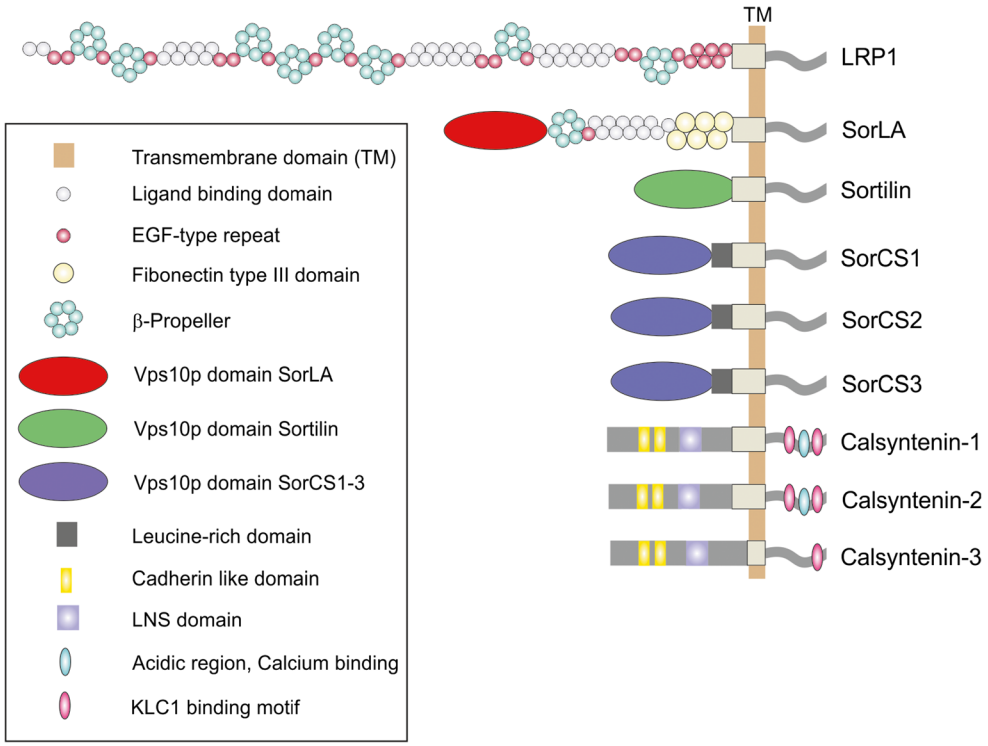


**Fig. 3** Schematic representation and domain structure of LRP1, members of the Vps10p-D receptor family and calsyntenin-1–3. Low-density lipoprotein receptor-related protein 1 (LRP1) is a type-I transmembrane protein. The extracellular domain consists of four ligand-binding repeats (also named complement type repeats) and epidermal growth factor (EGF) homology domains and β-propeller domains, which are important for pH-dependent release of bound ligands in endosomes. SorLA, sortilin, and SorCS1–3 are members of the vacuolar protein sorting 10 protein (Vps10p) domain receptor family. SorLA contains two additional types of domains not present in LRP1: the fibronectin type III domain and the Vps10p domain. The extracellular domain of sortilin is comprised solely of the Vps10p domain while SorCS1–3 contain an additional leucine-rich domain in the juxtamembrane region. The amino acid identity among all Vps10p-Ds is only modest, but high for SorCS1–3 and separates the SorCS subgroup from sortilin and SorLA. Calsyntenin 1–3 contain two cadherin-like domains in the ectodomain and one laminin, nectin, sex hormone (LNS) binding globulin) domain. Calsyntenin-1 and -2 contain an acidic region, which is able to bind calcium in their cytoplasmic tail and two KLC1 binding motifs. The acidic region and one KLC1 binding motif are lacking in Calsyntenin-3

APP C-terminal cytoplasmic domain [108]. As neurons express mainly APP695 lacking the KPI domain [109], the C-terminal interaction with APP appears more relevant in respect to brain function. The cytosolic interaction between APP and LRP1 is assumed to be mediated by the scaffolding protein Fe65, which binds with its PTB1 domain to the NPxY motif of LRP1 and with the PTB2 domain to the NPxY motif in the C-terminus of APP [108, 110, 111].

The LRP1 cytoplasmic tail contains two NPxY motifs, of which the distal motif is thought to be involved in its very fast endocytosis, with a half-life time of less than 30 s at the cell surface [112, 113]. LRP1 increases APP endocytosis and causes consistently an increased secretion of Aβ and sAPPβ, while a lack of LRP1 increases sAPPα (Fig. 4) [106, 111, 114–116]. Notably, this holds true for APP in its monomeric and dimeric form [117], although LRP1 binding to APP was significantly decreased after inducing dimerization of APP [118], which presumably affects APP trafficking.

Interestingly, the influence of LRP1B on APP processing is contrary to what is shown for LRP1 [119]. Both, LRP1 and LRP1B, are highly expressed in the brain [120–122] and LRP1 and LRP1B only differ from each other in one additional ligand binding type repeat in ligand binding domain IV of LRP1B and a larger distance between the NPxY motifs [123]. Even though these differences are subtle, LRP1B has much slower internalization kinetics than LRP1 [123]. Assuming, that LRP1B competes with LRP1 for binding to the Fe65-APP complex, APP would be endocytosed at a lower rate, explaining the increase of sAPPα and the decrease in Aβ (Fig. 2) [119]. However, other LDLR family members, such as VLDL could act similarly [124].

Accumulating evidence suggests that LRP1 affects APP transport also in the secretory pathway (Fig. 4). APP interacts with LRP1 before it is cleaved by furin, implying an interaction of APP with LRP1 early in the secretory pathway [111]. Accordingly, APP still binds LRP1 when a dilysine ER-retention motif (KKAA) is introduced to the LRP1

