Finding Memo: Versatile interactions of the VPS10p receptors in Alzheimer's disease

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Finding Memo: Versatile interactions of the VPS10p receptors in Alzheimer's disease

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ABSTRACT

The family of VPS10p receptors comprises five members named SorLA, Sortilin, SorCS1, SorCS2 and SorCS3. While their physiological roles remain largely unresolved, they are now recognized for their signaling engagements and trafficking abilities, navigating a number of molecules between endosome, Golgi compartments, and the cell surface. Strikingly, recent studies connected all the VPS10p receptors to the development of Alzheimer's disease (AD). In addition, they have been also associated with diseases comorbid with AD such as diabetes mellitus and major depressive disorder. This systematic review therefore elaborates on genetic, functional, and mechanistic insights into how dysfunction in VPS10p receptors may contribute to AD etiology, AD onset diversity, and AD comorbidities. Starting with their functions in controlling cellular trafficking of Amyloid precursor protein and the metabolism of the Amyloid beta peptide, we present and exemplify how these receptors, despite being structurally similar, regulate various and distinct cellular events involved in AD. This includes a plethora of signaling crosstalks that impact on neuronal survival, neuronal wiring, neuronal polarity, and synaptic plasticity. Signaling activities of the VPS10p receptors are especially linked, but not limited to, the regulation of neuronal fitness and apoptosis via their physical interaction with pro- and mature neurotrophins and their receptors. By compiling the functional versatility of VPS10p receptors and their interactions with AD-related pathways, we aim to further propel the AD research towards VPS10p receptor family, knowledge that may lead to new diagnostic markers and therapeutic strategies for AD patients.

KEYWORDS

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BACKGROUND

Alzheimer's disease pathophysiology

Over 55 million people worldwide suffer with dementia, which is expected to rise to 78 million by 2030 (*World Alzheimer Report 2021*). Alzheimer's disease (AD) accounts for 60-80% of all diagnosed dementia cases [1]. Disturbingly, no efficient treatment is currently available. This unmet medical need is likely a consequence of the complex biology of the disease which, despite intensive research efforts, remains far from understood. AD is clinically characterized by extensive neuronal cell death in the cerebral cortex and limbic system, which is manifested by cognitive impairments, memory deficits, disorientation, spatiovisual difficulties, linguistic problems, and emotional imbalances. At the histopathological levels, AD is defined by the accumulation of extracellular amyloid-β (Aβ) plaques and by the formation of intracellular neurofibrillary tangles composed of hyperphosphorylated Tau protein (pTau) in the brain parenchyma [2]. The Aβ plaques are considered the pathological hallmark of AD, nevertheless there is a synergistic effect of pTau leading to weakening and deterioration of synapses, dystrophic neurites, neuroinflammation, and progressive neuronal cell death [2, 3].

The Aβ peptide lies within the Amyloid-beta precursor protein (APP). Under normal conditions, the nascent APP is transported through the trans-Golgi network (TGN) to the plasma membrane where it is sequentially cleaved by α- and γ-secretases, respectively, disrupting the Aβ sequence. These processes produce and liberate the non-pathological, soluble fragment called sAPPα. The APP processing is depicted in (**Figure 1**). According to the "amyloid cascade hypothesis", APP may escape α-secretase cleavage. Following the internalization to the endosomal compartment, APP is then sequentially processed by β-secretase and γ-secretase, respectively, which generates the Aβ peptide. After secretion into the

extracellular space, Aβ peptides polymerize into detrimental Aβ oligomers (AβO), later forming the ultimately insoluble, cytotoxic Aβ plaques [4]. However, attempts to treat AD by lowering Aβ have failed in several clinical trials which questions the impact of Aβ plaques as the only factor that controls disease progression [5]. An imbalance between proapoptotic and neuroprotective stimulation by proneurotrophins and mature neurotrophins likely contributes to the AD pathophysiology by negatively impacting on synaptic plasticity and neuronal vulnerability and integrity [6, 7]. Strikingly, VPS10p domain receptors play a dual role in the pathobiology of AD: they control APP and Aβ trafficking and clearance, and they regulate the balance between the trophic and apoptotic signaling from neurotrophins such as BDNF and its precursor proBDNF. These activities may explain why members of this receptor family have surfaced as important risk genes in AD.

Genetic risks in AD

The strongest genetic evidence behind Ad pathogenesis is linked to familial early-onset AD (EOAD), which accounts for 5-10% of all AD cases. EOAD diagnosis has been mostly associated to autosomal-dominant mutations in three genes that result in the increased levels and aggregation of Aβ; they are: *APP*, and the APP-cleaving γ-secretase presenilin components, *PSEN1* and *PSEN2*. Nevertheless, the majority of patients are diagnosed with sporadic, late-onset AD (LOAD), the heritability of which is estimated to be between 60% and 80% [8, 9]. Hence, large genome-wide association studies investigating up to 150,000 AD cases have identified a number of risk genes underscoring the polygenic nature of the late-onset variant [8, 10, 11]. Most recently, a study incorporating more than 100,000 AD cases and almost 700,000 control individuals identified 75 risk loci of which 42 had not previously been described. Functional annotation of the risk genes indicated that amyloid, Tau, endocytosis, intracellular vesicle trafficking, and altered lipid metabolism and immune responses are critically involved in the pathogenesis of LOAD [2, 10-15]. Around 40% of LOAD patients carry a disease-associated SNP in the gene encoding Apolipoprotein E (*APOE*), which

exists in 3 polymorphic alleles called E2, E3 and E4. Due to such high incidence, *APOE* polymorphism represents the strongest genetic risk factor for LOAD [16-18]. ApoE has multiple physiological functions, but it is mostly known for transportation of cholesterol and other lipids through the circulation system as well as within the brain parenchyma. Even though all human ApoE isoforms interact with Aβ, they differ in their function [19]. While ApoE2 shows neuroprotective features, ApoE4 represents the major risk factor for AD due to its involvement in Aβ processing [20]. The possession of ApoE4 allele leads to intracellular accumulation of Aβ by enhancing the uptake of Aβ peptides, resulting in the enlargement of endosomal compartments, subsequent endosomal-lysosomal pathway dysregulation, and thus decreased clearance of Aβ [21]. Several other mechanisms have been described for ApoE4 in relation to AD, including neuronal hyperactivation [22], increased Tau phosphorylation [23], modulation of neuroinflammatory pathways [20], and impaired synaptic plasticity [24]. Such abnormalities, fueled by reduced trophic support, are considered major drivers behind the progression of AD. For this reason, impairments in proteins involved in endocytic trafficking and trophic signaling have surfaced as important AD risk factors including the members of the family of VPS10p receptors.

AD as imbalance between neurodegeneration and neuroprotection

Neurotrophin protein family (NTs) is a subgroup of secreted trophic factors that are essential for axonal outgrowth, neuronal differentiation, synaptic plasticity, and neuronal survival [25-27]. It comprises Brain-derived neurotrophic factor (BDNF), Nerve growth factor (NGF), Neurotrophin 3 (NT3) and Neurotrophin 4 (NT4); proteins that are expressed across the CNS in a spatiotemporal manner. Their actions depend on binding to transmembrane receptor complexes between tropomyosin receptor tyrosine kinases (Trk) that are ligand specific, and to a promiscuous neurotrophin receptor denoted p75 ($p75^{NTR}$). While all neurotrophins can bind $p75^{NTR}$, the NTs show strongest binding to their respective Trk receptor: NGF binds to TrkA, BDNF and NT4 binds to TrkB, and NT3 bind to TrkC. The $p75^{NTR}$ can form heterodimers with a

given Trk which increases the affinity and fidelity of the Trk receptor towards its cognate neurotrophin [27].

BDNF is considered particularly relevant to AD [27, 28]. Reduced BDNF expression in the hippocampus and cortex of AD patients have been consistently reported at both the transcript and protein levels [29-32]. In addition to its well established function in sustaining neuronal survival, BDNF is also important for cognitive abilities as it promotes learning and memory by increasing synaptic strength [28, 33, 34]. There is a naturally occurring single nucleotide polymorphism (SNP) in BDNF at codon 66, which results in the substitution of Valine with Methionine (BDNF-Val66Met). This mutation has been associated with reduced synaptic plasticity, dendritic spine elimination [35], and impaired memory and learning in AD patients [36-38]. Strikingly, in rodent and primate models of Alzheimer's disease, BDNF gene delivery administered after disease onset showed potent neuroprotective effects by increasing synaptogenesis and synaptic plasticity leading to restoration of cognitive function [39]. Likewise have transplantation of neural stem cells been able to rescue memory function in AD mice via BDNF-induced stimulation of synaptogenesis [40].

BDNF levels also shape the onset of AD neurodegeneration by regulating Aβ production and formation of Tau containing neuritic plaques and neurofibrillary tangles [33]. In cultured hippocampal neurons, BDNF deprivation leads to increased cell death by 50% and elevated levels of APP and PSEN1 levels, which can be rescued by inhibiting Aβ production [41]. Low BDNF levels increases expression of a δ-secretase that can cleave Tau to produce a pathogenic fragment [42]. The Tau peptide subsequently becomes hyperphosphorylated abolishing microtubule assembly and triggering formation of neurofibrillary tangles. Tau peptide also binds TrkB and leads to degradation of the receptor. This prevents trophic activity of TrkB and blunts APP phosphorylation thereby increasing Aβ production [43, 44]. The importance of BDNF is further substantiated by the beneficial effects of physical exercise, which increases BDNF and TrkB expression, reduces APP processing and amyloid aggregation, and protects against cognitive decline in

both animal models and AD patients [45-48]. Indeed, today regular physical activity is considered among the most efficient ways to slow AD progression. Taken together, the above findings suggests that treatment to increase BDNF can have therapeutic benefits in AD.

NTs are synthesized as precursor proteins named "proneurotrophins" (proNTs) that undergo proteolytic cleavage of the prodomain during their maturation [49, 50]. proNTs are active signaling molecules, but as opposed to their mature counterparts, they induce apoptosis, axonal growth cone retraction, and synaptic weakening; actions that require $p75^{NTR}$ and are independent of Trk [49, 51-55]. As a consequence, perturbed maturation and incorrect balance between proNTs and NTs may propel the neurodegenerative process and exacerbate the disease [32, 50, 56] (**Table 1**). Indeed, AD patients with mild to medium cognitive impairment commonly exhibit increased levels of proBDNF in cortex, hippocampus and cerebrospinal fluid (CSF) on the expense of reduced mature BDNF [39, 56-60]. The studies showed that while proNGF is increased, NGF is decreased in the CSF and in different brain regions. Notably, this is the case in the basal forebrain where cholinergic neurons are reliant on trophic stimulation from NGF while sensitive to proNGF induced apoptosis [58, 61-66]. Expression of the neurotrophin receptors are altered too. Hence, $p75^{NTR}$ is commonly upregulated in several regions affected in AD brains [67-72], while TrkA [58, 73-75], TrkB [76], and TrkC [76] are downregulated.

