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The Role of the Retromer Complex in Aging-Related Neurodegeneration: A Molecular and Genomic Review

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Abstract

The retromer coat complex is a vital component of the intracellular trafficking mechanism sorting cargo from the endosomes to the *trans*-Golgi network or to the cell surface. In recent years, genes encoding components of the retromer coat complex and members of the vacuolar protein sorting 10 (Vps10) family of receptors which play pleiotropic functions in protein trafficking and intracellular/intercellularsignaling in neuronal and non-neuronal cells and are primary cargos of the retromer complex, have been implicated as genetic risk factors for sporadic and autosomal dominant forms of several neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease and frontotemporal lobar degeneration. In addition to their functions in protein trafficking, the members of the Vps10 receptor family (sortilin, SorL1, SorCS1, SorCS2, and SorCS3) modulate neurotrophic signaling pathways. Both sortilin and SorCS2 act as cell surface receptors to mediate acute responses to proneurotrophins. In addition, sortilin can modulate the intracellular response to brain-derived neurotrophic factor (BDNF) by direct control of BDNF levels and regulating anterograde trafficking of Trk receptors to the synapse. This review article summarizes the emerging data from this rapidly growing field of intracellular trafficking signaling in the pathogenesis of neurodegeneration.

Keywords

retromer complex; VPS10 receptors; neurodegenerative disease; cell biology; genomics

INTRODUCTION

Recent molecular and genomic studies suggest that misprocessing and missorting of intracellular proteins within endosomal-lysosomal pathways is a key pathological mechanism in several age-related neurodegenerative diseases including Alzheimer's disease (AD), frontotemporal lobar degeneration (FTLD) and Parkinson's disease (PD). Numerous genome-wide association studies (GWAS) and biochemical studies have identified core components of the retromer (*VPS35* and *VPS26*) regulating endosomal sorting, and members of the vacuolar protein sorting-10 (Vps10) family of receptors (ie. *SORT1*, *SORL1*, *SORCS1*,

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SORCS2 and *SORCS3*) that are primary cargos of the retromer, as risk factors for neurodegenerative diseases highly prevalent in the elderly, consistent with the notion that dysfunction within these pathways is a major contributing factor to disease development and progression. This article reviews the physiological actions of the retromer complex and the Vps10 receptor family in intracellular sorting pathways and summarizes the rapidly growing evidence underlying the retromer-based pathogenesis of neurodegenerative disease.

THE RETROMER COAT COMPLEX

The retromer complex was first identified in the yeast *Saccharomyces cerevisiae* and was shown to mediate retrograde endosome-to-Golgi retrieval of the carboxy peptidase Y (CPY) receptor Vps10p. The complex, which sorts and traffics cargo from endosomes to the *trans*-Golgi network (TGN) or to the cell surface (Seaman 2012), comprises in yeast five proteins that are all encoded by vacuole protein sorting (*VPS*) genes: a trimeric core of VPS proteins, Vps35–Vps29– Vps26 binding a dimer of 'sorting nexin' (SNX) proteins Vps5 and Vps17 (Horazdovsky et al. 1997; Seaman et al. 1997; Seaman et al. 1998). The Vps5 and Vps17 SNXs contain Bin/Amphiphysin/Rvs (BAR) domains (SNX-BAR proteins) that can induce and/or sense the formation of membrane tubules (Carlton et al. 2004; van Weering et al. 2012). The trimeric complex of Vps26, Vps29 and Vps35 does not have intrinsic membrane-binding activity and relies on association with the Rab7 ortholog, Ypt7, for recruitment to the vacuole membrane (Liu et al. 2012; Vardarajan et al. 2012; Harrison et al. 2014). In addition, binding of the core retromer to endosomes is also mediated through binding to SNX3. (Harterink et al. 2011)

While SNX proteins differ significantly between species, the Vps35–Vps29–Vps26 heterotrimer is highly conserved (Koumandou et al. 2011) and therefore considered to be the core functional component. It has been shown to recognize cargo proteins and is therefore named the cargo-selective complex (CSC)(Seaman et al. 1998). Human VPS35 is composed of 17 two-helix repeats folding into an α-solenoid typical of vesicle coat proteins (Hierro et al. 2007). Mammals express two Vps26 orthologs, VPS26A and VPS26B (Kerr et al. 2005) possessing an arrestin fold and binding to the highly conserved amino-terminal region of VPS35 (Shi et al. 2006; Collins et al. 2008) (Figure 1). VPS29 possesses a non-functional metallophosphoesterase fold (Collins et al. 2005) and binds to the carboxy-terminal portion of VPS35 (Collins et al. 2008) where it is proposed to scaffold the helical solenoid of VPS35. Variably, the mammalian Vps35–Vps29–Vps26 core can form a complex with the homologues of Vps5p, namely SNX1 or SNX2 forming dimers with a Vps17p orthologue (either SNX5 or SNX6). Additionally, the mammalian retromer complex binds other proteins or protein complexes, such as the Wiskott-Aldrich protein and SCAR homolog (WASH) complex (Gomez and Billadeau 2009; Harbour et al. 2010; Burd and Cullen 2014), which modifies its precise function in trafficking cargo out of endosomes (Figure 1). Increasing retromer abundance suppresses degenerative phenotypes of mutations that affect the endolysosomal system. (Wang et al. 2014)

Cargo recognition

The mechanisms by which the CSC recognizes cargo are largely unclear. Some retromer cargoes possess at least one simple hydrophobic motif, F/W-L-M/V, required for retromer-

dependent sorting. (Seaman 2007) Vps35 has long been thought to provide the only site for cargo recognition. However, in recent years VPS26 was shown to bind a FANSHY sorting signal in the cytoplasmic domain of sorLA, (Fjorback et al. 2012) and several additional proteins binding to CSC including SNX1, SNX2, SNX5 and SNX6 forming the SNX-BAR sub-complex as well as SNX3 and SNX27 have also been implicated in cargo recognition, (Parks et al. 2001; Heydorn et al. 2004; Strochlic et al. 2007; Strochlic et al. 2008; Harterink et al. 2011; Temkin et al. 2011; Steinberg et al. 2013) suggesting that there are various direct and indirect mechanisms by which CSC recognizes cargo.