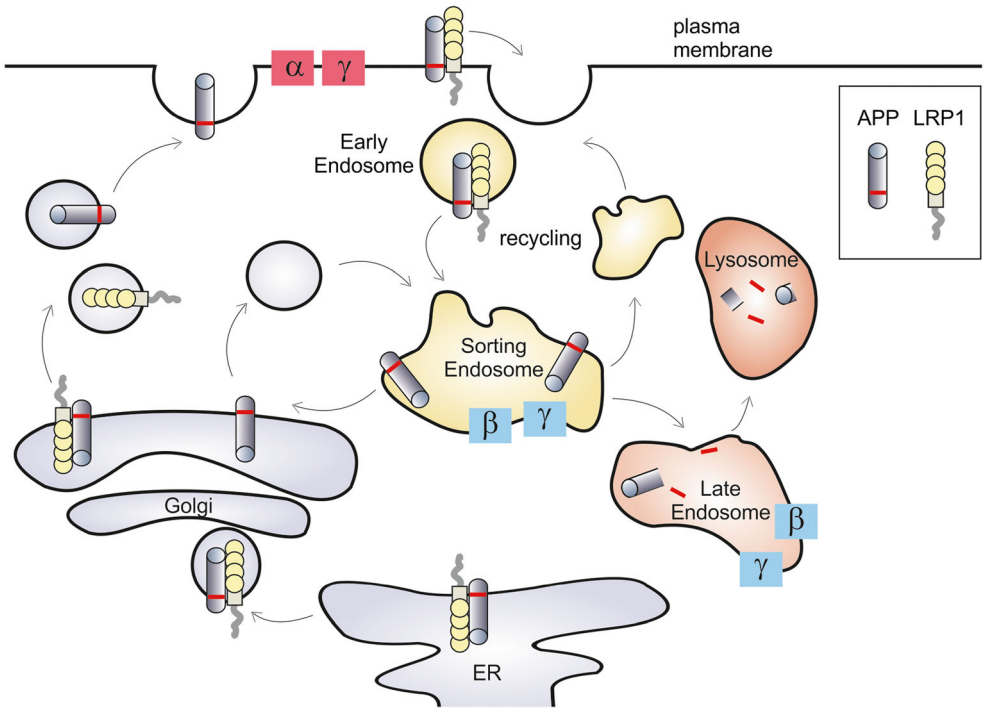


**Fig. 4** LRP1 modulates APP trafficking. APP interacts with LRP1 presumably early in the secretory pathway before LRP1 is cleaved by furin in the TGN. APP and LRP1 are trafficking in different transport vesicles in anterograde direction to the cell surface, APP with faster transport kinetics. Internalization of APP is facilitated by LRP1, which associates with APP on the cell surface, thereby increasing sAPPβ and Aβ production

cytoplasmic domain [100]. Moreover, co-localization and co-transport of LRP1 and APP along the secretory pathway has been reported recently [117]. Live cell imaging analyses revealed that LRP1 and APP are trafficked in distinct anterograde transport vesicles, whereby LRP1 is transported with velocities ≤ 1 μm/s and APP with velocities ≥ 1 μm/s. However, elevated expression levels of LRP1 altered APP transport kinetics to those observed for LRP1 before. In contrast, lowered levels of LRP1 lead to a significant decrease in APP stationary vesicles and to a significant increased mean velocity [117]. This strongly suggests that LRP1 affects APP transport by recruitment of APP into common transport vesicles, thereby regulating its cell surface localization and in turn, its processing by proteases located at the plasma membrane, including ADAM10, MT5-MMP, and Meprinβ.

LRP1 can be proteolytically processed and might therefore affect APP physiology and pathogenicity not only by modulating its transport kinetics but also through competition with APP for the secretase BACE1 [125, 126] and γ-secretase [127, 128].

Further, multiple studies showed that Aβ is taken up by LRP1 either through direct binding to the LRP1 N-terminal domain [129, 130] or bound to ApoE or α2M [131]. Here, LRP1 was demonstrated to function as one of the major Aβ clearance receptors from brain to blood through transcytotic transport over the blood-brain-barrier [132–134]. Also, LRP1 was shown to bind Aβ in the blood and to target it for degradation [135] and to play an important role in cellular uptake of Aβ in microglia [136].

Taken together, the actual data strongly argue that besides its role in endocytosis, LRP1 functions as a sorting receptor for APP, recruiting APP to specific transport vesicles. Here, LRP1 interestingly affects both, the secretory as well as the endocytic pathway, which might be pivotal for sorting in bipolar cells.

## Sortilin-Related Receptor Containing LDLR A Repeats

SorLA (also termed "LR11" or "SORL1") is a 250-kDa type-I transmembrane protein [85, 86] (Fig. 3) that shares several ligands with the LDL receptor family, including apolipoprotein E (ApoE), apolipoprotein A-V, LDLR-associated protein (RAP), lipoprotein lipase, platelet-derived growth factor-BB (PDGF-BB), and components of the plasminogen-activating system, such as urokinase-type plasminogen activator (uPA) and tissue-type plasminogen activator (tPA) [137–140]. These ligands probably all bind to the cluster of 11 complement-type repeats (CR) of SorLA (Fig. 3) [140, 141]. The Vps10p-D of SorLA functions as an additional ligand-binding domain. It specifically binds a variety of growth factors and neuropeptides including neurotensin, glial cell-derived neurotrophic factor (GDNF), ciliary neurotrophic factor (CNTF), and interleukin-6 [90, 141–143]. SorLA binds APP directly and sequesters APP in intracellular compartments which results in reduced processing into Aβ [144]. The interaction has been mapped to the carbohydrate (E2) domain of APP and the CR domains 5–8 of SorLA [144, 145]. Deletion of the CR cluster abolishes the ability of SorLA to protect APP from processing [145]. Moreover, a second interaction site involving the

cytoplasmic domains of APP and SorLA has been proposed [146]. As outlined above, the Vps10p-D of SorLA functions as an independent ligand-binding site. It binds monomeric Aβ in a pH-dependent manner and is thought to facilitate its subcellular targeting to lysosomes [147, 148]. This interaction seems specific for the SorLA Vps10p-D as the Vps10p-D of sortilin has been incapable to bind Aβ [147].

SorLA is highly expressed in the brain where it shows predominant localization in neurons of the cerebral cortex, hippocampus, and cerebellum, but it is expressed as well in a variety of other organs [149]. Genetic analysis revealed that SorLA modulates the risk for late onset as well as early onset AD (reviewed in [150]). SorLA expression levels are reduced in brains of AD patients as compared to healthy non-demented subjects [151]. Mouse models supported the significance of SorLA as a negative regulator of APP processing in vivo because knockout mice exhibit higher Aβ-levels in the brain as compared with wild-type mice [152]. Moreover, overexpression of SorLA in neurons decreased Aβ levels [152]. Taken together, the current data support the notion that SorLA is a sorting receptor for APP and Aβ. Thus, understanding the determinants of SorLA's subcellular itinerary is key to understand APP processing and degradation of monomeric Aβ.

On a subcellular level, SorLA is mainly localized to Golgi compartments and endosomes and only a minor fraction is present on the cellular surface [141, 153, 154]. This localization has been observed in undifferentiated cells [141] and recent studies demonstrated a predominant somatic-dendritic localization of SorLA in neurons and targeting of SorLA to the basolateral membrane and to sorting endosomes in polarized MDCK cells [155].