There is a functional interaction between APP/Aβ metabolism and neurotrophin systems. $P75^{NTR}$ can bind APP and enable its trafficking to the endosomal compartment. Hence, in mouse models of AD, removal of $p75^{NTR}$ or disruption of its internalization substantially lowers amyloidogenic processing, Aβ levels and reduces cognitive decline [77, 78]. $P75^{NTR}$ also promotes amyloid-induced neuritic dystrophy [79], while soluble $p75^{NTR}$ ectodomain is neuroprotective against Aβ [72]. Phosphorylation of APP has been shown to promote amyloid processing of APP along the amyloidogenic pathway. NGF induces binding between TrkA and APP, which downregulates APP phosphorylation and enables its retrograde trafficking into the trans-Golgi network (TGN) thereby bypassing β-secretase processing compartment [80, 81]. Taken together,

the imbalance between proNTs and NTs, and the expression levels of their receptors may shift their function from being neuroprotective to amplifiers of the neurodegenerative process.

Introduction to VPS10p receptor family

All members of the Vacuolar protein sorting 10p (VPS10p) receptor family have recently been identified as AD risk loci and are now considered hotspots in LOAD [11, 82, 83] and one member also associated with familial EOAD [84-86] (**Figure 2**). Accordingly, VPS10p receptors exhibit key functions in the causal pathways influencing Alzheimer's disease risk as identified by GWAS; i.e. APP catabolic processes, lipid metabolism, cholesterol and lipid metabolism endocytosis, cellular sorting and trafficking, and in immune response [2, 10-15]. This receptor family comprises five single-span transmembrane receptors: SorLA, Sortilin, SorCS1, SorCS2, and SorCS3 (**Figure 2**)**.** They are involved in the etiology of a number of neurological and psychiatric disorders [87-89], including AD and frontotemporal dementia [83, 90-93]. Strikingly, genetic variants in all VPS10p receptors have been associated with AD, with their expression being predominantly decreased in AD brains (**Figure 2**). Except for SorCS2, the receptors functionally interact with AD-related proteins (**Table 2**). The receptors predominate in neurons with their expression is regulated in a spatiotemporal manner from embryonic development to adulthood. Some VPS10p receptors come in more splice variants and some also in soluble forms that can act on cell signaling over long distances. These features broaden their molecular interactions and signaling diversity across distinct cell types [94-96]. VPS10p receptors act by two different signaling modalities; either they control signal transduction at the cell membrane where they bind their ligands and co-receptors, or they sort multiple types of cargoes by endocytosis and intracellularly trafficking for targeting to distinct cellular compartments. Dysfunction in endosomal and lysosomal pathways typically causes protein aggregation and altered cell signaling. Such abnormalities are cytotoxic, and are considered a major cause behind the progression of AD neurodegeneration. Importantly, in addition to the canonical AD related proteins,

VPS10p receptors also bind synaptic component, and pro- and mature neurotrophins and their respective receptors (**Table 3**) to control synaptic plasticity, synaptogenesis and cell fate decisions; processes that are severely affected in AD [51, 97, 98].

The VPS10p receptor family is named after the yeast sorting protein VPS10p that forms their N terminus. They contain an extracellular propeptide typically removed by Furin-mediated cleavage in late-Golgi compartments within the secretory pathway (**Figure 2**). This proteolytic event is usually a stringent requirement for the receptor activation, as it primes the VPS10p domain for ligand interaction. The propeptide is followed by a single VPS10p domain, which is a 10-bladed β-propeller and serves as a binding site for many target proteins [99]. All VPS10p receptors can undergo ectodomain shedding to a different extend, by which they can signal across long distances as well as modify the level and the distribution of their ligands [90, 100-103]. The VPS10p receptors contain a short cytoplasmic domain that interacts with cytosolic adaptor molecules. Structurally, the receptors differ from each other mostly by the unique sequences within their cytoplasmic domains, which determine their distinct signaling features and sorting capacities due to diverse interaction with adaptor molecules [98, 99]. Some VPS10p proteins can form homodimers or heterodimers with each other [104], as well as engage in complex formation with other transmembrane proteins including APP, $p75^{NTR}$, TrkA and TrkB [105]. Based on the receptor complex composition, they control APP/Aβ turnover and determine cell survival or proapoptotic cell behavior. A schematic representation Structure of the receptors is illustrated in (**Figure 2**).

The distinct expression profiles, diverse protein interactions, and high mobility of the VPS10p receptors highlight their pleiotropic function in cell-to-cell communication [97, 106, 107]. A few studies suggested synergistic activity of these receptors, likely due to their structural similarities and overlapping ligands when expressed in the same tissue, e.g. in the hippocampus [104, 107]. This may explain why their shared heritability can result in epistatic effects in AD risk [83]. Here we present an overview of the many shared

but also distinct roles played by the VPS10p receptors in neuronal signaling, with a particular focus on their contribution to AD pathogenesis.

MAIN TEXT

SorLA biology and its fundamental role in AD

The strongest genetic link to AD occurs for the *SORL1* gene that has now been included in the exclusive list of genes that can act as causal for AD (together with *PSEN1*, *PSEN2,* and *APP* [2]). Initially found in LOAD cohorts [82, 108-110], rare *SORL1* variants were recently identified also in EOAD families [84-86]. Its protein product, sorting-related receptor with A-type repeats (SorLA), is the largest member of the VPS10p receptor family. First identified in 1996, SorLA is found in most regions of the mammalian CNS with a predominant neuronal expression [111-113]. SorLA is mostly localized in endosomal sorting compartments, where it mediates the trafficking of variety of cargo molecules such as APP [114], β-secretase 1 (BACE1) [115], Aβ [116], or Glial cell line-derived neurotrophic factor (GDNF) [117]. SorLA also interacts with transmembrane receptors at the synapse such as TrkB [118], the GDNF receptors GFRα1 and RET [117], and EphA4 [119] in order to modulate neuronal integrity and synaptic plasticity events. It is worth noticing that SorLA undergoes differential trafficking and polarized distribution, which subsequently influences axonal or dendritic guidance of its cargos [120]. Strikingly, SorLA transcription can be enhanced by BDNF, which has a neuroprotective effect, and also can reduce the production of Aβ levels [121]. In addition to its intracellular functions, SorLA ectodomain can be cleaved by ADAM17 and released into the extracellular space as soluble sSorLA [100]. It was shown that sSorLA binds and activates EGF receptor to induce neurite outgrowth and neurite regeneration [102]. In the following paragraphs we will describe the molecular interactions of SorLA with AD-related pathways and function in neuroprotection. A schematic representation of these functions is shown in (**Figures 3-4)**.

- *SorLA interactions in amyloidogenic cascade*

While uncovering differences in gene expression between AD and control brains, Scherzer et al identified that *SORL1* expression is dramatically reduced in hippocampus and frontal cortex from patients with sporadic AD [122]. Soon after, SorLA was identified as an interaction partner for APP determining its intracellular trafficking and processing (**Figure 3**) [114]. SorLA activity influences APP metabolism by preventing APP proteolytic cleavages into Aβ peptide in endosomal compartments [114]. SorLA also regulates the polarized distribution of APP within a neuron [120, 123]. Kinetic studies from Schmidt et al revealed that the receptor is able to inhibit the oligomeric assembly of APP both *in vitro* and *in vivo*, which influence its processing as the dimer form of APP is a preferred substrate of its secretases [124]. These observations were confirmed using SorLA deficient mouse line that exhibits increased production of Aβ peptides in the brain parenchyma [125]. AD mouse models APP/PSEN1 and PDAPP further revealed that cerebral levels of Aβ peptides and the deposition of plaques were significantly exacerbated in a SorLA concentration-dependent manner [125, 126]. Interestingly, overexpressed SorLA mediates an increased uptake of sAPP from the medium [123]. Altogether, these findings propose that SorLA may critically influence molecular events underlying the AD pathology and nominate the receptor as a potential target for the therapeutic interventions.

The physical interaction of SorLA with APP occurs within the complement-type repeats cluster of SorLA. The two proteins form a 1:1 stoichiometric complex observed more efficiently at acidic rather than neutral pH. This finding fosters a model of SorLA and APP interacting inside secretory and endosomal vesicles where the luminal pH is maintained in a range of 5.5 – 6.5 as opposed to the neutral pH at the cell surface [127]. Maturation of APP O-glycans in the Golgi compartment is required for the release of APP precursor into the secretory pathway, determining how APP cleavage is regulated, thus affecting the formation of its soluble forms (sAPPα and sAPPβ) [128, 129]. Interestingly, engineered SorLA mutants were found to

influence the breakdown of APP by regulating its O-glycosylation, which exemplifies yet another mechanism how this receptor can interfere with amyloidogenesis [127].

Besides APP trafficking and processing, SorLA controls additional events in the amyloidogenic cascade. Overexpression studies by Spoelgen et al showed that SorLA's cytoplasmic tail forms a protein complex with the beta-site APP-cleaving enzyme 1 (BACE1), a secretase initiating the proteolysis of APP. As SorLA interacts with both BACE1 and APP, the authors proposed that SorLA can render APP less accessible to the secretase, by which it can prevent the formation of the BACE1-APP complex in the endosome, thus reducing the APP cleavage. SorLA-BACE1 interaction therefore directly affects APP processing and Aβ production [115]. Importantly, a secreted form of SorLA is released into CSF, which was found to positively correlate with sAPPβ and Tau in AD patients [130]. Moreover, SorLA can bind ApoE at the cell surface and mediate ApoE-dependent Aβ endocytosis [112]. Overexpression studies showed how ApoE4 binds stronger to SorLA than ApoE3, and ApoE2 having the lowest affinity for SorLA of the three isoforms, and how that also relates to a higher SorLA-mediated cellular uptake of ApoE3 and ApoE4 compared to the ApoE2 isoform. The same isoform trend was valid when examining the ApoE-dependent uptake of extracellular Aβ by SorLA [131]. These findings suggest a physiological role of SorLA in clearing out the extracellular Aβ oligomers and their subsequent degradation in lysosomes. Impairment in these processes may potentially increase vulnerability of the neurons, a feature that could escalate the intracellular concentration of Aβ, and thus provide extensive pool of peptides to form cytotoxic AβO. Caglayan et al further demonstrated that overexpressed SorLA also binds Aβ in the absence of ApoE [132]. This interaction takes place via a peptide-binding site inside of the propeller tunnel of the VPS10p domain [116]. On the contrary, no Aβ binding was observed for the sortilin receptor, suggesting a unique role of SorLA in regulating Aβ trafficking. Kitago et al suggested that SorLA transports newly generated Aβ peptides from late endosomal compartment to the lysosomes for its degradation, by which it controls the amount of amyloid beta secreted into the extracellular space [116]. In line with these observations, a

SORL1 variant p.G511R that segregates with AD in a family [86], was shown to impair the binding between Aβ and the VPS10p domain, providing yet a mechanistic link how disturbed SorLA functionality increases production and impaired clearance of Aβ [132].