The SNX-BAR sub-complex

Sorting nexins SNX1, SNX2, SNX5 and SNX6 forming the SNX-BAR sub-complex are recruited to cargo-containing endosomes through a phosphatidylinositol 3-monophosphate (PtdIns(3)P)-binding Phox homology (PX) domain, and use the carboxy-terminal Bin-amphiphysin-Rvs (BAR) domain to drive membrane deformation and to generate membrane tubules. (Cullen 2008) In recruiting the cargo-selective subcomplex to the forming tubules, the SNX-BAR coat complex is thought to mediate retrograde transport between endosomes and the trans-Golgi network (TGN) through tubular-based endosomal trafficking. (Cullen 2008)

Additional cargo-specific sub-complexes

Over the past two years, additional cargo-specific adaptors have been identified that mediate recycling by capitalizing on the SNX-BAR-retromer pathway. In yeast, the sorting nexin Grd19/Snx3p9 sub-complex recycles the Fet3p-Ftr1p reductive iron transporter through recognition of the cytoplasmic domain of Ftr1p and binding to the SNX-BAR-retromer allowing recycling of the Fet3p-Ftr1p back to the plasma membrane via the Golgi apparatus. (Strochlic et al. 2007) In addition, two novel WD-40 domain proteins, Ere1 and Ere2 (Endosomal Recycling proteins) appear to function as adaptors for SNX-BAR-retromer-mediated sorting. In mammalian cells SNX27, a PDZ domain-containing SNX, functions as an adaptor for recycling of the β2-adrenergic receptor (β2AR) through SNX-BAR-retromer decorated tubules. (Temkin et al. 2011) SNX27 associates with the SNX-BAR-retromer through binding to the WASH complex and mediates recycling of β2AR through a direct Rab4-dependent endosome-to-plasma membrane pathway. (Lauffer et al. 2010; Temkin et al. 2011) SNX27 also regulates the endosomal sorting of other PDZ ligand-containing transmembrane spanning proteins including 5-hydroxytryptamine type 4 receptor (5-HT4R), (Joubert et al. 2004) the G protein-gated inward rectifying potassium (GIRK, or Kir3) channels, (Lunn et al. 2007; Balana et al. 2011) and the NMDA receptor subunit NR2C. (Cai et al. 2011) As SNX27 also contains a FERM-like domain, it may further act as an adaptor for NPxY motif-containing cargoes.

Accessory proteins for SNX-BAR-retromer

In addition to cargo-specific adaptors the CSC and SNX-BAR binding sites recruit a number of accessory proteins that further stabilize the growth and formation of retromer tubules. Among these is EHD1 belonging to the carboxy-terminal Eps15 homology domain (EHD) family (Gokool et al. 2007) showing similarities to dynamin GTPases (Daumke et al. 2007) and capable of assembling into oligomeric structures, inducing liposome tubulation in vitro,

and hydrolysing ATP (not GTP)(Naslavsky and Caplan 2011). Binding of EHD1 to SNX-BAR-retromer is required to stabilize tubule formation possibly by assisting further sculpturing of the maturing tubule (Gokool et al. 2007). In addition, ATP hydrolysis may induce conformation changes that lead to scission of SNX-BAR-retromer tubules (Daumke et al. 2007). As EHD proteins also associate with proteins containing the tripeptide NPF motif, EHD1may recruit additional proteins required for further cargo capture and/or processing of the SNX-BAR-retromer tubules (Naslavsky and Caplan 2011).

For the SNX-BAR-retromer further membrane re-modelling including membrane scission is connected to the underlying actin and microtubule cytoskeleton. SNX5 and SNX6 bind to the p150glued component of dynactin thereby coupling to the microtubule motor dynein. (Hong et al. 2009; Wassmer et al. 2009) Through a decrease in the efficiency of tubule scission uncoupling from dynein leads to extended SNX-BAR-retromer tubules (Wassmer et al. 2009).

A link with actin polymerisation is provided through the association of the CSC to the WASH complex (Gomez and Billadeau 2009). WASH is, a member of the WASP family regulating actin nucleating properties of the Arp2/3 complex (Campellone and Welch 2010) and is associated with a regulatory complex composed of FAM21, SWIP, strumpellin and CCDC53. It interacts with the VPS26-VPS29-VPS35 CSC sub-complex through binding of VPS35 to FAM21 and additional interactions between VPS35 and SNX1/SNX2 to WASH and FAM21 (Gomez and Billadeau 2009). Knock down of WASH leads to the formation of elongated SNX-BAR retromer tubules. The WASH complex also associates with the scission factor dynamin- II, and CAPZ, a capping protein for the barbed ends of actin filaments leading to the generation of longitudinal force which by promoting branching (Gomez and Billadeau 2009; Jia et al. 2010). Thus, the SNX-BAR-retromer assembles a motor–dependent pulling force on the tubule and a pushing force on the endosomal vacuole generated by a localized burst of actin polymerisation. These two opposing forces appear to combine to enhance the efficiency of membrane scission by increasing membrane tension. For fusion with the recipient compartment the carrier must undergo uncoating. In the SNX-BAR-retromer pathway this may be achieved by binding of VPS26-VPS29-VPS35 to TBC1D5 (Seaman et al. 2009).