SorLA is synthesized as a precursor and converted in the *trans*-Golgi network to mature receptor by proprotein convertase-mediated cleavage and subsequent dissociation of its N-terminal propeptide which is a prerequisite for binding of exogenous ligands to its Vps10p-D [141]. Ectodomain shedding followed by regulated intramembrane proteolysis as described for APP has been also observed for SorLA. It serves as a substrate for ADAM17, whose active site is located in the aqueous environment of the extracellular domain and can function as α-secretase which can be stimulated by phorbol esters or by some ligands. PDGF-BB, for example, stimulates shedding of SorLA, whereas other ligands have no effect [156]. The primary cleavage elicits subsequent gamma-secretase-mediated proteolysis within the transmembrane segment. This cleavage releases the cytoplasmic domain, which is rapidly degraded [156, 157]. Interestingly, a nuclear localization of the SorLA cytoplasmic domain fused to green fluorescent protein was demonstrated and a transcriptional activity of the SorLA cytoplasmic domain suggested [157].

SorLA conveys rapid internalization of ligands, but as compared to LRP1, SorLA is endocytosed more slowly [140]. SorLA contains canonical cytoplasmic interaction motifs and a number of cytosolic adaptors have been identified. It has been demonstrated that internalization of SorLA depends on an acidic cluster and on adaptor protein-2 (AP-2) interaction [158]. SorLA binds additional cytosolic adaptors, including AP-1; Golgi-localized, gamma adaptin ear-containing, ARF-binding (GGAs); phosphofurin acidic cluster sorting protein 1 (PACS1), and retromer, which govern the itinerary between TGN and endosomal compartments. The acidic cluster of the SorLA cytoplasmic domain is a functional interaction motif for AP-1 and PACS1 [158, 159]. Both adaptors are engaged in retrograde endosome to TGN sorting and deletion of one of the adaptors results in an altered subcellular localization of SorLA [158, 159]. The interaction of AP-1 with the acidic cluster and additional amino acids in SorLA's cytoplasmic domain underlie the polarized distribution of SorLA in neurons and other polarized cells [155]. Anterograde Golgi to endosome sorting of SorLA depends on the acidic cluster combined with a dileucine motif and on the GGA-binding motif DXXM [158]. GGA1 and GGA2 interact with SorLA and have been suggested to guide this type of sorting [158–161]. However, disruption of the GGA interaction motif in mice in vivo had no impact on APP processing but increased Aβ levels in the brain [162]. Thus, the disrupted motif might rather modulate SorLA-mediated lysosomal targeting of Aβ. The SorLA cytoplasmic domain interacts via its FANSHY motif with retromer, an adaptor complex engaged in endosome to Golgi retrieval [163]. In mammals, retromer is composed of a trimer comprised of VPS26, VPS29, and VPS35 and a dimer of two sorting nexins (SNX) [164]. Retromer deficiency in mice and flies increases production of Aβ and the retromer-dependent endosomal-*trans*-Golgi sorting pathway has been suggested to be implicated in late onset AD [165, 166]. In agreement, VPS35 and VPS26 expressions are reduced in vulnerable regions of AD brains and knockdown of retromer elements in cell culture led to increased Aβ production, while overexpression of retromer elements decreased Aβ levels [167]. So far, there is no evidence that retromer interacts directly with APP. Knockdown of VPS35 or SNX1 results in reduced SorLA expression [158], VPS26 interacts directly with SorLA and mutations in the SorLA cytoplasmic domain that affect the retromer binding site result in APP missorting and enhanced processing [163] and in agreement, disruption of part of the FANSHY motif in mice in vivo resulted in accumulation of SorLA in endosomes and increased APP processing [162]. This is in line with very recent time lapse imaging results in primary cortical neurons showing that after co-expression of SorLA, APP stationary vesicles and anterograde vesicles were significantly decreased while there is clear increase in the number of retrograde vesicles, suggesting that SorLA is mainly involved in retrograde transport of APP [118] (Fig. 5). Interestingly, the percentage of vesicles co-transporting APP and SorLA is only about 10% [118] and the co-transport rate of APP and SorLA

was significantly reduced after inducing dimerization of APP [118], which is in line with results from Willnow and colleagues showing an impact of SorLA on the extent of APP dimerization [168].

Thus, SorLA likely connects retromer and APP. In addition, an interaction of SorLA and SNX27 was proposed [169]. SNX27 contains a PDZ domain and has been shown to serve as a cargo selector for the retromer complex. The binding of other transmembrane proteins occurs through the SNX27 PDZ domain and respective binding motifs in the cytoplasmic domain of the cargo [170]. In contrast, the binding of SorLA appears independent of the SNX27 PDZ domain [169]. However, SNX27 mediates sorting from endosomes to the plasma membrane [171] and in agreement with this, SNX27 enhances SorLA and APP surface levels and promotes non-amyloidogenic APP processing [169].

In conclusion, current data suggest a dual role for SorLA in modulating APP processing and Aβ accumulation. One function is retrograde sorting of APP from endosomal compartments to the *trans*-Golgi and thereby reducing amyloidogenic processing of APP. The other function is targeting of already processed monomeric Aβ for lysosomal degradation.

## Sortilin-Related Receptor CNS Expressed 1

Another member of the Vps10p-D receptor family, sortilin-related receptor CNS expressed 1 (SorCS1), has been genetically linked to late onset AD [172–176]. SorCS1 is a 130 kDa type-I transmembrane protein with an N-terminal Vps10p-D followed by a leucine-rich domain, a transmembrane domain, and a short cytoplasmic tail (Fig. 3) [177]. SorCS1 binds PDGF-BB and presumably other growth factors through its Vps10p-D [156]. In addition, the SorCS1 Vps10p-D interacts directly with neurexin1 (Nrxn1) [178, 179]. Proteomic analysis of the synaptic SorCS1 interactome revealed that SorCS1 forms a complex with Nrxn1 and Nrxn2, neuroligin 1 (Nlgn1) and Nlgn3, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) subunits, Ntrk2 (also known as brain-derived neurotrophic factor receptor, TrkB) and APP [178]. Accordingly, other studies had demonstrated the interaction of SorCS1 and APP by co-immunoprecipitations before [174, 180, 181].