SorLA is linked to AD also through its interaction with subunits of retromer [133, 134], an evolutionary conserved heteropentameric complex which is a key player in neuronal protein endosomal recycling [135]. Retromer is important for cargo export from the endosome both in the retrograde pathway to Golgi/TGN and recycling to the cell surface [134]. The retromer complex is composed by two sub-complexes: the trimer VPS26-VPS29-VPS35 forming the core assembly, and the dimer of sorting nexin proteins (i.e. SNX1 and SNX2) binding to phosphatidylinositol phosphate membrane lipids. Impaired retromer activity has been observed in AD patients [134, 136, 137]. The interaction between SorLA and the retromer occurs via binding of the VPS26 subunit to a six amino acids FANSHY sequence located in the cytoplasmic tail of SorLA. The deletion of the retromer binding site in SorLA is correlated with defective endosomal sorting and the consequent misguidance of cargo proteins. These findings are in agreement with SorLA and retromer forming a functional unit that engage in neuronal endosomal recycling [133].

- *SorLA in neuroprotection, neurotrophic signaling and synaptic transmission*

Rohe and colleagues showed that one of the main components of neurotrophic signaling, BDNF is a specific enhancer of *Sorl1* transcription *in vitro* and *in vivo,* whereas *Sort1* expression, encoding sortilin, was not altered. This observation also correlated with reduced levels of BDNF in the striatum during neurodegeneration. Strikingly, this finding may have therapeutic potential as the induction of SorLA via BDNF treatment reduced the production of Aβ by 40% (**Figure 4, BOX A**) [121]. Later studies uncovered that the BDNF receptor TrkB is not only upstream but also downstream SorLA. Hence, SorLA can physically associate with TrkB to enhance its anterograde and retrograde trafficking between the cell body and its synaptic destinations, thereby potentiating BDNF-dependent neurotrophic signaling and synaptic

plasticity (**Figure 4, BOX C**) [118]. Any impairments in this machinery via abnormal functionality of SorLA is therefore likely to lead to deterioration of synapses and propel the neurodegenerative processes.

More recently, a new role for SorLA in signal transduction was identified thanks to its interaction with Ephrin type-A receptor 4 (EphA4) [119], a tyrosine kinase regulating synaptic structure and functionality [138] (**Figure 4, BOX B**). EphA4 binds multiple ligands at the plasma membrane, such as Ephrin A1, which is necessary for the EphA4 clustering and its subsequent activation prior to axonal outgrowth and synaptic plasticity [139]. EphA4 exhibits altered distribution in hippocampus of AD patients, where it localizes in Aβ plaques [140]. Aβ oligomers bind EphA4 and leads to aberrant activation of the receptor, which ultimately enhance synaptotoxicity and memory deficits in AD mouse models but this interaction is inhibited by SorLA [141-143]. While SorLA does not modulate EphA4 localization, it reduces the aberrant clustering and activation of EphA4/c-Abl pathway triggered by intracellular AβO, particularly in response to Ephrin A1 ligand binding. This is why EphA4 has become a novel therapeutic target for AD [141]. SorLA interacts with the extracellular region of EphA4 via its YWTD/EGF-like domain, by which it controls growth cone collapse in hippocampal neurons [119]. Interestingly, SorLA-T947M variant carrying mutation in the YWTD domain was identified in LOAD patients [144]. Functional studies exploring this mutation further demonstrated that SorLA-T947M is unable to bind EphA4 (without or in presence of Ephrin A1), and to repress its Aβ-dependent activation. Strikingly, elevated EphA4 activation in human AD brains correlates with the reduced SorLA-EphA4 association [119]. Huang et al also showed that SorLA-mediated inhibition of EphA4 improved spatial learning and memory of mice injected with human AβO. This mechanism might thus be fundamental for the potential use of SorLA as a neuroprotective agent against cognitive impairment in AD patients resulting from abnormal activation of EphA4.

Overall, the versatility of SorLA as a crucial player in distinct sorting pathways, amyloidogenic, neurotrophic as well as neuroprotective processes makes the receptor a powerful clinical target for

approaching synaptic plasticity impairments and impeding the AD onset and progressive neurodegeneration.

Sortilin biology and its links to AD

By combining a new GWAS dataset with existing data to increase sample size followed by meta-analysis, Belenguez et al recently identified *SORT1* as a high-impact AD risk gene [11]. The magnitude of the association was similar whether the patients were diagnosed by questionnaires or clinical evaluation, which substantiates the robustness of the association. Among the SNPs, the lead variant encoded a rare missense variant that substitutes an arginine with a glutamic acid at residue 302 and is located in the in the β-propeller of the VPS10p-domain harboring the ligand binding site was particularly prominent. In a Swedish cohort Anderson et al identified *SORT1* SNPs that are associated with reduced disease risk, which could suggest the existences also of gain of function variants [145].

Sortilin was identified as the second member of the VPS10p receptor family in 1997 [146]. Its expression is highly abundant in the CNS and in peripheral nervous system (PNS) neurons [147, 148], and it is enriched in forebrain, in particular in temporal cortex [147, 149]. It binds a vast number of ligands to control their sorting or signaling activities [105]. Important roles of sortilin is to mediate anterograde trafficking from the secretory pathway along neurites and to endosomes and lysosomes, and to mediate endocytosis and retrograde transport from the cell surface to the TGN by evading lysosomal targeting and degradation [150]. In the endosomal compartments the low pH causes conformational change and dimerization of sortilin and collapse of the binding site, which triggers the release of its cargo and enable recycling of the receptor back to the cell surface vis the TGN [151]. As also the case for SorLA, the complex trafficking pattern pathways are controlled via binding to a number of cytoplasmatic proteins and include Golgi-localized, γ-ear-containing, Arf-binding proteins (GGA1 -3) [150], adaptor protein complex 1 and 2 (AP1 and -2) [152], Rac-p21-activated kinases 1 to 3 (PAK1-3)[153], Ras-related protein (Rab7b) and

phosphofurin acidic cluster-sorting protein 1 (PACS-1). The retromer complex, comprising a cytosolic receptor complex composed of Vps26, Vps29, and Vps35 and SNX-1, a member of the sorting nexin family, binds sortliin and is required for its proper sorting [154, 155]. Notably, in the GWAS study by Belenguez et al, *SNX-1* was like *SORT1* identified as a novel top-risk gene for AD [11].

Among other ligands sortilin transports BACE1 and APP [123, 156, 157], by which it regulates the production and endocytosis of sAPP [123]. Similarly, sortilin facilitates the uptake of AβO [158] and ApoE [159]. Perhaps most well established is the role of the receptor in regulating neurotrophic signaling. It forms a receptor complex with $p75^{NTR}$ at the plasma membrane by which it modulates binding of proNTs and controls their pro-apoptotic activity [51, 52, 160, 161]. For instance, proNGF-Sortilin-$p75^{NTR}$ signaling is fundamental to pruning of retinal ganglion cells and for age-dependent degeneration of sympathetic neurons [52]. Sortlin also enable the anterograde transport of neurotrophin receptors such as TrkB as well as the secretion of its ligand BDNF [148, 162]. Further, it undergoes ectodomain shedding at the cell surface as well as during intracellular trafficking which inhibit lysosomal degradation of its cargos including BDNF [163]. Put together, any impairment of sortilin function affects cell survival and homeostasis in the brain, particularly during aging [52].

Contrary to SorLA, sortilin protein levels are enhanced in temporal cortex and cerebellum in some AD patients [156, 164, 165]. Further, C-terminal fragments of sortilin are deposited in neuritic Aβ plaques in human cerebrum [165] (**Figure 5, BOX A**) but not in cerebrums from transgenic AD mouse models nor aged macaques exhibiting amyloid plaque deposition [166] highlighting the interspecies differences in the formation/composition of senile plaques in regards to VPS10p receptors. It has been suggested that temporal *SORT1* expression levels in cortex positively correlate with the severity of the AD pathophysiology while *SORT1* expression does not change in patients with mild cognitive impairments [167]. These observations propose an important but clearly distinct involvement of sortilin in AD

pathogenesis compared to SorLA. In the following paragraphs, we will discuss studies that highlight the function of sortilin function in AD, (see **Figure 5**).

- *Sortilin's interactions in amyloidogenic cascade*

The intracellular trafficking of BACE1 between TGN and endosomes is necessary for its functioning [168, 169], and it is governed by adaptor proteins such as Golgi-localized γ-ear-containing ARF-binding proteins (GGA) [170]. GGA3 targets BACE1 for its lysosomal degradation [171]. Accordingly, the inhibition of GGA3 activity results in local, cytotoxic accumulation of BACE1 in axonal swellings leading to enhanced BACE1 activity, and later axonal dystrophy observed even before enhanced levels of Aβ [172]. Indeed, reduced levels of GGA3 protein in AD brains correlate with increased levels of BACE1, APP, and Aβ [171, 173]. Sortilin cytoplasmic tail also contains a consensus motif for binding GGA adaptor proteins which facilitate sortilin transport from the Golgi compartment to endosomes and lysosomes [150, 174, 175]. Finan et al showed that sortilin forms a complex with BACE1 in the human brain, by which it regulates retrograde trafficking of BACE1 from the early endosomes to the perinuclear region of TGN (**Figure 5, BOX B**). The authors further suggested that sortlin-BACE1 interaction facilitates BACE1-mediated first cleavage of APP, leading to an increased formation of sAPPβ and accumulation of Aβ peptides. Importantly, they showed that this process is partially regulated by sortilin's but not by SorLA's or SorCS1b's cytoplasmic tails [156]. These data highlight the nonredundant, pro-amyloidogenic function of sortilin and the specificity of its cytoplasmic tail in BACE1-dependent first cleavage of APP (**Figure 5, BOX C**).