THE ROLE OF RETROMER IN NEURODEGENRATIVE DISEASE

Over the past couple of years evidence accumulated that disturbed CSC function is causally involved in several neurodegenerative disorders highly prevalent in the elderly. The retromer was first linked to neurodegenerative disease by model guided microarray analysis of the dentate gyrus and entorhinal cortex from AD tissue (Small et al. 2005) which showed that protein levels of the CSC components Vps35 and Vps26 are reduced within the entorhinal cortex subregion which is particularly vulnerable to AD. (Small et al. 2005) In addition, a recent study suggests *SNX1*, *SNX3* and *RAB7A*, which are essential for membrane association of the retromer, as possible AD risk genes and a role of SNX3 and RAB7A in membrane association of the retromer through interaction with the CSC (Vardarajan et al. 2012). There is evidence from some *in vitro* and *in vivo* models that the retromer negatively regulates Aβ production, with *Vps35*-deficient mice exhibiting increased Aβ40 and Aβ42

production (Muhammad et al. 2008; Wen et al. 2011). However, other models have suggested that retrograde trafficking is required for efficient Aβ40 production. (Sullivan et al. 2011; Choy et al. 2012) Interestingly, Sullivan et al. (Sullivan et al. 2011) observed increased secretion of APP CTFs via exosomes, suggesting that retromer dysfunction might redirect trafficking of APP CTFs into exosomes leading to an alternative pathway for secretion of APP fragments and a potential source of extracellular Aβ. Several mutations in retromer-assembly and associated genes have also been associated with late-onset PD. A mutation in *VPS35* (D620N (c.1858G>A)) showing incomplete, age-associated penetrance disrupts the trafficking of cathepsin D, a CI-M6PR ligand and protease responsible for degradation of α-synuclein, (Follett et al. 2014) and leads to poor association with the WASH complex impairing WASH recruitment to endosomes leading to abnormal trafficking of the autophagy protein ATG9A and thereby autophagy dysfunction. (Zavodszky et al. 2014) In a viral-mediated gene transfer rat model, (Tsika et al. 2014) the expression of *VPS35* D620N induced the marked degeneration of substantia nigra dopaminergic neurons and axonal pathology, cardinal pathological hallmarks of PD. A recent experimental study further demonstrated that loss of SNX27 contributes to excitatory synaptic dysfunction by modulating glutamate receptor recycling in Down's syndrome. (Wang et al. 2013) A mutation in the receptor-mediated endocytosis 8 gene (*RME8*), DNAJC13 (p.Asn855Ser) regulating the dynamics of clathrin coats on early endosomes confers a toxic gain-of-function and impairs endosomal transport. (Vilarino-Guell et al. 2014) PD-associated mutations in RAB7L1 or LRRK2 lead to endolysosomal and Golgi apparatus sorting defects and deficiency of the VPS35 component of the retromer complex. (MacLeod et al. 2013) Expression of wild-type VPS35, but not a familial PD-associated mutant form, rescues these defects. Additional mutations that have been reported but are at present not considered established risk or susceptibility variants for late-onset PD include R524W, P316S and p.E787K in *VPS35* (Nuytemans et al. 2013)), p.K93E in VPS26A and p.N72H in *VPS29* (Table 1) (Vilarino-Guell et al. 2011; Zimprich et al. 2011; Lesage et al. 2012; Chen et al. 2013; Shannon et al. 2014). The locus for human *VPS26A* has also been genetically associated with type 2 diabetes (T2D) in South Asians. (Kooner et al. 2011) T2D is a confirmed risk factor for AD. (Ott et al. 1996; Luchsinger et al. 2001)

THE VPS10 RECEPTOR FAMILY

Yeast VPS10p, the first retromer cargo identified, has five mammalian homologs. These five members of the Vps10 receptor family are type 1 transmembrane proteins characterized by a Vps10 homology domain within the N terminus acting as a site for ligand binding and canonical internalization, and sorting motifs within the cytoplasmic tails mediating rapid internalization and intracellular sorting of ligands. (Jacobsen et al. 2001; Nielsen et al. 2001) They are abundantly expressed in the brain with differential distribution in hippocampal subregions, and are induced by neuronal activity. (Hermey et al. 2001; Hermey et al. 2004)

SORL1

SORL1 was the first Vps10 receptor identified as genetically associated with sporadic late-onset AD (Table 2), (Rogaeva et al. 2007) and over the past two years *SORL1* mutations have also been implicated in familial AD (Pottier et al. 2012). Numerous studies have

replicated the association of *SORL1* with AD in different datasets, and a recent comprehensive meta-analysis of the performed candidate gene studies (Reitz et al. 2011a) as well as a GWAS by the International Genomics of Alzheimer's Project (IGAP) in over 75,000 subjects (Lambert et al. 2013) confirmed that multiple *SORL1* variants are associated with AD. Consistent with this notion, *SORL1* transcripts are decreased in the brains of patients with mild cognitive impairment (Sager et al. 2007) and AD, (Dodson et al. 2006) and genetic variants in *SORL1* have also been associated with AD endophenotypes including age of onset of AD, white matter hyperintensities, hippocampal atrophy, CSF Aβ42 levels, cognitive function and *SORL1* expression in the brain. (Seshadri et al. 2007; K et al. 2008; Kolsch et al. 2008; Grear et al. 2009; Kolsch et al. 2009)