SorCS1 is predominantly expressed in the developing and adult brain and neuronal activity can induce its expression in the hippocampus [182–184]. Genetic variations in SORCS1 are associated with memory performance [185]. In addition, expression analysis revealed lower SorCS1 levels in the amygdala from AD brains as compared to unaffected brains

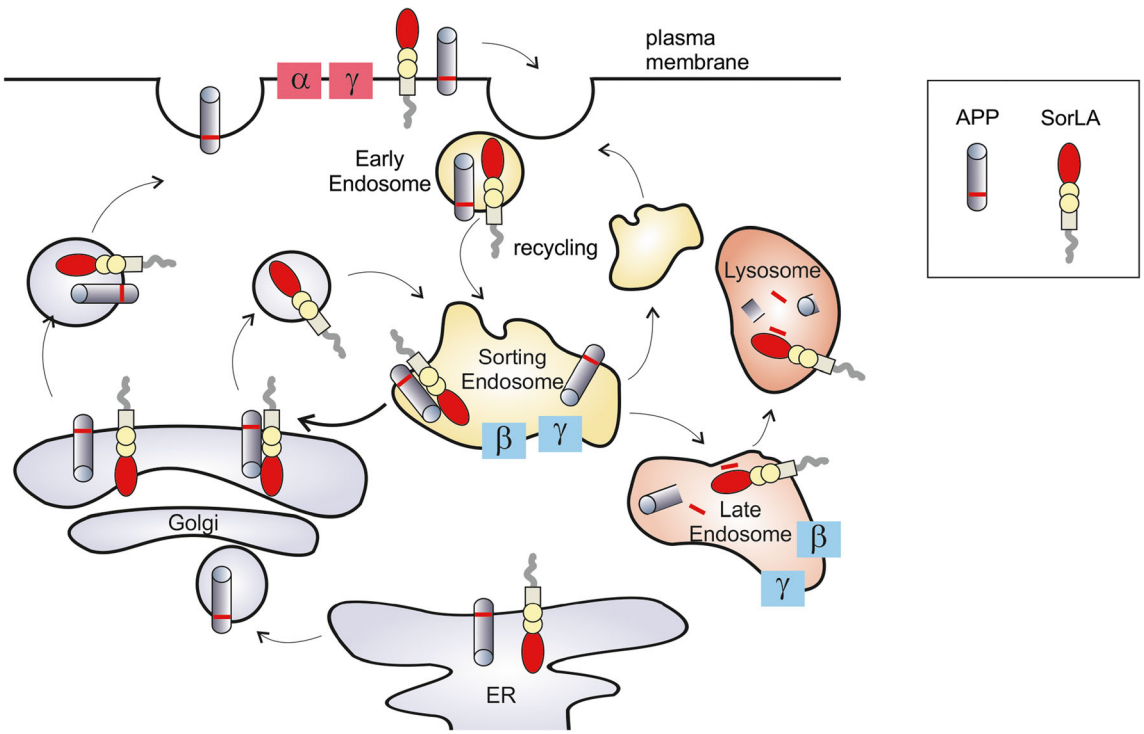


**Fig. 5** SorLA modulates APP trafficking. SorLA is mainly localized to Golgi compartments and endosomes, where it strongly co-localizes with APP. Only a minor fraction of SorLA is present on the cellular surface and can be shed by α- and γ-secretase. After endocytosis, SorLA binds cytosolic adaptors which shuttle SorLA between endosomes and the TGN (black arrow). SorLA likely connects retromer and APP. Binding of SorLA to GGAs or AP1 in the TGN shuttles SorLA back to endosomes. Co-expression of SorLA leads to a significant decrease in APP stationary vesicles and anterograde vesicles with a concomitant increase in the number of APP containing retrograde vesicles, indicating that SorLA is mainly involved in retrograde transport of APP

[174]. Cellular analyses demonstrate that high SorCS1 expression levels result in a modest decrease of Aβ and a reduction of SorCS1 expression leads to an increase of Aβ levels [174, 180]. Moreover, studies in hypomorphic SorCS1 mice support the impact of SorCS1 on APP processing [180]. These observations are reminiscent of SorLA modulating APP processing. Like SorLA, SorCS1 is subject to ectodomain shedding by ADAM17 which can be stimulated by phorbol esters or PDGF-BB and is followed by γ-secretase-mediated proteolysis within the transmembrane segment [156].

SorCS1 is expressed in different alternative splice variants with identical extracellular and transmembrane moieties, but different cytoplasmic domains conveying varying trafficking properties [87, 181, 186, 187]. Whereas some cytoplasmic domains mediate rapid cellular uptake of ligands, others direct the receptor to the cellular surface and do not mediate rapid internalization. It has been demonstrated that the endocytic isoforms of SorCS1 are internalized in an AP-2-dependent manner and are capable of targeting internalized cargo to lysosomes [187]. In accordance, affinity-purified SorCS1 complexes revealed the presence of AP-2 [178] and a direct interaction of SorCS1a and AP-2 has been shown [187]. SorCS1 has been linked to SorLA and the retromer subunit Vps35 by co-immunoprecipitation [180]. However, a direct binding of SorCS1 to the retromer complex or a retromer-mediated transport of SorCS1 awaits demonstration. All analyzed SorCS1 cytoplasmic domains failed to convey Golgi to late-endosomal transport in an assay in which the SorLA cytoplasmic domain was mediating this type of intracellular transport (Fig. 6) [158, 187]. Moreover, none of the SorCS1 cytoplasmic domains interacts with GGAs [186, 188]. Therefore, it was concluded that SorCS1 isoforms are not engaged in mediating Golgi to late-endosomal transport [187]. This is an important difference to SorLA, which conveys this type of sorting [158]. Thus, it is likely that SorCS1 has a function different from SorLA in APP trafficking. In neurons SorCS1 presents mainly a somato-dendritic localization [178, 181] and depending on the splice variant, SorCS1 is localized to endosomes or to the plasma membrane [181, 186]. SorCS1 is translocated to postsynaptic sites where it regulates Nrxn and AMPAR surface trafficking and in agreement SorCS1 deficiency leads to reduced glutamatergic synaptic transmission [178]. Uptake of APP appears to be independent of SorCS1 [181], but APP and the endocytic splice variant SorCS1c share a common postendocytic pathway. Both proteins share vesicular transport characteristics and overexpression of SorCS1c, but not of SorCS1b, reduces neuronal anterograde transport of APP and increases the fraction of APP localized to stationary vesicles [181].

Taken together, current data suggest that SorCS1 is engaged in the regulation of sorting and anterograde targeting of APP. Notably, SorCS1 is genetically associated as well with type-I and -II diabetes [189–192]. Diabetes is a known risk factor for AD. Therefore, SorCS1 might link diabetes and AD pathology.

## Sortilin

Sortilin (SORT1), also known as neurotensin receptor3 [193] or gp95 (glycoprotein of 95 kDa) [138] is expressed in neurons of the CNS and PNS [138, 194, 195] as well as in non-neuronal tissues like heart, lung, skeletal muscle, and testis [138].

Sortilin is synthesized as an inactive precursor which is converted in the TGN to the mature receptor by furin-mediated cleavage of a 44-residue N-terminal propeptide [196]. The propeptide of sortilin precludes binding of ligands by sterical hindrance [196]. Therefore, the unprocessed receptor is unable to bind ligands. This characteristic has been described as well for the SorLA Vps10p-D whereas receptors of the SorCS subgroup seem to bind ligands independently of their N-terminal processing [141, 186, 197]. Remarkably, sortilin binds the propeptide of SorCS1 which itself does not bind its propeptide [198]. However, the functional relevance of this interaction is not completely understood, but it has a pronounced effect on sortilin's ability to mediate specific cellular functions [198].