Later studies revealed that the extracellular domain of sortilin can bind APP both *in vitro* and *in vivo* [123, 157]. It should be noted, that sortilin is a substrate of γ-secretases PSEN1 and PSEN2 that establish the last cleavage of APP fragments, and are responsible for Aβ production [90, 176]. Moreover, α-secretases ADAM10 [163, 177] and ADAM17 [100] that are responsible for the first, non-amyloidogenic cleavage of APP, also facilitate sortilin ectodomain shedding. These data suggest that sortilin is cleaved in the same subcellular compartments as APP. Indeed, Yang et al showed that sortilin co-localizes with APP in

perinuclear space and in axons of cultured neurons, where it facilitates APP trafficking from late endosomes to lysosomes for its degradation [157]. The cleavage of APP and ectodomain shedding of sortilin may explain why the C-terminal domain of the receptor accumulates and represent a prominent constituent of the amyloid plaques [165, 166]. However, these data were contradictory with Gustafsen et al who proposed that APP and sortilin primarily co-localize in the neurites [123]. Gustafsen et al found that sortilin directly enhances the production of secreted sAPPα, and mediates uptake of the extracellular sAPP. Interestingly, the authors detected decreased levels of sAPPβ in the presence of sortilin, opposing the Finan study [156]. The authors proposed that sortilin has opposite effect on APP processing in non-amyloidogenic pathway (sAPPα) when compared to the pro-amyloidogenic pathway (sAPPβ) in contrast to SorLA that reduces the levels of both, sAPPα and sAPPβ [123]. These observations are supported by a recent study by Ruan et al that used a triple transgenic AD model (APP/PSEN1) deficient in sortilin. The authors reported that the lack of sortilin enhances the Aβ deposition, neuronal loss, and astrocytic activation during aging. They also demonstrated sortilin's intracellular domain mediates APP degradation [178]. According to these studies, sortilin thus has a neuroprotective feature against APP-dependent amyloidosis likely because it consequently decreases the cleavage of cytotoxic sAPPβ (**Figure 5, BOX C**). In comparison with SorLA that can act as a retention factor for APP in the TGN, these results suggest that proteolytic cleavage of APP can undergo two different intracellular processing which is dependent on the activity of specific VPS10p receptors and their relative expression within different cellular environment. However, it should be noted that the biochemical studies addressing sortilin localization and the mechanism of its action on APP processing are not consistent, possibly due to the limitations between the used models. These discrepancies may be the consequence of the use of C-terminally tagged variants of sortilin in Finan and Yang studies [156, 157], whereas in study by Gustafsen only untagged sortilin was used [123]. The C-terminal tagging likely will lead to aberrant sortilin localization since binding of the GGA adaptors requires the C-terminal acid cluster of the receptor tail, as demonstrated by Cramer et al [179].

More functional studies using untagged proteins or both models in parallel are therefore critical to determine the precise molecular mechanism by which sortilin regulates APP transport and catabolism in (non)-amyloidogenic pathways.

It is well established that sortilin forms a receptor complex with $p75^{NTR}$ which mediates pro-apoptotic cell responses [51, 160]. Accumulation of extracellular Aβ oligomers facilitate the neurotoxicity and neuronal cell death via their physical binding to $p75^{NTR}$ [180] while the addition of Aβ peptides increases expression of sortilin in an *in vitro* likely via activation of the $p75^{NTR}$/RhoA pathway [164]. In line with these data, Takamura et al found that extracellular AβO, as opposed to non-oligomerized Aβ, act as sortilin ligands, and that sortilin loss-of-function suppresses AβO-targeted authophagy and AβO-induced cell death [158]. Interestingly, extracellular AβO triggers the co-localization of sortilin with $p75^{NTR}$ at the neuronal surface, proposing a model where sortilin-$p75^{NTR}$ receptor complex mediates apoptotic response upon binding of AβO, a mechanism that can contribute to the progressive neurodegeneration in AD patients [158].

Besides regulating the amyloidogenic cleavage of APP, sortilin is also the major neuronal ApoE receptor for endocytic uptake and catabolism of Aβ [92]. Binding studies revealed that sortilin is able to interact with each of the three major ApoE variants, but the most abundant interaction was shown for the cytotoxic ApoE4 [159]. Carlo et al further showed that AD mice (PDAPP and FAD lines) deficient for sortilin exhibit higher levels of Aβ and ApoE in cortex and hippocampus than $sortilin^{+/+}$ AD mice. Surprisingly, they observed no difference in sAPPα and sAPPβ levels, neither in BACE1 activity. Importantly, no changes in ApoE levels were seen in glia cells, known to be the main site of apolipoprotein synthesis. However, the absence of sortilin significantly attenuated the uptake of ApoE-Aβ complexes, demonstrating that impaired ApoE clearence by sortilin causes accumulation of Aβ in the brain [92]. Most recently, the same research group went on to study the relevance of the sortilin-mediated uptake of ApoE for brain lipid metabolism [181, 182]. They found that sortilin is required to accumulate and facilitate the metabolism

of polyunsaturated fatty acid into endocannabinoids; lipids with potent anti-inflammatory and neuroprotective functions. Remarkably, sortilin expression had no impact on endocannabinoid production in transgenic mice expressing the AD risk variant ApoE4, demonstrating that this function was restricted to the ApoE3 isoform. The authors explain this apparent paradox by ApoE4 being unable to uncouple from sortilin in the endosomal compartment, which disrupts recycling and re-exposure of the receptor at the plasma membrane. The combined findings suggest a protective role of sortilin in AD by lowering Aβ levels, reducing production of neuroinflammatory cytokines [182, 183], stimulating synapse function, and sustaining neuron viability (**Figure 5, BOX D**).

- *Sortilin-dependent neurotrophin signaling in AD*

Sortilin is also an important neurotrophic receptor. ProBDNF as well as proNGF form a ternary complex with sortilin and $p75^{NTR}$, which promotes signaling towards neuronal cell death [51, 160]. On the other hand, when sortilin binds BDNF receptors TrkA, TrkB or TrkC, it controls their anterograde trafficking along neurites to promote neurotrophin signaling to support neuronal outgrowth, neuronal survival and synaptic plasticity [148]. ProBDNF increases the expression of sortilin and $p75^{NTR}$ *in vitro* which prevents its proteolytic cleavage and processing, possibly as a consequence of its binding to the high-affinity sortilin and $p75^{NTR}$ receptor complex [160, 164]. Chen et al showed that binding of proBDNF to sortilin is mediated by the prodomain of proBDNF (amino acids 44-102), and that this interaction is reduced in the BDNF-Val66Met mutated protein [162]. They further showed that sortilin traffics wild-type BDNF into the pathways for regulated secretion whereas the BDNF-Val66Met mutation disrupted this sorting [162]. The reduced binding of BDNF Met66 to sortilin may explain the faster cognitive decline in AD that harbors this mutation [36-38]. A recent study from Fleitas et al further proposed that accumulation of reactive oxidative species (ROS) in AD patients stabilizes proBDNF and disables its maturation into BDNF which will increase proapoptotic signaling and blunt its trophic actions [56]. The authors examined hippocampal tissue from AD patients and found a significant increase in sortilin and proBDNF levels, which translated

into an enhanced proBDNF/BDNF ratio in CSF of the patients. Strikingly, when the authors applied CSF from AD patients on cultured WT hippocampal neurons, they observed enhanced proBDNF-$p75^{NTR}$-dependent apoptosis whereas they did not when using CSF from healthy controls [56]. These data propose the proBDNF/BDNF ratio as a biomarker for AD diagnosis or disease progression.

A hallmark of AD is the early and progressive dysfunction, synaptic loss and degeneration of basal forebrain cholinergic neurons (BFCN). The reason for their selective vulnerability is not fully understood but BFCN are reliant on mature NGF that is produced by and transported retrogradely back from their target neurons in cortex and hippocampus. In AD patients NGF levels and TrkA expression are decreased in the cholinergic neurons of the nucleus basalis whereas proNGF is increased [61, 73, 184, 185]. Given the expression of $p75^{NTR}$ and sortilin is preserved in AD brains, these alterations favor an increase in proapoptotic signaling on the expensive trophic stimulation. In support of such a model, transgenic mice expressing an anti-NGF-antibody that electively targets mature NGF leaving the proform unperturbed accelerates BFCN pathology and cognitive impairments [186]. Likewise, mice with proNGF overexpression develop age-dependent memory impairments, cholinergic deficits and, surprisingly, also increased formation of Aβ oligomers [187]. To demonstrate the requirement of the $p75^{NTR}$ – sortilin receptor complex for executing these functions, BFCN pathology and cognitive impairments in the mice expressing the neutralizing anti-NGF antibodies were recused on the genetic background of $p75^{NTR-/-}$ and $Sort1^{-/-}$, respectively [188, 189].

- *Sortilin in AD related pathology and neurodegenerative disorders*

Increased Tau phosphorylation, its subsequent misfolding and prion-like spreading are common pathological features in AD brains [4]. By using mutant Tau transgenic mice (P301S), prion-propagation assay and inhibitory antibodies against sortilin, Johnson et al found that sortilin activity suppresses replication of Tau prion in the forebrain thus protecting it against neurotoxic pTau aggregation. On contrary, sortilin expression is lower in the hindbrain where it does not protect against p-Tau

accumulation [149]. AD shares several other mechanisms with Prion diseases, a group of fatal neurodegenerative disorders which major genetic component is neuronal Prion protein (PrP^C). Prp^C is a transmembrane receptor localized in lipid rafts [190] that regulates neuronal excitability and neurite outgrowth [191]. PrP^c inhibits BACE1 and Tau expression, which subsequently reduces the levels of Aβ in the brain [192]. During AD, PrP^C converts into its polymerizing, misfolded form called scrapie isoform PrP^{Sc}, which binds AβO, and transduces their cytotoxic signals across the neuronal membrane [193-195] causing synaptic failure and cognitive impairments [196-200]. A recent study discovered that a PrP^C antagonist blocks the aggregation, and rescues the Aβ-related synapse loss and memory deficits in AD transgenic mice [201]. Strikingly, Uchiyama et al. showed that sortilin is neuroprotective against the prion spreading as it internalizes PrP^C and PrP^{Sc}, and transports them into lysosomes for their degradation. However, it is also reported how PrP can be a determinant of sortilin activity, as increased accumulation of cytotoxic PrP^{Sc} leads to lysosomal degradation of sortilin resulting in progressive propagation of PrP^{Sc} [202]. Accordingly, sortilin deficiency leads to early accumulation of PrP^{Sc}, and accelerated disease progression and death of the mice These observations pinpoint the neuroprotective role of sortilin sorting against protein misfolding and prion-related spreading that might include internalization of other proteins than just Tau and PrP.