In vitro and *in vivo* studies have demonstrated that SorL1 is required for endosome to TGN trafficking of APP (Vieira et al. 2010; Fjorback et al. 2012) (Figure 2). Disruption of the Vps26 binding motif within the SorL1 cytoplasmic tail results in increased localization of APP to endosomal compartments and increased amyloidogenic processing of APP to produce Aβ (Fjorback et al. 2012). SorL1 has also been demonstrated to regulate exit of APP from the TGN, (Schmidt et al. 2007) exit of APP from early endosomal compartments (Offe et al. 2006) and oligomerization of APP which regulates its affinity for the secretases. (Lao et al. 2012; Schmidt et al. 2012)

The neuronal retromer, while not present within long-range moving vesicles, is nonetheless required for long-range retrograde transport of APP I-containing vesicles (Bhalla et al. 2012). Using cultured hippocampal neurons, it has been demonstrated that the CSC components Vps35 and Vps26, partially colocalize with SorL1 and APP to distinct puncta that are positive for early endosome markers and are localized within neuronal processes. (Bhalla et al. 2012) Under Vps35 knockdown conditions, APP long-range transport is reduced, resulting in a more static behavior of APP-positive vesicles, indicating that Vps35 may also be required for the regulated exit of APP from early endosomes in distal processes. This block of APP exit from early endosomes parallels an increase in endosomal size and Aβ production (Bhalla et al. 2012), potentially consistent with previous observations of enlarged endosomes during the earliest stages of AD before amyloid deposition (Cataldo et al. 1997; Cataldo et al. 2000; Cataldo et al. 2004) and in patient derived stem cells (Qiang et al. 2011; Israel et al. 2012). In summary, disruption of the retromer-SorL1 interaction seems to impact APP metabolism and Aβ production by affecting endosome to TGN trafficking of APP, (Vieira et al. 2010; Fjorback et al. 2012) exit of APP from the TGN, exit of APP from early endosomal compartments and oligomerization of APP; (Muhammad et al. 2008; Vieira et al. 2010; Fjorback et al. 2012) and retromer dysfunction seems to increase clustering of APP and Aβ production in early endosomes.

SorLA also binds glial cell line–derived neurotrophic factor (GDNF) in complex with its receptor GFRalpha1, mediates their uptake and subsequent intracellular sorting, and may therefore play a crucial role in the regulation of GDNF activity. (Glerup et al. 2013)

SORCS1

Also *SORCS1* was identified as a potential risk factor for AD (Liang et al. 2009) and implicated in retromer-related regulation of APP metabolism and Aβ generation (Lane et al.

2010; Reitz et al. 2011c). Several groups reported genetic associations of *SORCS1* SNPs with LOAD (Liang et al. 2009; Laumet et al. 2010; Reitz et al. 2011c; He et al. 2012; Wang et al. 2012; Xu et al. 2013) or changes in memory retention in various ethnic groups (Table 2). (Reitz et al. 2011b) In several of these studies the associations were strongest in females. Complexes containing SorCS1, APP, Vps35 and SorL1 were isolated from mouse brain tissue, and Vps35 and SorL1 protein levels were reduced in the brains of *Sorcs1-deficient* mice, suggesting disruption of the retromer in the absence of SorCS1. (Lane et al. 2010) Analysis of APP metabolites and Aβ in the brains of female *Sorcs1-deficient* mice revealed increased processing of endogenous APP as shown by elevated levels of α/β CTF and Aβ production. (Lane et al. 2010) In cultured cells, SorCS1 interacts with APP and regulates Aβ generation, (Lane et al. 2010; Reitz et al. 2011c) potentially through an impact on γ-secretase processing of APP. (Reitz et al. 2011c)

Interestingly, *SORCS1*, was also identified as a quantitative trait locus for T2DM in rats and mice (Clee et al. 2006; Granhall et al. 2006) and identified in GWAS as a risk factor for type 1 diabetes (Paterson et al. 2010) and T2DM (Goodarzi et al. 2007). While the mechanism through which *SORCS1* contributes to T2DM remains uncharacterized, the interaction with the retromer provides a potential point of junction between AD and T2DM, not only for SorCS1 but also for other Vps10 receptors including sortilin and SorL1. Sortilin is involved in trafficking of Glut4-containing, insulin-responsive vesicles (IRVs), and a screen to identify additional components of IRVs identified both SorL1 and Vps35 in rat adipocytes (Jedrychowski et al. 2010). Recycling of Glut4-containing IRVs from endosomal compartments to the TGN is dependent on retrograde trafficking pathways and is essential for correct Glut4 trafficking in response to insulin (Vassilopoulos et al. 2009). As described above, genetic data now also point toward the retromer in T2DM with *VPS26a* recently identified as a novel susceptibility locus (Kooner et al. 2011). Finally, genetic variation in SORCS1 has also been associated with attention deficit hyperactivity disorder (ADHD). (Lionel et al. 2011)

SORCS2 and SORCS3

There is evidence from candidate gene studies that also genetic variation in *SORCS2* and *SORCS3* is associated with AD (Table 2). (Rogaeva et al. 2007; Reitz et al. 2013) A recent study by Reitz et al. (Reitz et al. 2013) further suggests that there may be additive epistatic effects of genetic variants in *SORCS1*, *SORCS2* and *SORCS3* on AD risk. These observations are in line with the notion that knockdown of these genes using short hairpin RNAs in HEK293 cells causes a significant increase in APP processing. (Reitz et al. 2013) Variation in SORCS2 has also been associated with changes in temporal brain structure, (Kohannim et al. 2012) bipolar disorder and schizophrenia (Christoforou et al. 2011) and body mass index, (Wei et al. 2012) and variation in SorCS3 is associated with ADHD. (Lionel et al. 2011)

The mechanisms by which SORCS2 and SORCS3 exerts its effects remain poorly understood. Hippocampal expression of SorCS3 is induced by neuronal activity (Hermey et al. 2004; Hermey et al. 2013). This activity-dependent transcriptional induction is transient and independent of new protein synthesis, a characteristic of immediate early genes.