In addition to its own propeptide, the extracellular/luminal domain of sortilin interacts with neuropeptides, such as neurotensin, and neurotrophic factors, such as the proforms of nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) and ciliary neurotrophic factor (CNTF) [193, 199–201], but as well with ligands typical for the LDLR family, such as the LDLR-associated protein (RAP), lipoprotein lipase (LpL), lipoprotein AV, and apolipoprotein E (APOE) 2, 3, 4 [196, 202–204]. Sortilin appears promiscuous as it binds various ligands and is unique as it is the only known non-LDLR family member that binds RAP. In addition, it interacts with other ligands of the LDLR family, whereas the Vps10p-Ds of SorCS1, -2, and -3 do not bind RAP and other typical LDLR ligands [90, 186].

Sortilin enters the secretory pathway and might transport ligands anterogradely [154]. However, once internalized from the plasma membrane, the receptor is capable to direct cargo to late endosomal compartments and to lysosomes for degradation [202]. Sortilin is internalized through clathrin-coated pits and this depends on canonical AP-2 binding motifs. Like SorLA, sortilin interacts with GGAs, AP-1, and retromer complex and these interactions convey the cycling of sortilin between the TGN and late endosomes (Fig. 7) [202, 205–207].

Sortilin functions as an APOE receptor [204], a known risk factor in sporadic AD [208]. Sortilin mediates cellular uptake of Aβ bound to APOE and sortilin KO mice crossed to two different AD mouse models show increased Aβ plaque burden and significantly increased Aβ40 levels, but no changes

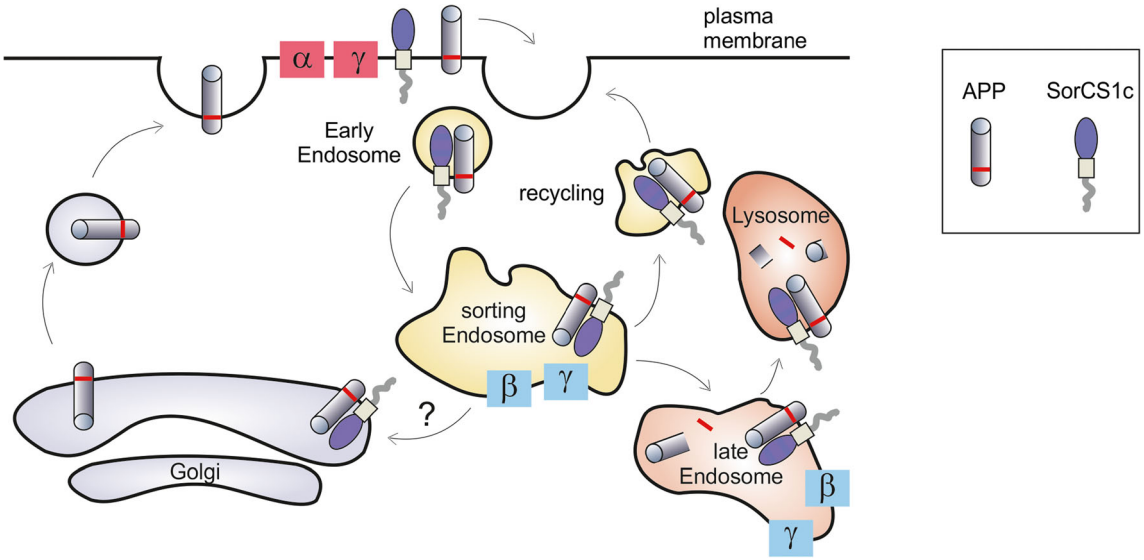


**Fig. 6** SoCS1c modulates APP trafficking. SorCS1c is an endocytic receptor, but internalization of APP appears to be independent of SorCS1, although SorCS1c and APP share a common postendocytic pathway. SorCS1c was shown to reduce the anterograde transport rate of APP in neurons. Further involvement of SorCS1c in APP trafficking from sorting endosomes to the Golgi needs to be determined

on C-terminal fragments of APP generated by α- or β-secretase [204]. Therefore, sortilin might play a role in catabolizing Aβ peptides.

Sortilin has also been shown to co-localize and to interact with APP in neurons [154, 209]. FRET analysis and co-immunoprecipitation identified the ectodomain as well as the intracellular region as interaction domains, whereby binding via the C-terminus seemed to be more prominent [209]. The binding site in APP was mapped to amino acids 1–141 [209] within the E1 domain (aa 31–191) [210], more specifically mainly to the growth factor-like domain (GFLD) (aa 28–123). In agreement, Gustafsen et al. detected the interaction of sortilin and APP by co-immunoprecipitation, demonstrated that the extracellular domain of APP is internalized by sortilin and sorted differentially by SorLA and sortilin [154]. However, Gustafsen et al. mapped the APP-sortilin interaction via surface plasmon resonance analysis to a different region (6A) within the APP ectodomain, further distal to the E1 domain and binding was inhibited by the sortilin propeptide [154]. Although more than one binding site may exist, these