Along with aggregation of TAR DNA-binding protein 43 (TDP-43), Tau pathology is also a hallmark of frontotemporal dementia (FTD) [203]. Haploinsufficiency for *GRN*, that encodes progranulin (PGRN) and a factor with widespread neuroprotective and anti-inflammatory functions, is one cause of FTD [204]. Haploinsufficent patients have a 50% reduction in PGRN levels, why inhibiting its clearance from the brain extracellular space has been proposed as a therapeutic approach. In a human cohort a SNP in *SORT1* was identified that increases sortilin expression is associated with reduced plasma PGRN concentration [205]. Hu et al found that sortilin binds PGRN and mediates its endocytic uptake and extracellular clearance and

that preventing its function can normalize PGRN levels in *Grn*$^{+/-}$ mice [206]. Accordingly, a phase II clinical trial using a sortilin inhibiting antibody recently achieved positive results in FTD patients [204].

TDP-43 pathology is also common in AD with more than 55% of the patients having these inclusions [207]. Interestingly, *SORT1* can be alternatively spliced to generate an mRNA transcript named Ex17b that includes a premature stop codon that translates into a truncated soluble receptor variant that retains its ligand binding abilities [208, 209]. In the healthy brain nuclear TDP-43 inhibits this splicing leading to exclusion of Ex17b and expression of the full-length receptor. In FTD and AD, the nucleus is depleted TDP-43 favoring its cytoplasmatic aggregation and this will drive splicing and produce the soluble and dominant negative Ex17b decoy receptor [208, 209]. The functional link between sortilin and FTD and AD finds further support in the GWAS by Bellenguez et al which, in addition to *SORT1*, also identified *GRN* as a critical risk gene in AD [11]. Remarkably, the rare sortilin K302E predicted loss of function mutation present in AD patients [11] has been identified also as a causal patient-only variant in FTD patients [93].

To conclude, there is substantial evidence that sortilin regulates a number of activities involved in (non)-amyloidogenic pathways, Aβ clearance, neurotrophic signaling, and prion-related spreading during AD neurodegeneration. The complex modalities by which the receptor operates with some functions being protective and others detrimental, may explain why certain *SORT1* SNPs reduce disease risk whereas others increase risk of AD.

SorCS1 biology and its links to AD

SorCS1 was identified as the first SorCS proteins from mouse brain by Hermey et al in 1999 [94], followed by SorCS2 and SorCS3 in 2001 [210]. SorCS1, 2 and 3 hold high structural homology, and thus they partially overlap in their functions when expressed in the same tissue. They mostly differ from each other in their cytoplasmic tail which interact with various adaptors to control cellular trafficking and signaling [107, 210]. SorCS1 is unique as it exists in (at least) five isoforms, SorCS1a-e, that vary in their cytoplasmic tails and in

their expression pattern. When overexpressed, murine SorCS1a undergoes rapid internalization via its binding to clathrin adaptor AP-2, whereas SorCS1b predominates at the plasma membrane and shows little trafficking activity [211]. Rather, SorCS1b may engage in signal transduction given that its cytoplasmic tail contains consensus sequences for a SRC Homology 3 Domain (SH3) binding motif. SH3 motif is recognized by many protein tyrosine kinases including Src family such as Src, Fyn, Blk or Lyn which regulate many cellular functions including cell proliferation, differentiation, migration, and survival [212]. SorCS1c can bind Vps35, the core protein of the retromer complex that controls transport out of the endosomal compartment but its intracellular domain also harbors interaction site for adaptors involved in cellular signaling [98, 99, 211, 213]. As a consequence, SorCS1 is present both in the soma, dendritic vesicles, and at the plasma membrane in neurons [214-216] (**Figure 6**). The physiological functions of the receptor variants are only slowly emerging and needs to be investigated in more detail. SorCS1 can form homodimers as well as heterodimers with SorCS2 and -3 but the functional consequence has not been studied [217]. However, the N-terminus sequence of SorCS1 can bind sortilin, which substantially reduces the ability of sortilin to mediate cellular uptake of its ligands and hampers its ability to support signaling by ciliary neurotrophic factor [218] (**Figure 6, BOX A**). SorCS1 shows the highest expression in neurons from cerebral cortex, amygdala, hippocampus, and thalamus, while during mouse development it is mostly expressed in forebrain [98, 215]. The expression is very dynamic and can be regulated by synaptic activity [107, 215]. For example, kainic acid, a glutamate analog, induces high expression of SorCS1 in the hippocampus [107, 215]. More physiologically, during memory consolidation SorCS1 is upregulated 220-fold in engram cells, the cells that encode a specific memory [219]. Whether this upregulation is specific to one or more of the splice variants is not known. A function for SorCS1 in neurotrophin signaling has only been sparsely studied. SorCS1 binds and facilitates intracellular trafficking of TrkB, and it is able to inhibit BDNF activation (**Figure 6, BOX C**) in contrast to the stimulatory activity seen for sortilin and SorCS2 (see below) [53, 148, 220].

Several human genetic studies linked SNPs in *SORCS1* gene to memory retention [221] and the risk of AD [82, 83, 222-228]. Accordingly, gene expression analysis of amygdala from 19 AD patients revealed significantly lower *SORCS1* expression compared to healthy controls [225]. Further, *SORCS1* genetically interacts with SNPs in *APOE* [229, 230], *SORCS2* and *SORCS3* [83], respectively, to increase AD risk suggesting that these proteins functionally associate in shared actions. Several SNPs in *SORCS1* have also been linked to neurodegenerative transmissible spongiform encephalopathies caused by accumulation of PrP^{sc}. Given that prion seeding characterizes many deteriorating brain disorders, it may suggest a broader involvement of SorCS1 in neurodegenerative processes, similarly to sortilin [231].

- *SorCS1 and amyloid beta homeostasis*

There are several functional studies uncovering the importance of SorCS1 in Aβ metabolism. Several studies demonstrated that APP can physically interact with both the SorCS1a, -b, and -c isoforms suggesting that SorCS1 may function in trafficking of and potentially also signaling by APP [213, 214, 225]. In accordance with a function in cellular sorting, SorCS1c but not SorCS1b retains APP from insertion into anterogradely transported vesicles in hippocampal neurons [214, 232] (**Figure 6, BOX B**). Knockdown of SorCS1a and -c expression in neuroblastoma cells increase Aβ production [214, 225], and disrupting the binding site in SorCS1c for the retromer complex perturbed APP sorting through endosomal compartments, decreased retrograde TGN trafficking, and increased Aβ production resembling SorCS1 loss of function [213]. On the other hand, overexpression of SorCS1a, -b, and -c decreased levels of Aβ, as well as lowered levels of secreted APP products [91, 213, 225] (**Figure 6, BOX D**). Studies in SorCS1 knockout mice have confirmed many of the *in vitro* observations. Hence, receptor deficiency translated into an increase in APP C-terminal fragments in brain of females but apparently the male mice were not affected by SorCS1 deletion [213]. This is especially interesting given that genetic association between SorCS1 and AD is strongest for women. Strikingly, Hermey et al recently found that the progressive amyloid plaque formation in aged AD mice (APP/PS1) decreases the levels of SorLA, SorCS1, and SorCS3

in frontal cerebral cortex and to a minor extent also in hippocampus, forming a virtuous self-amplifying loop [232]. It has also been reported that SorCS1 itself is a substrate for PSEN-dependent γ-secretase cleavage [90] and ADAM17 α-secretase, which will downregulate receptor expression adding yet another loop to the complex function of SorCS1 (**Figure 6, BOX E**) [100].

- *SorCS1 in AD comorbidity*

Type 2 diabetes (T2DM) is characterized by hyperglycemia and insulin resistance and it is commonly comorbid with AD, increasing the risk of AD diagnosis by approximately 2-3 folds ([233], reviewed in [234, 235]). On contrary, approximately 80% of AD patients exhibit insulin resistance and impaired glucose handling [236-238] suggesting that likely there are common molecular pathways involved in both disorders. Hyperinsulinemia is associated with impaired cognitive performance while hyperglycemia has been proposed to increase Aβ accumulation, exacerbate oxidative stress, neuroinflammation, and mitochondrial dysfunction, ultimately leading to impaired neuronal integrity, and ultimately neurodegeneration. In recent years this shared comorbidity is sometimes called Type 3 diabetes mellitus. Interestingly, SorCS1 regulates insulin metabolism and secretion as it facilitates the release of insulin from pancreatic β cells [239]. Therefore it is not surprising that impairments in SorCS1 activity are strongly associated with Type 1 and Type 2 diabetes [240-244]. Strikingly, T2DM has been identified as a contributing risk factor to AD etiology patients carrying SNPs in SorCS1 [245, 246]. Put together, these data suggest that aberrant SorCS1 function in the brain might fail to not only integrate the APP sorting and processing, but also the signaling of another contributing trophic factor, insulin. Impairments in SorCS1 can thus lead to the pathophysiological events that are behind the AD onset and progressive neurodegeneration.

- *SorCS1 links to AD by altering synaptic plasticity*

Decreased levels of synaptic membrane proteins like neurexins [247-249] and enlargement of early endosomes [250] have been proposed as novel biomarkers for AD diagnosis. Trans binding of neurexins

which are expressed on the presynapse to neuroligins present at the postsynapse is required for synaptogenesis and synaptic stabilization. However, neurexins can also bind AβO which disrupts the interaction with neuroligins leading to severe damages of excitatory synapses [251, 252]. Recently, Joris de Wit's group described that SorCS1 is a key sorting molecule regulating the axonal-dendritic polarization of synaptic proteins, which is a critical for neuronal wiring and synaptic plasticity [98, 216]. They discovered that SorCS1 localizes into early and recycling endosomes, where it controls trafficking of neurexin and postsynaptic AMPA glutamate receptor (AMPAR) to the neuronal surface. Since SorCS1 expression must be tightly regulated, the overexpression and the loss of SorCS1 activity leads to perturbed sorting and a shifted ratio in the localization of neurexin1α, AMPARs, neuroligin and other polarized synaptic adhesion molecules at the axonal and dendritic surfaces [98, 216] (**Figure 6, BOX F**). The imbalance in synaptic proteins distribution is caused by impaired SorCS1 interaction with Rab11-family-interacting protein 5 (Rip11), which governs the transition from early endosomes to Rab11-positive recycling endosomes. The alterations translate into reduced glutamatergic and GABAergic neurotransmission in cortical layer 5, an area where neurons are substantially affected in AD [98]. This is in accordance with observation that fluctuations in neurexin and AMPA receptor activity sways the balance between excitatory and inhibitory neurotransmission in AD [253]. Notably, GABAergic and AMPA receptor neurotransmission is compromised in AD patients, and such alterations are associated with the cognitive decline [254-256]. Therefore, the impairments in SorCS1-dependent APP catabolism, trafficking of adhesion molecules, neurotransmitter receptors and trophic receptors may jointly cause synaptic dysfunction, synapse loss and neurodegeneration in AD patients. Unfortunately, the molecular mechanisms of SorCS1 signaling are still largely unknown. Future studies should thus functionally address the spectra of SorCS1 isoforms in relations to its binding partners in order to fully understand the regulatory mechanisms directly or indirectly involved in AD pathogenesis.