(Loebrich and Nedivi 2009) Therefore, SorCS3 may play a role in plasticity-related events in the nervous system. This notion is supported by additional studies. Expression of a constitutively active form of cAMP response element binding protein (CREB), a transcription factor with established function in synaptic plasticity, results in upregulation of Npas4 and SorCS3 transcripts. (Benito et al. 2011) Moreover, SorCS3 expression is misregulated in the absence of Npas4, (Lin et al. 2008) a transcription factor that regulates the formation and maintenance of inhibitory γ-aminobutyric acid (GABA)ergic synapses in response to excitatory synaptic activity on hippocampal neurons. (Lin et al. 2008; Coutellier et al. 2012) Recently, it has been reported that long-term depression (LTD), ie. a longlasting reduction in synaptic transmission, is impaired in SorCS3 knockout mice and that these mice display defects in spatial learning and memory and show increased fear extinction. (Breiderhoff et al. 2013)

Sortilin

Sortilin has been implicated in AD (Mufson et al. 2010; Finan et al. 2011), FTD (Hu et al. 2010), several psychiatric disorders including depression and bipolar disorder (Dube et al. 2011; Nykjaer and Willnow 2012) and cardiovascular (Musunuru et al. 2010) and aortic anorysmal (Saratzis and Bown 2014) disease. In the AD brain, increased sortilin expression (Finan et al. 2011) together with a positive correlation between temporal cortex sortilin levels and severity of pathology has been reported. (Mufson et al. 2010) *In vitro*, sortilin interacts with BACE1 and appears to positively regulate BACE1 cleavage of APP and Aβ production. Deletion of the sortilin intracellular domain possessing the putative retromer binding domain, results in increased endosomal localization of sortilin and BACE1 (Finan et al. 2011).

Sortilin is causally liked to FTD as a receptor for progranulin in neurons affecting the uptake and targeted delivery of progranulin to the endosomal-lysosomal pathway (Hu et al. 2010). In line with this notion, candidate gene and GWA studies identified *SORT1* as a regulator of plasma progranulin levels (Carrasquillo et al. 2010; Nicholson et al. 2014b). Progranulin localizes extensively with sortilin at the plasma membrane with binding dependent on the sortilin β-propeller domain (Hu et al. 2010) *In vitro* and *in vivo* models demonstrated that sortilin regulates extracellular progranulin levels through endocytosis and lysosomal accumulation of progranulin (Hu et al. 2010). Deletion of sortilin results in a 2.5- to 5-fold increase in progranulin levels and reversal of progranulin deficiency in the $GRN^{+/-}$ FTD model.

ROLE OF VPS10 RECEPTORS IN PRONEUROTROPHIN SIGNALING

In addition to their abovementioned actions, several of the VPS10 receptors are also involved in the regulation of proneurotrophin signaling. The outgrowth of dendrites and axons and thereby the formation of neuronal networks in the developing nervous system is influenced by several factors. (McAllister et al. 1995; Cohen-Cory et al. 2010) Among these are neurotrophins, which include nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin 3 (NT-3), and NT-4, which are required for neuronal survival and differentiative, synapse formation, and synaptic plasticity. (Snider 1994) These secreted proteins act through two classes of receptors: the tropomyosin-related kinase (Trk) receptor

and the p75 neurotrophin ($p75^{NTR}$)-sortilin receptor. Neurotrophins including NGF and BDNF are synthesized as precursor proteins (proneurotrophins) that are cleaved of their prodomains during maturation. However, following injury, or in neurodegenerative disease, pro-NGF is induced. Numerous studies have indicated that pro-NTs (NGF and BDNF) bind the $p75^{NTR}$-sortilin complex to signal proapoptotic pathways while mature NTs bind the Trk receptor complexes to signal growth cone tuning, extension, and neuronal survival (Teng et al. 2010). While sortilin functions directly in apoptotic signaling pathways when complexed with $p75^{NTR}$, it is also involved in anterograde trafficking of the Trk receptors from the soma to the nerve terminal thereby positively regulating neurotrophin signaling and cell survival (Vaegter et al. 2011), and regulation of BDNF levels through influencing both anterograde and lysosomal trafficking. (Chen et al. 2005; Evans et al. 2011) Disruptions in NGF and BDNF signaling have been demonstrated to contribute to AD pathology. Aberrant processing of pro-NGF and/or altered axonal trafficking resulting in an imbalance of pro-NGF to mature NGF has been implicated in disease progression and decreased BDNF has been reported in AD.

Also SorCS2 binds to pro-NGF, thereby mediating acute collapse of growth cones of hippocampal neurons (Deinhardt et al. 2011). This retraction is initiated by an interaction between the p75 neurotrophin receptor ($p75^{NTR}$) and SorCS2. Binding of proNGF to the $p75^{NTR}$-SorCS2 complex induces growth cone retraction by initiating the dissociation of the guanine nucleotide exchange factor Trio from the $p75^{NTR}$-SorCS2 complex, resulting in decreased Rac activity and, consequently, growth cone collapse. The actin-bundling protein fascin is also inactivated, contributing to the destabilization and collapse of actin filaments. Collectively, these results suggest dual synchronized mechanisms by which pro-NGF mediates acute neuronal remodeling. This increase in $p75^{NTR}$ in injured neurons, and the increase in pro-NGF in AD suggests that SorCS2/$p75^{NTR}$ may play a role in disease pathogenesis. SorCS3 has also been reported to bind NGF (Westergaard et al. 2005) but this interaction remains to be further characterized.