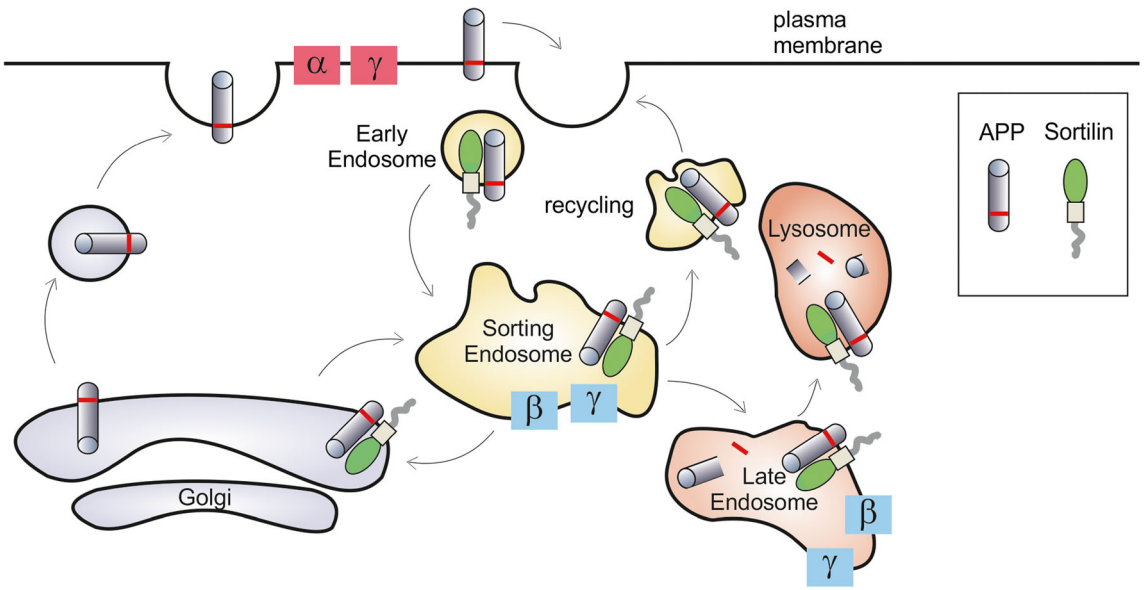


**Fig. 7** Sortilin modulates APP trafficking. Sortilin is located predominantly in the TGN and cycles between endosomes and TGN similarly as SorLA. In contrast, sortilin might shuttle APP mainly in anterograde direction and then to the cell surface. Sortilin is an endocytic receptor, which internalizes various ligands by receptor-mediated endocytosis and delivers them to lysosomes, but its possible role on APP endocytosis needs to be determined

potentially conflicting results need clarification. Yang et al. further identified within the APP C-terminus, the NPTYKFFE sequence (residues 759–766) as a sortilin interaction site [209]. This contains the internalization motif for clathrin-dependent endocytosis NPTY [211] and the KFFE motif, which had been shown to be important for APP transport mediated via the μ4 subunit of AP4 [212].

Microarray expression analysis of sortilin in brain tissue of the occipital lobe and cerebellum showed no significant difference between AD and control patients [213]. A different study reported unchanged sortilin protein levels in frontal or temporal cortical tissue and no association between sortilin levels and antemortem cognitive test scores [214]. However, there was a positive association between temporal cortex sortilin levels and severity of neuropathology by Braak and NIA-Reagan diagnoses [214]. Moreover, sortilin fragments were identified in senile plaques [215]. In contrast to the microarray data, protein levels of sortilin were found to be significantly increased in postmortem temporal cortex of AD patients, which may relate to the finding that sortilin overexpression leads to increased BACE1 cleavage of APP and thereby also to elevated Aβ production [216–218]. Remarkably, sortilin also interacts with BACE1 and influences its retrograde transport to the TGN [216]. Increased levels of sAPPβ and Aβ after sortilin overexpression in cultured cells were reported while RNAi-mediated suppression of sortilin resulted in decreased BACE1 mediated cleavage of APP [216]. Thus, sortilin seems to influence the proteolytic conversion of APP. Albeit, a different study suggests that overexpression of sortilin leads to increased sAPPα and decreased sAPPβ levels [154] while overexpressed SORLA leads to decreased sAPPα/sAPPβ products. This supports a different impact on APP trafficking of these two APP sorting molecules.

Like APP, SorLA, and SorCS1, sortilin is cleaved by α- and γ-secretases [156, 219]. The metalloproteinases ADAM10 and ADAM17 are thought to act mainly as α-secretases. ADAM10 and ADAM17 can be activated experimentally by two different reagents. Phorbol 12-myristate 13-acetate (PMA), an activator of metalloproteinases via the protein kinase C (PKC) pathway specifically activates ADAM17, whereas ionomycin, a calcium ionophore strongly activates ADAM10 in a calmodulin-dependent manner [220]. PMA has been demonstrated to activate shedding of SorLA and SorCS1 [156]. In parallel experiments, shedding of sortilin induced by PMA was only minor. Using ionomycin to induce cleavage by ADAM10 significantly increased the level of shed sortilin [221]. Analysis of mouse embryonic fibroblasts lacking either ADAM10 or ADAM17 revealed that in these cells, shedding of sortilin was mainly carried out by ADAM10 [221]. Therefore, the proteolytic conversion of sortilin in the juxtamembrane stalk region is thought to be mainly mediated by ADAM10. However, shedding of sortilin has been analyzed in different cell types [156, 221, 222] and has been reported to be activated by PKC in a tumor cell line [222]. This may indicate that sortilin could be cleaved by ADAM17 in a certain cellular environment.

Different studies indicate that sortilin plays a role in other human diseases like cardiovascular diseases (CVD) or frontotemporal lobar degeneration (FTLD). Remarkably, single nucleotide polymorphisms (SNPs) within and in the vicinity of the *SORT1* gene, encoding sortilin, have been associated with CVD [223–228] and CVD is considered as a risk factor for AD [229]. A number of studies analyzed SNPs in different populations regarding AD, but in contrast to SorLA and SorCS1, no higher risk has been directly associated with AD so far in this kind of surveys [213, 230–236].

Although no strong genetic association has been reported for sortilin in AD so far, there are several indications that sortilin seems to be involved in another neurodegenerative disease, in FTLD [237, 238], which is the second most prevalent form of early onset dementia after AD (between age 45 and 65) [239]. One important player in FTLD is progranulin, since pathogenic mutations in progranulin (*GRN*) were identified throughout the gene, and all cause the disease via haploinsufficiency resulting in reduced progranulin levels [238]. Sortilin was the first identified receptor of progranulin [240, 241]. Sortilin binds progranulin with high affinity, mediates its rapid endocytosis, and subjects it to lysosomal degradation [240, 242]. Sortilin has been additionally linked to FTLD via the TAR DNA-binding protein 43 (TDP-43) which has been described as a major risk protein in amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration with ubiquitin inclusions (FTLD-U) [243]. TDP-43 is involved in splicing events of sortilin and progranulin [244] and dysregulation of sortilin splicing via TDP-43 was shown to lead to an altered progranulin metabolism [245].

In conclusion, sortilin is an additional member of the Vps10p family interacting with APP, shown to modulate APP processing. There is no strong genetic association for sortilin in AD so far, but sortilin might play a role in FTLD.