SorCS2 biology and its relations to AD

SorCS2 was described by Rezgaoui et al in 2001 as a gene dynamically expressed during mouse brain development, particularly in dorsal thalamus and midbrain floorplate [257]. In adulthood, SorCS2 is highly expressed in hippocampus (particularly in dentate gyrus, CA2 and CA3 regions), piriform cortex and in striatal medium spiny neurons [107, 257-259]. It is localized mostly in soma in form of vesicles, but also in neurites, dendritic spines, filopodia-rich projections, and in the growth cone of projecting axons [35, 53, 54, 97]. Like other VPS10p receptors, SorCS2 engages in cellular trafficking and signaling controlled by its expression and the presence of co-receptors and ligands. Expression of SorCS2 can be altered by external stimuli, which was demonstrated by deep brain stimulation of subthalamic nucleus [260] (**Figure 7, BOX B**). This feature is crucial for acute morphological responses, such as neurite regrowth, synaptogenesis as well as disassembling of synapses, and the control of synaptic plasticity [54]. Nykjaer's group showed that SorCS2 exists in three active isoforms: an immature proform, and mature single- and two-chain variants. These isoforms are generated by sequential proteolytic cleavage, and are presented uniquely by neurons and glial cells during intercellular communication in order to activate either trophic (single-chain) or pro-apoptotic (two-chain) signaling [97] (**Figure 7, BOX A**). The receptor can also form homodimers which may adopt at least two distinct conformations that is controlled by binding of its ligands [217, 261]. Potentially, this might modify its interaction with co-receptors or cytosolic adaptor proteins, and thus regulate SorCS2-dependent signaling and sorting. Among its many functions, SorCS2 facilitates intracellular sorting and distribution of synaptic proteins, and protects neurons from oxidative stress and neuronal death [259, 262]. It also transduces signals that mediate neuronal remodeling and synaptic plasticity [53, 54, 97]. As such it has been genetically linked to a number of psychiatric and neurodegenerative disorders [259]. Human genetic studies uncovered more than 18 SNPs in *SORCS2* that were associated to AD [82, 83]. They also observed epistatic interactions with SorCS1 and SorCS3 in AD patients [83]. Despite the genetic data and established functions in signaling and neurotransmission, SorCS2 is the least studied VPS10p receptor

when it comes to AD. In the following paragraphs we will discuss the possible molecular and functional implications of SorCS2 in AD pathogenesis.

- *SorCS2 in neurotrophic signaling and synaptic plasticity*

In the adult brain, the major function of SorCS2 is to govern synapse morphology, synaptic plasticity, and control neurotrophin signaling; processes crucially involved in AD. SorCS2 binds and mediates intracellular sorting and synaptic localization of the NMDA receptors GluN2A and GluN2B [259, 263], and the excitatory amino acid transporter EAAT3 [262] (**Figure 7, BOX E**). The studies showed that SorCS2 deficiency in these neurons leads to enhanced cellular stress responses, excitotoxicity, and neurodegeneration. Strikingly, mass spectrometry analysis of rat brains revealed that SorCS2 interacts with neurexin1β [98], which manifests the central role of SorCS2 in synaptogenesis, synaptic proteome composition, and synapse stability.

Particularly well studied is SorCS2 function in signaling established by pro- and mature neurotrophins, which is illustrated in **Figure 7, BOX C**. ProNGF and proBDNF bind to SorCS2 at the plasma membrane and both single- and two-chain SorCS2 variants can be in complex with a proneurotrophin ligand and $p75^{NTR}$ [97] forming higher-order signaling complexes [261]. During neuronal development, the SorCS2-$p75^{NTR}$ complex is essential for proBDNF and proNGF to induce growth cone collapse of extending neurites thereby controlling neuronal wiring and connectivity. Notably, this activity is specifically reliant on the single-chain isoform of SorCS2. In contrast, two-chain SorCS2 is required for induction of apoptosis of glia cells by proNTs [97]. Binding of the cytosolic guanine-nucleotide exchange factor Trio to SorCS2-$p75^{NTR}$ is required for the retraction of extending axon [54]. As demonstrated for proNGF, the engagement of the SorCS2-$p75^{NTR}$ complex with a proNT displaces Trio and downregulates Rac1 signaling while activating Protein kinase C. Jointly, these events destabilize actin filaments, and lead to impaired filopodia retraction and subsequent growth cone collapse [54]. If defective, such impairments perturb neuronal connectivity

and synapse function, causing increased neuronal vulnerability and neuronal death in the aging brain [97, 264-266].

The biological function of single-chain SorCS2 is not limited to the neurodevelopmental stage. In the postnatal hippocampus, binding of proBDNF released from the presynapse to the SorCS2-p75^{NTR} complex located in the postsynapse will induce long-term depression (LTD) and synaptic weakening [53]. Notably, SorCS2 can engage with TrkB to enable the recruitment of TrkB from extrasynaptic sites to PSD95-positive domains, which is necessary for induction of long-term potentiation (LTP) and synaptic strengthening by mature BDNF [53] (**Figure 7, BOX D**). Studies by Mizui et al further revealed that cleaved propeptide of BDNF (pBDNF) can be independently secreted in the activity-dependent manner to facilitate LTD [267]. Strikingly, the propeptide containing the naturally occurring pBDNF-Val66Met mutation, which is associated with memory impairment and predicts cognitive decline in AD patients [36-38], binds to SorCS2 with a greater affinity than pBDNF-WT [268]. While SorCS2 binding to pBDNF-WT increases LTD [267], the interaction with the pBDNF-Val66Met abolishes LTD as it induces Rac1 downregulation followed by the loss of Trio-positive dendritic spines, and acute growth cone retraction [35, 268]. This regulation is followed by reduced dendritic spine density in CA1 region of hippocampus, altered prelimbic projections and maturation of fear extinction circuitry [35, 267, 268].

So far SorCS2 has not been studied in the context of the amyloidogenic pathways. However, its multiple activities in neuronal wiring, synapse dynamics, neurotransmission and synaptic plasticity governed by proNT-SorCS2-p75^{NTR} and BDNF-SorCS2-TrkB signaling and by trafficking of neurotransmitter receptors and transporters, clearly demonstrate the critical role played by SorCS2 in neuronal integrity and functionality. Although disturbances in SorCS2 increase neuronal vulnerability [259] and may precipitate earlier AD onset and propel disease progression for those at risk, studies are required to address whether SorCS2 may also directly impact on amyloid and Tau biology and pathology.

SorCS3 biology and its links to AD

Despite very limited knowledge about the molecular function of SorCS3, there is substantial evidence for its implications in AD. Similarly to SorCS1 and -2, SorCS3 exhibits spatiotemporal expression during development. In the adulthood, SorCS3 is expressed across the brain, with the highest expression in the CA1 region of hippocampus and in cerebral cortex [106, 107]. SorCS3 mostly localizes at the plasma membrane where it binds its ligands, even prior to its maturation by propeptide cleavage [269]. The SorCS3 cytoplasmic tail is responsible for its intracellular trafficking as it navigates SorCS3 into dendrites and to a lower extent also into axons [106] (**Figure 8**). The major function of SorCS3 is to control synaptic structure and function, via binding of scaffold proteins and controlling glutamate receptor trafficking [270, 271]. However, a function in neurotrophin signaling has also been demonstrated [220, 269]. In 2013, Reitz et al described for the first time that *SORCS3* is genetically associated to AD (12 SNPs). An epistatic analysis of the AD cohort revealed a strong interaction of *SORCS3* mutations with those in *SORCS2* (24 SNP pairs) and *SORCS1* (8 SNP pairs). These mutations were all located in introns 1 and 2, thus the introns contiguous to the exons encoding the ligand-binding VPS10 domain (similarly to SNPs found in *SORCS1* and *SORCS2*) [83]. Further, a recent whole genome sequence analysis of a multiethnic cohort comprising 11,000 women, found a strong genome-wide significant association between *SORCS3* and dementia with an odds-ratio of no less than 4.4. Transcriptome analysis confirmed that SorCS3 expression is indeed substantially decreased in the context of AD [272]. These studies found that SorCS3 is consistently downregulated in AD [83, 273]. The Psychiatric Genomic Consortium recently identified *SORCS3* as a shared top-risk gene across 8 different psychiatric disorders highlighting the pleiotropic though unclear function of SorCS3 in healthy and diseased human brain [89]. A GWAS analysis from a Han Chinese cohort of AD patients with major depression disorder further identified 675 SNPs in *SORCS3* gene, thus bridging these two commonly comorbid disorders [274, 275] with one risk factor [89, 276]. In the following paragraphs we will discuss the direct and indirect functional links of SorCS3 to AD.

- *SorCS3 and amyloidosis*

Ni et al found a differential expression of *SORCS3* in AD brains when comparing hippocampus, entorhinal cortex, frontal cortex, and temporal cortex [276]. Additionally, Reitz et al showed that expression of three *SORCS3* exons (exons 10, 17 and 21) is reduced in the amygdala of AD patients. In contrast, the occipital lobe and cerebellum that also express *SORCS3* were unaffected by the disease [83]. The authors proposed that SorCS3 is involved in the amyloidogenic pathway by regulating the activity of γ-secretase and APP processing. Indeed, overexpression of SorCS3 leads to downregulation of γ-secretase activity, whereas SorCS3 knock-down causes an increase in γ-secretase processing of APP [83] (**Figure 8, BOX B**). A recent study by Hermey et al investigated SorCS3 expression in specific brain regions during healthy aging and after amyloidosis. They compared SorCS3 expression in aging wild-type mice with APP/PS1 mice that model AD and develop Aβ plaque within the first year of life. They found that amyloid plaques formation, but not aging, reduces SorCS3 expression in the frontal cerebral cortex, with no change in the hippocampus [232]. These data suggest that the AD pathogenesis is associated with impaired SorCS3 activity in a brain region-specific manner.