SorLA binds glial cell line–derived neurotrophic factor (GDNF) in complex with its receptor GFRalpha1, and mediates their uptake and subsequent intracellular sorting. It may therefore play a crucial role in the regulation of GDNF activity. (Glerup et al. 2013)

CONCLUSIONS

Over the past few years significant evidence from genetic and cell biology studies has accumulated implicating intracellular trafficking as a key mechanism in the generation of toxic protein species involved in a number of age-related neurodegenerative diseases. In addition to these “end-stage” phenotypes, genetic and cell biology studies have now also correlated retromer function and proteins involved in intracellular trafficking with intermediate disease endophenotypes highly prevalent in the elderly, including hippocampal atrophy, memory retention or white matter hyperintensities. Evidence suggests that the Vps10 family of receptors regulates trafficking of proteins central to several neurodegenerative diseases within endosomal-lysosomal compartments through their interaction with the retromer complex which itself is implicated in AD, PD, and T2DM.

Importantly, several of the Vps10 family members additionally regulate neurotrophic survival and apoptotic signaling pathways.

In considering retromer assembly or accessory proteins as targets for drug discovery, the exact mechanisms by which these pathways lead to age-related neurodegeneration need to be clarified. While there are several potential scenarios, studies showing that increasing retromer levels and interaction between individual retromer proteins stabilizes the retromer core complex and enhances retromer-mediated trafficking and transport (Small et al. 2005; MacLeod et al. 2013), suggest that retromer function is especially important in clearing 'toxic proteins' from the cell accumulating over time. In line with this notion, a recent study seeking to identify potential pharmacological chaperones stabilizing retromer to limit APP processing identified a molecule that stabilized retromer against thermal denaturation, increased the levels of retromer proteins, shifted APP away from the endosome, and decreased the pathogenic processing of APP. (Mecozzi et al. 2014) These findings suggest that retromer stability affects its function and that pharmacological chaperones can stabilize this function and may have potential therapeutic implications. (Mecozzi et al. 2014)

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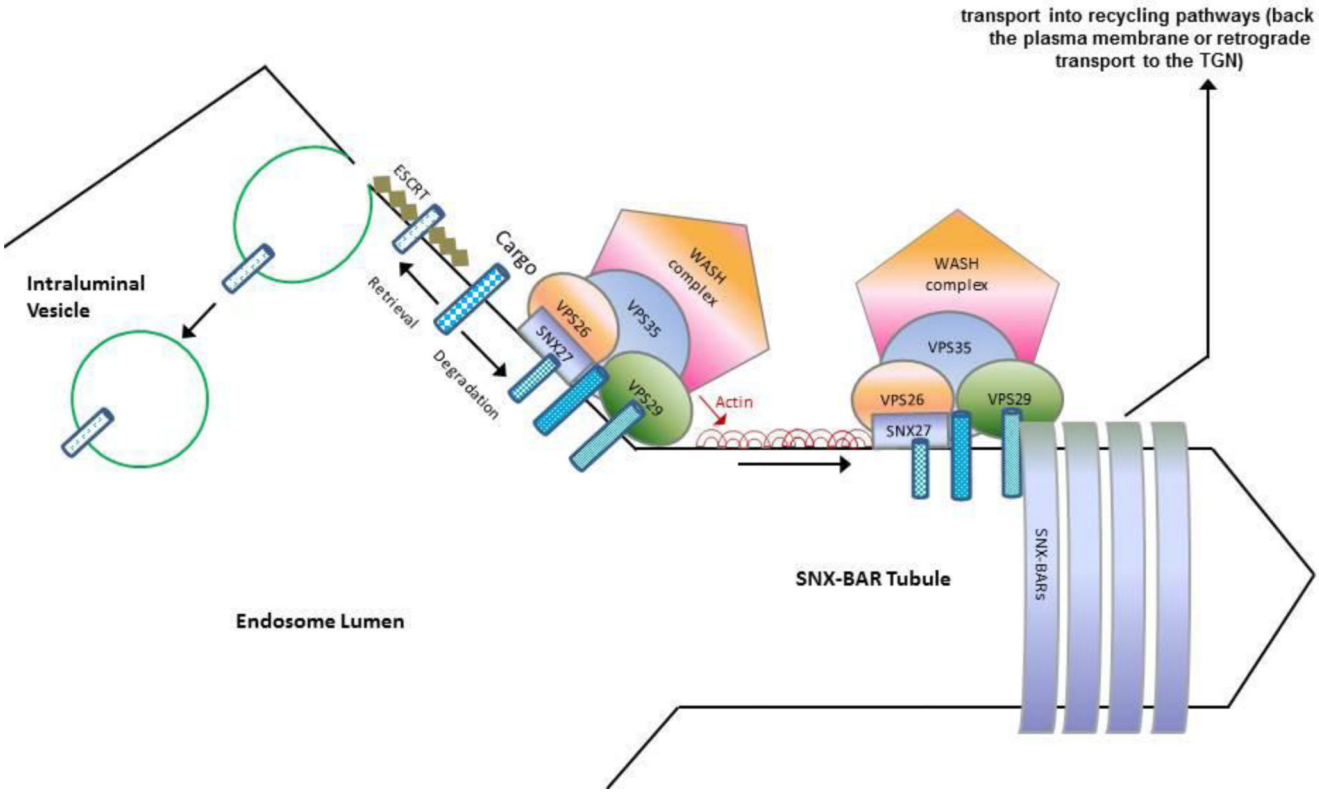

Figure 1.