## Calsyntenin

Calsyntenin-1 was first identified in a screen for proteins released from synapse forming spinal cord neurons [91]. A different study used the binding partner of the APP cytoplasmic domain, X11L/X11β/mint2 [246], as a bait in a yeast two-hybrid screen to identify the molecular machinery which regulates APP trafficking [97] (Fig. 8). Thereby, Alcadein (Alzheimer-related cadherin-like protein) (Alc) was found, which is identical to calsyntenin-1 [97]. The protein belongs to a family of three homologs (Fig. 3) in humans and in mice, alcadeinα, β, and γ or calsyntenin 1–3, which are all predominantly expressed in neurons [91, 93, 97]. In addition, there exist two splice forms of alcadeinα termed "alcadeinα1" and

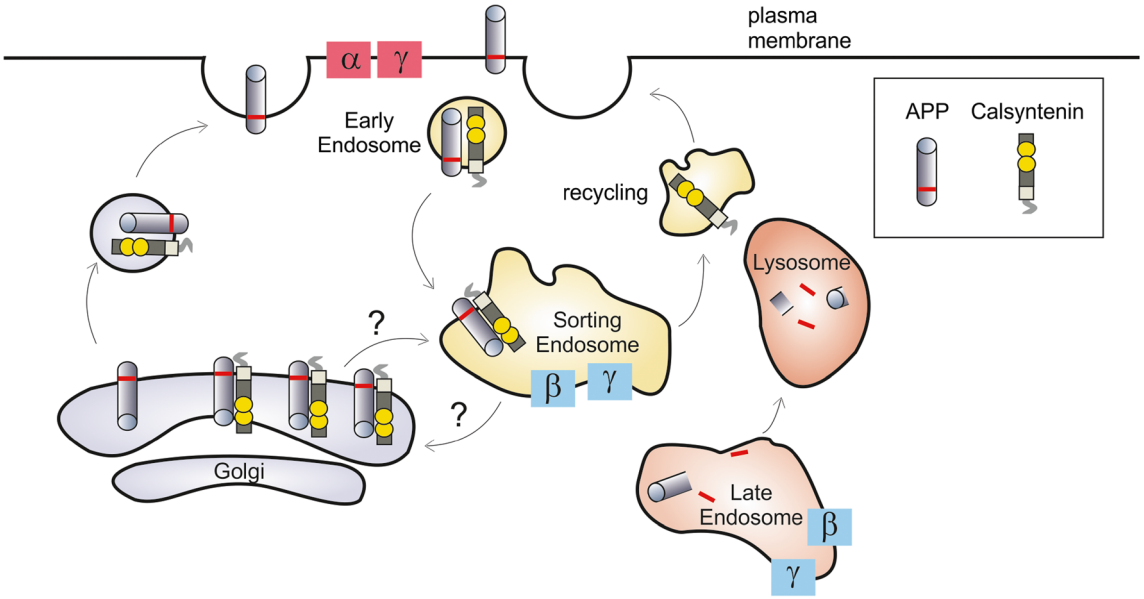


**Fig. 8** Calsyntenin-1 modulates APP trafficking. Calsyntenin-1 and APP are mainly co-localized in the TGN and interact indirectly via X11L. Knockdown of calsyntenin-1 inhibits anterograde movement of APP leading to an accumulation in the TGN. Additionally, calsyntenin-1 and APP are co-localized in Rab5 positive early endosomes, but not in Rab11 positive recycling endosomes. The synaptogenic calsyntenin-3 is thought to act differently and shows a more abundant localization at the cell surface than calsyntenin-1 or -2

"alcadeinα2" [97]. For simplification, we will use the term "calsyntenin."

In situ hybridizations of different developmental murine stages (E14–P48) revealed calsyntenin-1 mRNA expression throughout the body and in all brain regions [91, 247]. In contrast, calsyntenin-2 and -3 mRNAs are restricted to the CNS. Calsyntenin-2 is mainly present in the hippocampus and the olfactory bulb, at later stages also in cortex and cerebellum while calsyntenin-3 is present in various brain areas [247]. Moreover, calsyntenin-2 and -3 are expressed in interneurons of the hippocampus and the neocortex [93, 94] and calsyntenin-1 was localized to excitatory and inhibitory postsynapses [91].

The 150 kDa full-length calsyntenin-1, -2, and -3 can be proteolytically cleaved into one secreted 115-kDa fragment and one C-terminal 34-kDa fragment (CTF) by ADAM10 as well as ADAM17 [91, 248, 249]. Cleavage of calsyntenin-1 mainly takes place in the secretory pathway [250]. Moreover, it has been shown that calsyntenin-3 is extensively shed since in mouse brain less than half of calsyntenin-3 is present as full-length protein and more than half of it as the shed ectodomain [94]. The 34-kDa CTF fragment can be further processed by γ-secretase which results in release of the intracellular domain (ICD) and a secreted Aβ-like fragment which was also termed p3 [248, 249, 251]. The calsyntenin ICD can suppress gene transactivation of the APP ICD possibly by titrating away Fe65 binding partners of APP [248].

Calsyntenins have been suggested as biomarkers in AD because altered levels were observed in AD. Thus, in presenilin 1 familial Alzheimer's disease (FAD) mutants, which lead to an altered $A\beta_{40/42}$ ratio for APP concomitantly altered C-termini for the calsyntenin-1 $p3_{35/38}$ fragments were observed [249]. Furthermore, elevated levels of calsyntenin-1 $p3_{38}$ fragments were detected in the CSF of patients of various clinical populations including sporadic AD [251]. Additionally, calsyntenin-1 full-length protein levels were decreased in the brains of AD patients [252] and an involvement of calsyntenin-3 in AD has been implicated in a recent proteomics study showing decreased calsyntenin-3 levels in CSF of FAD patients [253]. A potential role of calsyntenins in AD is in line with a survey indicating that calsyntenin-3 accumulates in dystrophic neurites surrounding amyloid-β (Aβ) plaques [254].

So far, calsyntenins have not been genetically linked to AD, but there is accumulating evidence that calsyntenin-1 is involved in APP transport. Several studies demonstrated partial co-localization of APP and calsyntenin-1, which are both present in the soma, in dendrites, and axons of neurons [252, 255]. In the soma, both proteins are mainly localized to the *trans*-Golgi network [252, 255, 256]. About 29–41% of vesicles in axons of the sciatic nerve, hippocampal, or cortical neurons contained both APP and calsyntenin-1 [95, 252, 257]. Additionally, immunostainings revealed that APP and calsyntenin-1 co-localize to about 48% in the central domain of growth cones in hippocampal neurons, but only to about 12% in the peripheral domain of growth cones [96, 257]. Live cell imaging analyses of cells transfected with fluorophore-tagged calsyntenin-1 or APP have been performed in different cellular systems. Velocities of antero- and retrograde moving vesicles containing one of the proteins varied in the different

surveys [6, 62, 95, 96, 252, 258, 259]. However, co-transfection in neurons demonstrated co-transport of both proteins [252]. Those results suggest that APP and calsyntenin-1 co-localize and are partially co-transported (Fig. 8). However, attempts to prove a direct interaction of calsyntenin-1 and APP failed. The association of both proteins is rather bridged by the cytoplasmic interaction partner X11L [97]. X11L expression leads to a decrease in $A\beta_{40}$ and sAPP production [260–262]. Expression of the tripartite complex X11L/calsyntenin-1/APP leads to an even more severe reduction of Aβ levels, but not calsyntenin-1/APP expression alone. X11L expression enhances the half-life time of APP and this effect is even more pronounced in the presence of calsyntenin-1 [97].