- *SorCS3 in synaptic transmission, learning, and memory*

During development, SorCS3 acts as a downstream effector of Transcription factor T-box brain1 (Tbr1) expression that restricts dendritic projections towards their synaptic targets [277] (**Figure 8, BOX A**). Immature as well as cleaved SorCS3 receptor can bind proNGF and NGF *in vitro* but the functional consequences have not been explored [269]. Moreover, SorCS3 can physically interact with TrkB which abrupts BDNF-dependent TrkB activity in the hypothalamus and likely contributes to energy metabolism balance [220] (**Figure 8, BOX C**). Aside from these observations, SorCS3 relations to neurotrophin signaling and plasticity remain unknown. Recent studies highlighted SorCS3 as an important regulator of synaptic events in excitatory neurons but with only minimal impact on the inhibitory input [270, 271]. Moreover, SorCS3 deficient mice exhibit loss of NMDAR and mGluR-dependent LTD in the hippocampal CA1 region,

while LTP is preserved. These mice have no sign of brain atrophy but respond to repetitive stimulation with synaptic facilitation and reduced synaptic depression; a phenotype that progressively worsened as the animals aged [271]. This is particularly interesting because fear conditioning enhances *Sorcs3* expression by 170-fold in the hippocampal engram cells arguing that SorCS3 signaling and/or sorting may contribute to memory formation and consolidation [219]. Indeed, studies using S*orcs3 KO* mice reported that the animals exhibited impaired spatial learning but increased fear extinction [270]. Interestingly, protein levels of PSD95, AMPA receptors, NMDA receptors, metabotropic glutamate receptor mGluR5, $p75^{NTR}$ and TrkB are not changed in postsynaptic density fraction extracted from hippocampi of *Sorcs3 KO* mice [270]. However, Breiderhoff et al showed that SorCS3 crosstalks with some synaptic proteins. SorCS3 localizes at the postsynaptic density where it binds PSD95 via its putative PDZ domain binding motif in its cytoplasmic domain [270]. The authors also proposed that SorCS3 interacts with an adaptor molecule Protein interacting with C-kinase 1 (PICK) by which it controls the necessary removal of the AMPA receptors from the postsynaptic side [270], similarly to SorCS1 [98]. This study was further supported by electrophysiological observations that LTD deficiency in CA1 region is age-dependent, and that the loss of SorCS3 impacts on AMPA receptors mobility [271]. SorCS3 actions at postsynapse of excitatory neurons during memory formation are depicted in (**Figure 8, BOX D**).

Given the genetic association to AD and the important functions of SorCS3 in APP processing, synaptic transmission, and synaptic retraction of excitatory neurons involved in learning and memory, additional studies are merited to examine its role in the context of AD. SorCS3 remains the least studied of the VPS10 p receptors. Future studies should thus: 1) determine SorCS3 binding partners in amyloidogenic pathways and synaptic events, and 2) describe the molecular mechanisms by which SorCS3 regulates synaptic transmission in the healthy and AD brain. Moreover, SorCS3 possible interaction with the neurotrophic signaling deserves more attention as the rest of this receptor family serves critical functions in neurotrophin-dependent neuronal survival and death.

Therapeutic perspectives of VPS10p receptors in AD

It remains unclear whether certain neurons in AD brains become vulnerable mostly due to intrinsic or extrinsic factors. The largest therapeutic potential used to lie within blocking the pro-amyloidogenic cascade and/or dissolving the amyloid plaques and Tau-containing tangles. Unfortunately, the current strategies are inefficient and do not stop the disease progression. In this review, we illustrated that the AD pathogenesis has been tightly connected with impaired activity of VPS10p receptors in neurons. However, not much is known about VPS10p receptors signaling in the context of intercommunication between cell types such as microglia-neuron, a feature largely implicated in AD. Microglia are non-neuronal cells that support neurons by secreting trophic factors and performing phagocytic clearance during synapse remodeling and tissue repair. Together with astrocytes they are responsible for ApoE production which controls the deposition and clearance of Aβ peptides. With AD progression and increased Aβ accumulation, activated microglia compromise their phagocytic abilities, alter their secretome, and mediate chronic neuroinflammation leading to synaptic loss and AD neurodegeneration. The possession of ApoE4 allele triggers and sustains the microglia-driven neuroinflammation. Enhancing phagocytosis and decreasing neuroinflammation in AD patients has become a new therapeutic target, even though this cell communication remains a black box [278, 279]. Since neuronal VPS10p receptors closely and diversely interact with ApoE, Aβ and synaptic proteins, understanding the molecular mechanisms involved in this intercellular communication is key when targeting AD pathogenesis.

The importance of VPS10p receptors in neurotrophic signaling during CNS development and homeostasis also possesses a high translational value. Current advances in regenerative medicine show that reactivating the developmental features related to neurotrophic signaling during trauma and neuroinflammation promotes healing and improves the cognitive decline as it provides substantial functional recovery [280]. The potential of cell replacement therapies in AD represents a symptomatic solution with limited efficacy due to the broad spread of neurodegeneration. However, recent studies

uncovered that elevating the neurotrophin levels (such as BDNF, NGF and GDNF) in AD mice supports neuronal integration of grafted cells into the circuits, which improves the cognitive deficits [281, 282]. Recent work from Choi et al combined pharmacological and genetic approaches to elevate BDNF levels in the AD mouse model (5xFAD) to trigger adult neurogenesis in hippocampus. Indeed, this strategy improved cognitive performance of the mice [283]. Similarly, conditional BDNF delivery provided by astrocytes rescued dendrite outgrowth, neuronal connectivity and memory deficits in another AD study [284]. As boosting the BDNF concentration increases the neuroprotective levels of SorLA [121], such therapy could provide a relief of the AD symptoms.

Neurotrophins and Trk receptors facilitate a vast spectrum of functions in the CNS, and thus they represent a difficult therapeutic target. We therefore suggest that novel pharmacological interventions should instead aim for their binding partners, the VPS10p receptors, because they control more defined processes. Promoting the interaction between Trk receptors and VPS10p receptors might have positive effects on neurotrophin-dependent cell survival. *Sortilin KO* mice are resistant to acute and senescent neurodegeneration [52]. Therefore, drug discovery of sortilin antagonists that block the ability of sortilin interaction with $p75^{NTR}$ also represents a novel way of intervention against progressive cell death in AD. This approach has been proven functional for treating another neurodegenerative disease, frontotemporal dementia (FTD) which exhibits impaired sortilin-progranulin signaling axis [206, 285]. Currently, there is an ongoing FTD immunotherapy entering Phase 3 clinical trials that uses a monoclonal anti-human sortilin antibody called AL001 (Identifier: NCT04374136) [286]. If approved, this treatment could be expanded to AD patients.

Indeed, the various molecular interactions of VPS10p receptors in AD-related cell communication, their functional involvement in amyloidogenic pathways, and most importantly, their genetic links to AD identify these receptors as highly promising clinical targets for future advances in AD diagnostics and therapy.

CONCLUSIONS

Several human genetic and functional studies have repeatedly linked the VPS10p receptor family to AD, and to its pathophysiological features including accumulation of extracellular Aβ. Importantly, simultaneous deregulation of multiple members of this family has an epistatic effect on the AD onset. For example, both SorLA, sortilin, and SorCS1 play a major role in controlling APP trafficking, but they guide the precursor to different subcellular destinies. Similarly, SorLA directly interacts with Aβ, whereas the other receptors influence amyloid accumulation by acting in its metabolic processing. Impaired signaling of VPS10p proteins also leads to altered ratio between the amount of immature and mature neurotrophic factors thereby altering synaptic plasticity and neuronal cell fate, common features of AD. Last but not least, VPS10p receptor family has been linked to major depression disorder, prion-like infections, and diabetes mellitus, thus diseases that often accompany AD diagnosis. At present, we still have poor understanding about the precise molecular mechanisms by which these receptors signal in healthy and AD brains. Nevertheless, it is indeed clear that the versatility of VPS10p receptors and their broad molecular interactions with AD-related pathways can help explaining the AD diversity and its comorbidities. We therefore expect that this exciting field will soon escalate, and lead to uncovering many new diagnostic and therapeutic possibilities for AD patients in the future, in particular with focus on SorLA, SorCS1 and SorCS3.

LIST OF ABBREVIATIONS

AD - Alzheimer's disease

AMPAR - AMPA glutamate receptor

AP1/AP2 – Adaptor protein complex 1 and 2

APOE – Apolipoprotein E

APP - Amyloid-beta precursor protein

Aβ - Amyloid beta

AβO – Cytotoxic amyloid beta oligomers

BACE1 – Beta-secretase 1

BDNF - Brain-derived neurotrophic factor

BDNF-Val66Met – Brain-derived neurotrophic factor carrying a substitution of Valine with Methionine

BFCN - basal forebrain cholinergic neuron

CNS – Central nervous system

EOAD – Early-onset Alzheimer's disease

FTD – Frontotemporal dementia

GDNF - Glial cell line-derived neurotrophic factor

GGA - Golgi-localized gamma-ear-containing ARF-binding protein

LOAD – Late-onset Alzheimer's disease

LTD – Long-term depression

LTP – Long-term potentiation

NGF - Nerve growth factor

NT3/4 - Neurotrophin 3/4

p75NTR - Neurotrophin receptor denoted p75

PAK 1-3 - Rac-p21-activated kinases 1 to 3

pBDNF – propeptide of BDNF (after cleavage of proBDNF)

PGRN - progranulin

PNS – Peripheral nervous system

proBDNF – Precursor of Brain-derived neurotrophic factor

proNGF – Precursor of Nerve growth factor

proNTs – Proneurotrophins

PrP^{C} – Prion protein

PrP^{Sc} – Scrapie isoform of prion protein

PSEN1/2 – Presinilin 1/2

pTau – Hyperphosphorylated Tau

Rab7 - Ras-related protein

sAPP – Soluble Amyloid-beta precursor protein

SNP – Single nucleotide polymorphism

SNX-1 – Sorting nexin 1

TDP-43 - TAR DNA-binding protein 43

T2DM – Type 2 Diabetes Mellitus

TGN – Trans-Golgi network

TrkA/B/C - Tropomyosin receptor tyrosine kinases A/B/C

VPS10p - Vacuolar protein sorting 10p

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Not applicable

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

AS wrote the majority of the manuscript, prepared the figures, and coordinated the finalization of the article. GM wrote the section about SorLA, and overall contributed to the main text of the manuscript. OA initiated this project and contributed to writing and correcting the text. AN contributed to the writing and correcting the manuscript.