SNX-BAR-retromer-mediated cargo exit from lysosomal-mediated degradation. The VPS26:VPS29: VPS35 CSC engages cargo in a signal-dependent manner. Through WASH-mediated actin polymerization a cargo-enriched endosome subdomain is assembled thereby avoiding ESCRT-mediated sorting into forming intraluminal vesicles (Strochlic et al. 2008). Subsequent transport into recycling pathways back to the plasma membrane or retrograde transport to the TGN is mediated through retromer SNX-BAR-mediated tubule formation. Actin polymerization may aid further membrane remodeling and the efficiency of tubule scission to form a cargo-enriched tubular transport carrier. [ESCRT = endosomal sorting complexes required for transport (*ESCRT*) machinery]. Figure adapted from Burd et al. (Burd and Cullen 2014), with permission from Society for Neuroscience.

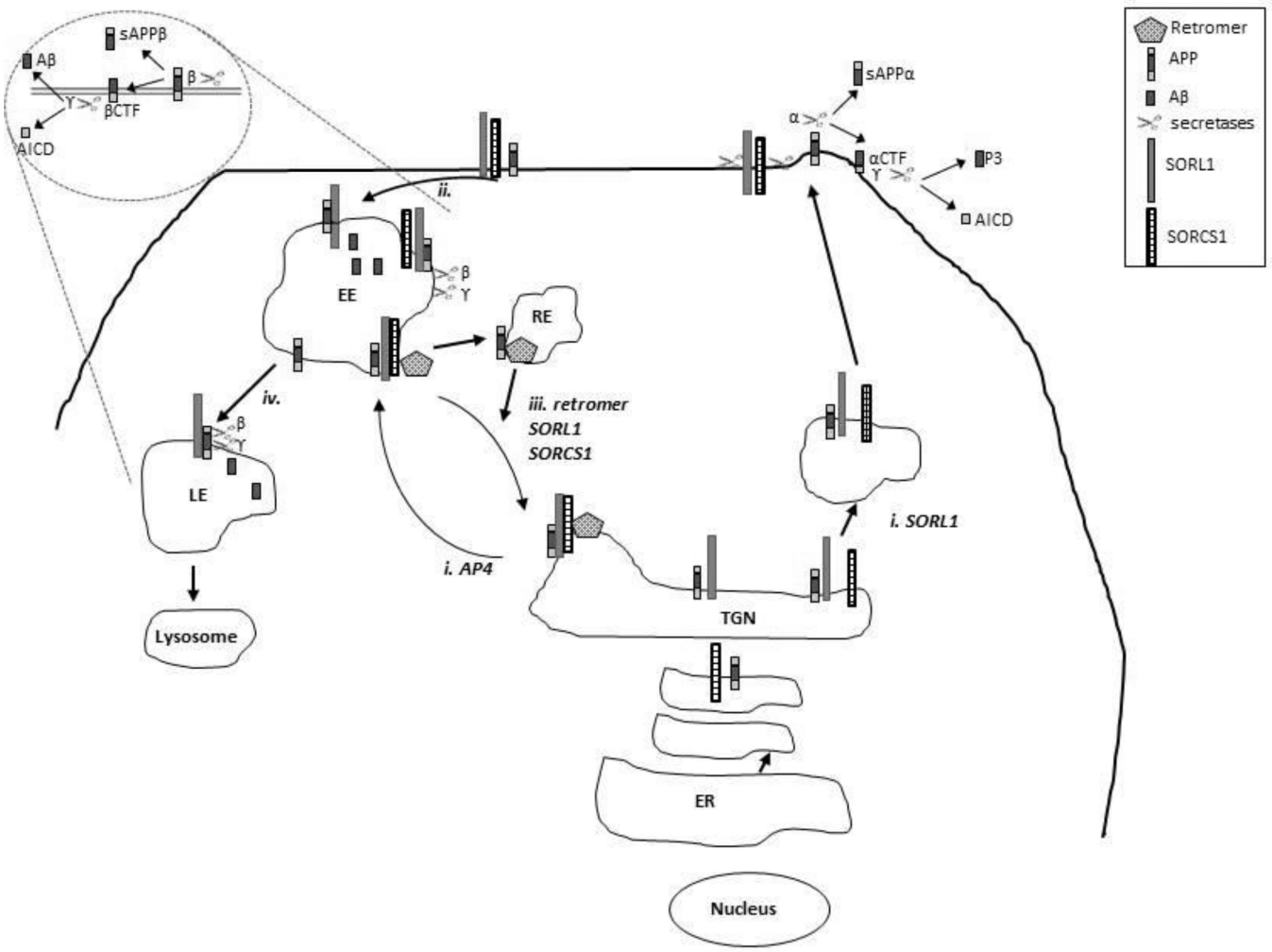

Figure 2.