As exemplified above, a large body of evidence suggests that APP represents one of several transmembrane proteins that undergo fast axonal transport by means of conventional kinesin but does not interact directly with kinesin (reviewed in [263]). A number of studies strongly indicate that calsyntenin-1 acts as an organelle adaptor that links kinesin-1 light chain to transport vesicles because it directly binds KLC's via its C-terminal domain [95, 96, 256]. Immunostainings showed that calsyntenin-1-positive organelles are aligned along microtubules in axons of neurons and co-localize partly with kinesin-1 [96]. Calsyntenin-1 can induce vesicle association with KLC1, as shown via live cell imaging [95]. Taken together, current results suggest that calsyntenin-1 links certain types of vesicles to kinesin.

Immunoisolates of calsyntenin-1 from mouse brains identified two different types of calsyntenin-containing transport organelles [257]. One was characterized by early endosomal markers like Rab5 and contained APP [257]. In contrast, the other calsyntenin-containing transport organelle which was characterized by the recycling vesicle marker Rab11 was lacking APP [257]. The presence of APP in early endosomal vesicles is consistent with previous studies, showing co-localization of APP with Rab5-positive endosomes [264, 265]. Rab5 immunoisolates contained mainly the calsyntenin CTF while APP immunoisolates contained calsyntenin mainly in the full-length form [257]. These data together with time lapse imaging analyses lead to the hypothesis that calsyntenin-1 docks kinesin to different endosomal carriers transporting APP and other cargo anterogradely along the axon to the growth cone [255, 257].

In line with this notion are calsyntenin-1 knockdown experiments which resulted in a significant increase in APP levels in the TGN [252], corroborating the idea that calsyntenin-1 mediates kinesin-1 transport of cargoes on post-Golgi carriers [255, 256]. Knockdown of calsyntenin in neurons leads to suppressed anterograde (64.3%) and retrograde transport (46.6%) of APP [252], but not to a complete inhibition of APP movement. This supports the assumption that calsyntenin function underlies only one of several transport mechanisms of APP.

Remarkably, knockdown or overexpression of calsyntenin seems to influence APP processing, presumably by altering APP transport. So far, the corresponding data are conflicting. A significant increase in α- and β-CTF production after knockdown of calsyntenin-1 was shown [255]. On the contrary, coexpression of calsyntenin-1 or of the ICD of calsyntenin with APP suppressed APP anterograde transport and facilitated $A\beta_{40}$ and $A\beta_{42}$ production [95]. In contrast, a study of Vagnoni et al. showed an increase in $A\beta_{40}$ and $A\beta_{42}$ levels and β-CTF and sAPPβ after knockdown of calsyntenin-1 while sAPPα and α-CTFs were reduced. Moreover, calsyntenin-1 levels are reduced in AD brains which correlates inversely with Aβ levels [252]. Therefore, further studies are required to understand the impact of calsyntenin-1 on APP processing.

Calsyntenin-1 and -2 seem to play similar cellular roles, whereas a different function for calsyntenin-3 is likely, because this protein lacks the C-terminal KLC1 binding motifs as well as the calcium-binding region in its C-terminus [93] and shows a more prominent surface localization than calsyntenin-1 and -2 [94]. This is consistent with the fact that, so far, no role for calsyntenin-3 has been demonstrated in organelle transport [96]. Albeit, the impact of calsyntenin-3 on APP transport has not been analyzed in detail. In accordance with a different function, it has been recently reported that calsyntenin-3, but not calsyntenin-1 or -2, is able to induce presynaptic differentiation [94, 247]. It shares this capacity with APP and other well characterized synaptic adhesion molecules (SAMs) [266–270]. One of the best described SAM's are neuroligins, which are located at the postsynapse interacting in *trans* with presynaptic neurexins [271]. Neurexin genes each encode a longer α form and a shorter β form [272]. Conflicting results described an interaction of postsynaptic calsyntenin-3 with neurexin1α in a direct fashion [94, 273], but not with neurexin1β [94]. However, a different study failed to reproduce the direct interaction between calsyntenin-3 and neurexin1 in similar cell surface binding assays, raising the question whether calsyntenin-3 binds neurexin1 directly [247]. Moreover, calsyntenin-1 and -2 were reported not to interact with neurexin [94]. The physiological relevance of these findings still needs to be resolved but calsyntein-3 might affect synapse formation and or stabilization, which are important determinants in AD [274].

In conclusion, current knowledge implies that calsyntenins are not genetically linked to AD, although altered calsyntenin fragment levels have been observed in AD brains. Calsyntenin-1 and most likely calsyntenin-2 modulate APP transport and presumably its processing.

## Conclusions

Intracellular transport of APP determines its processing by different proteolytic enzymes and altered subcellular trafficking of APP is thought to directly affect the degree to which Aβ is generated. The type-I transmembrane proteins LRP1, SorLA, SorCS1, sortilin, and calsyntenin-1 have been demonstrated to modulate APPs intracellular targeting and processing. Genetic linkage analyses underscore the role of SorLA in the development of EOAD and LOAD, whereas LRP1 and SorCS1 were identified in some studies as LOAD risk factors. On the other hand, a genetic association of sortilin and calsyntenin-1 with AD has not been demonstrated so far.

APP interacts directly with LRP1, SorLA, SorCS1, and sortilin and these interactions are thought to link APP to specific intracellular sorting machineries. Thus, SorLA seems to link APP to the retromer complex which has been suggested as an AD risk factor, but retromer does not interact directly with APP. In contrast, LRP1 also interacts indirectly with APP via Fe65 and calsyntenin-1 interacts indirectly with APP and this interaction is bridged by the cytosolic adaptor protein X11L. This indirect interaction could link APP through calsyntenin-1 to kinesins and enable microtubule-dependent axonal transport.

In addition to full-length APP, LRP1, SorLA, and sortilin interact directly, or in the case of sortilin indirectly, with Aβ and are expected to partake in its clearance. It is under debate which cells convey Aβ clearance. However, recent human genome-wide association studies and systems-biology approaches have identified an unexpectedly dominant role of the microglial innate immune response in increasing the risk of developing AD [275]. SorLA, LRP1, and calsyntenin-1 are expressed in microglia [276] and LRP1 associates with the lipid transporter ABCA7 on the cell membrane [277]. ABCA7 and other transmembrane proteins such as Trem2 and CD33 have been recognized as LOAD risk factors, identified in microglia, related to the immune response and Aβ clearance [275, 278, 279]. Future studies will have to prove if SorLA in addition to LRP1 functions as a microglial scavenger receptor for Aβ.

In conclusion, our understanding which proteins are modulating APPs intracellular transport has improved, but we still lack detailed information on the specific sorting steps determining APPs subcellular targeting and which miss targeting events underlie disease development.

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