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FIGURE LEGEND

Figure 1: A simplified scheme of APP proteolytic processing and the origin of Aβ plaques. APP is a type I transmembrane receptor that contains Aβ peptide within its sequence. α-secretases such as ADAM10/17 cleave APP inside the Aβ peptide, which is disrupting, and produces soluble, secreted sAPPα fragment. sAPPα is neuroprotective, and thus this cleavage is called non-amyloidogenic pathway. The sequence is further cleaved by γ-secretase producing soluble P3 peptide. In contrast, APP can be cleaved by β-secretase, for example BACE1, creating a cytotoxic, soluble sAPPβ. The proteolysis by β-secretase exposes Aβ peptide, which is further cleaved by γ-secretases such as PSEN1/2. This cleavage results in the release of Aβ monomers into the extracellular space, where they can further polymerize forming Aβ oligomers, and later Aβ plaques. This pathway is neurotoxic and is called amyloidogenic pathway.

Figure 2: VPS10p receptors – their structure and genetic and transcriptional relations to AD. Except for SorLA, the receptors exhibit similar structure, mostly differing in the sequence of their intracellular cytoplasmic tails. SorCS1-3 are paralogs that often form homodimers. All the receptors have been genetically linked to AD diagnosis. Independently from the genetic background, AD patients display changes in the receptors' expression levels within the brain parenchyma. These are predominantly diminished, and likely contribute to the disease progression such as decreased neuroprotection.

Figure 3: The role of SorLA in APP processing. ***Panel A)*** APP is directed from the trans-Golgi network (TGN) to the plasma membrane via the secretory pathway. APP molecules are either cleaved by α-secretase at the plasma membrane or recycled through endocytosis, and trafficked by early endosomes. There, APP is sequentially cleaved by β- and γ-secretases, thus generating Aβ monomers that are secreted to the extracellular space. ***Panel B)*** A model of SorLA involvement in the amyloid cascade. *1.-3.* SorLA interacts with APP in TGN acting as a retention factor, which reduces α-secretase cleavage and secretion of sAPPα from the cell surface. *4.-6.* In addition, SorLA forms a complex with APP that shuttles between the TGN

and endosomes. In this way, the sorting receptor is responsible for reducing the interaction between APP and β- and γ- secretases. Finally, binding of SORLA to BACE1 blocks the APP-BACE1 interaction, which reduces the production of secreted Aβ peptides.

Figure 4: SorLA localization within a neuron and its signaling in AD. SorLA predominantly localizes in neural soma and dendrites, either in sorting vesicles or at the plasma membrane. **Box A)** The presence of extracellular BDNF in human brain mediates expression of *SORL1*, which increases SORLA protein levels attenuating the production and secretion of Aβ. **Box B)** A scheme of how SorLA regulates EphA4 signaling. Under physiological conditions (*left panel*), EphA4 binds its juxtapositioned ligand EphA1 which triggers clustering of EphA4 receptors, and their subsequent phosphorylation. EphA4 activation triggers disassembly and retraction of F-actin filaments causing growth cone collapse crucial e.g. for dendritic spine pruning. AD patients (*right panel*) show increased levels of EphA4 in close proximity to Aβ plaques. Moreover, EphA4 binds Aβ oligomers which results in increased AphA4 activation and abnormal actin filaments retraction causing dendritic spine retraction and synaptic loss. SorLA (*middle panel*) binds EphA4, which prevents EphA4 clustering. Increased SorLA levels thus diminish the EphA4 activation, which lowers the responsiveness of the neurons to growth cone retraction even in presence of AβO, thus protecting the neurons against synaptotoxicity. **Box C)** SorLA binds and traffics TrkB receptor towards the synapse where they remain as a receptor complex. Upon BDNF release and subsequent activation of TrkB, SorLA further drives TrkB internalization, which is a critical step for the subsequent BDNF-dependent neurotrophic response and synaptic plasticity.

Figure 5: Functional involvement of sortilin in AD-related signaling. Sortilin localizes in sorting vesicles and on the plasma membrane (PM) in neuronal somas, dendrites and axons. **Box A)** Sortilin undergoes ectodomain shedding by ADAM10/17, which produces soluble sortilin fragments. In humans, C-terminal fragments are found within the Aβ plaques. **Box B)** Sortilin binds BACE1 in TGN and facilitates its intracellular trafficking via anterograde and retrograde pathways, the later directed either towards the

recycling pathway or for the lysosomal degradation. **Box C)** Sortilin binds APP at PM; however, its involvement in APP processing is controversial. *Left panel* - Sortilin binds APP at axonal PM where they undergo internalization. Sortilin either traffics APP for its lysosomal degradation (*a.*) or engages in amyloidogenic pathway by enhancing APP cleavage by BACE1 (*b.*), subsequently causing an increased formation and secretion of sAPPβ and Aβ. Sortilin is also a PSEN1/2 substrate. *Right panel* – Sortilin has a neuroprotective role as it mediates the uptake of soluble APP from the extracellular space (*1.*) for lysosomal degradation thus decreasing their extracellular concentration. Moreover, sortilin binds APP in neurites where it drives its preferential cleavage by ADAM10/17 (*2.*), thus elevating sAPPα levels. Consequently, there is less APP internalized (*3.*) prior the sequential cleavage by β- and γ-secretases (*4.*), resulting in decreased production of sAPPβ and Aβ (*4.-5.*). However, the molecular mechanisms are rather unknown (marked with "?"). **Box D)** Upon proNGF binding, sortilin forms a complex with $p75^{NTR}$ receptor, which mediates pro-apoptic cell responses (*left*). The presence of AβO increases sortilin expression, which likely enhances the formation and activity of sortilin-$p75^{NTR}$ complexes. Sortilin-$p75^{NTR}$ complex binds and internalizes AβO leading to increased intracellular neurotoxicity, and later cell death (*middle*). Sortilin can also bind and sequester extracellular ApoE, subsequently facilitating its lysosomal degradation, which has a neuroprotective effect (*right*). It is not clear if sortilin sequesters ApoE-Aβ complexes (marked as "?").

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regulates its cleavage by BACE1 and PSEN1/2. This way SorCS1 controls the physiological levels of secreted sAPPβ and Aβ. The abortion of SorCS1c-VPS35 interaction (*left panel*) enhances the APP anterograde trafficking causing an increased production and release of neurotoxic Aβ and sAPPβ. SorCS1 overexpression (OE; *right panel*) seems to strengthen the APP retention in TGN, thus significantly reducing the production and secretion of Aβ and sAPPβ, which has a neuroprotective effect against the formation of Aβ oligomers. **Box E)** SorCS1 is a substrate for PSEN1/2 and ADAM17, which attenuates its protein levels. However, molecular mechanisms involved in this regulation are unknown. **Box F)** SorCS1 sorts and recycles a number of synaptic receptors including Neurexin, AMPAR or Neuroligin at the postsynaptic side, by which it establishes the correct axon-to-dendrite polarization of synaptic proteins, processes critical for correct neurotransmission, connectivity, and synaptic plasticity.

Figure 7: SorCS2 signaling in neuronal networks relevant for AD. SorCS2 is found in neural soma, dendrites and axons. **Box A)** SorCS2 exists in three isoforms that have different signaling profiles. SorCS2 is initially produced as a proform, which can be cleaved by Furin from its propeptide, giving rise to a single-chain receptor. The single-chain can be further cleaved within the leucine-rich domain, producing a two-chain isoform. **Box B)** SorCS2 expression changes upon external stimuli, which affects synaptic plasticity. **Box C)** SorCS2 interactions with neurotrophins. *1.* SorCS2 single-chain binds $p75^{NTR}$ and Trio, which mediates Rac1 and Fascin signaling. Fascin activation leads to F-actin filaments assembly and growth cone outgrowth. *2.* ProBDNF or proNGF binding to SorCS2 leads to dissociation of Trio causing Rac1 signaling inactivation, actin filaments disassembly and retraction, and grow cone collapse, which is important for synaptic pruning and neuronal wirening. *3.* Propeptide of BDNF-WT binding to SorCS2 does not affect the growth cone outgrowth. *4.* Propeptide of BDNF with Val66Met mutation exhibits high binding affinity to SorCS2, subsequently dissociating Trio, and inhibiting Rac1 signaling. This pathway promotes elimination of spines and loss of synaptic adaptability. *5.* SorCS2 two-chain binds $p75^{NTR}$, which mediates proBDNF-dependent apoptosis. **Box D)** SorCS2 controls synaptic plasticity. Upon proBDNF release (*1a.*), SorCS2 mediates synaptic weakening (*4a.*) via its interaction with proBDNF and $p75^{NTR}$ (*2a.*), which induces long-

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Figure 8: SorCS3 localization and AD-related signaling. SorCS3 is predominantly located at the plasma membrane of dendrites where it binds its ligands. It is also found in axons but at much lower extent. **Box A)** SorCS3 is a downstream effector of transcription factor Tbr1, which restricts dendritic projections to their synaptic targets during development. **Box B)** SorCS3 signaling is involved in amoyloidogenic pathway. SorCS3 overexpression (OE) reduces γ-secretase activity and APP processing resulting in lower production and secretion of Aβ. SorCS3 gain of function is thus neuroprotective against accumulation of Aβ oligomers. In contrast, SorCS3 downregulation (KD) results in an enhanced γ-secretase activity and thus larger formation and secretion of Aβ into the extracellular space. Thus, SorCS3 loss of function is neurotoxic as it promotes the amyloidogenic pathway. However, molecular mechanisms behind these observations are unknown. **Box C)** SorCS3 can signal upon its ligands' binding already as a proform. Both SorCS3 isoforms bind proNGF and NGF, however the functional consequences remain unknown. SorCS3 can bind TrkB, by which it blunts BDNF-mediated TrkB activation. It is believed that this signaling axis is important for energy metabolism balance. **Box D)** SorCS3 signaling at the synapse is critical for memory formation and consolidation of excitatory neurons. SorCS3 resides at the postsynaptic side of excitatory neurons where it interacts with PSD95 and PICK1, which mediates the endocytosis and sorting of AMPA receptors, a critical step for GluR- and NMDAR-dependent long-term depression (LTD), spatial learning and fear extinction memory. Moreover, *Sorcs3* expression is dynamically regulated by external stimuli such as fear conditioning.

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Supplementary Files

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- Table1.pdf
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- Table3.pdf