APP sorting and processing. ***i***. From the *TGN*, APP is -dependent on the *AP4* adaptor protein complex- either sorted to the plasma membrane (secretory pathway) or into clathrin-coated vesicles entering the endosomal pathway. Within the secretory pathway, APP is cleaved at the plasma membrane by the α-secretases into soluble APPα (sAPPα) and a membrane-bound αCTF. The αCTF is subsequently cleaved by γ-secretase generating the p3 fragment and the APP intracellular domain (AICD). ***ii***. At the plasma membrane, some unprocessed APP escapes α-secretase cleavage and is internalized into the endosomal pathway. Within low pH endosomal compartments, APP is cleaved by β-secretase resulting in generation of sAPPβ and the βCTF. Cleavage of the βCTF by γ-secretase generates Aβ peptides of varying lengths and the AICD. ***iii and iv***. Via the retromer complex and its receptors, the Vps10 family members, APP is recycled from the early endosomal compartments to the *TGN*. Figure adapted from Lane et al. (Lane et al. 2012)with permission from Society for Neuroscience.

Table 1

Genetic association studies reporting genetic variants in genes encoding retromer assembly components in neurodegenerative disease

Author (year)	gene	polymorphism/haplotype	phenotype
Vilariño-Güell (2011)(Vilarino-Guell et al. 2011)	VPS35	p.Asp620Asn (D620N)	Familial PD
Zimprich et al (2011)(Zimprich et al. 2011)	VPS35	p.Asp620Asn (D620N)	Familial PD
Sheerin et al (2012)(Sheerin et al. 2012)	VPS35	p.Asp620Asn (D620N)	Familial PD
Lesage et al (2102)(Lesage et al. 2012)	VPS35	p.Asp620Asn (D620N)	PD
Kumar et al (2012)(Kumar et al. 2012)	VPS35	p.Asp620Asn (D620N)	PD
Ando et al (2012)(Ando et al. 2012)	VPS35	p.Asp620Asn (D620N)	PD
Sharma et al (2012)(Sharma et al. 2012)	VPS35	p.Asp620Asn (D620N)	Familial and sporadic PD
Nuytemans et al (2013)(Nuytemans et al. 2013)	VPS35	possibly p.P316S, p.Y507F, p.E787K	PD
Gagliardi et al (2014)(Gagliardi et al. 2014)	VPS35	p.Asp620Asn (D620N)	Familial PD
Shannon et al (2014)(Shannon et al. 2014)	VPS26A	possibly p.K93E	PD
Shannon et al (2014)(Shannon et al. 2014)	VPS29	possibly p.N72H	PD
Vardarajan et al (2012)(Vardarajan et al. 2012)	KIAA	Gene-based analyses	AD
Vardarajan et al (2012)(Vardarajan et al. 2012)	SNX1	Gene-based analyses	AD
Vardarajan et al (2012)(Vardarajan et al. 2012)	SNX3	Gene-based analyses	AD

Table 2

Genetic association studies reporting genetic variants in genes encoding VPS10 receptor proteins in neurodegenerative disease

Author (year)	gene	polymorphism/haplotype	phenotype
Rogaeva et al. (2007) (Rogaeva et al. 2007)	SORL1	2 haplotypes (SNPs 8–10, 23–25)	AD
Lee et al (2007)(Lee et al. 2007)	SORL1	2 haplotypes (SNPs 8–10, 23–25)	AD
Meng et al (2007)(Meng et al. 2007)	SORL1	haplotype (SNPs 23–25)	AD
Seshadri et al (2007) (Seshadri et al. 2007)	SORL1	SNP 24	AD endophenotypes
Bettens et al (2008) (Bettens et al. 2008)	SORL1	haplotype (SNPs 8–10)	AD
Webster et al (2008) (Webster et al. 2008)	SORL1	SNPs 8–9	AD
Li et al (2008) (Li et al. 2008)	SORL1	SNP 24	AD
Lee et al (2008)(Lee et al. 2008)	SORL1	SNPs 8, 24	AD
Cellini et al (2009)(Cellini et al. 2009)	SORL1	SNPs 4,7–10	AD
Kolsch et al (2009)(Kolsch et al. 2009)	SORL1	SNPs 19,21,23	AD, CSF biomarkers
Kimura et al (2009) (Kimura et al. 2009)	SORL1	SNPs 19, 23–25	AD
Tan et al (2009)(Tan et al. 2009)	SORL1	SNPs 19, 22–24	AD
Reynolds et al (2010) (Reynolds et al. 2010)	SORL1	SNPs 8,9,10, 19,22,23,24	AD
Alexopoulos et al (2012) (Alexopoulos et al. 2012)	SORL1	SNPs 23,24	AD CSF biomarkers
Caglayan et al (2012) (Caglayan et al. 2012)	SORL1	SNPs 19–22	receptor expression in the brain of patients with AD

Author (year)	gene	polymorphism/haplotype	phenotype
Guo et al (2012)(Guo et al. 2012)	SORL1	SNPs 4, 8–10, 19–23	AD CSF biomarkers
Ning et al (2012)(Ning et al. 2010)	SORL1	SNPs 19–24	AD
Wen et al (2013)(Wen et al. 2013)	SORL1	rs985421,SNP 7,rs4598682, rs3781834 rs378183	AD
Elias-Sonnenschein (2013)(Elias-Sonnenschein et al. 2013)	SORL1	rs73595277	p-tau
Miyashita et al (2013) (Miyashita et al. 2013)	SORL1	rs3781834, rs11218343	AD
Izzo et al (2013)(Izzo et al. 2013)	SORL1	SNP 10	AD
Oligati et al (2013)(Olgiati et al. 2012)	SORL1	haplotype (SNPs 8–10)	AD
Jin et al (2014)(Jin et al. 2014)	SORL1	rs985421	MCI, AD
Xue et al (2014)(Xue et al. 2014)	SORL1	SNP 19	AD
Liang et al (2009)(Liang et al. 2009)	SORCS1	rs17277986	AD
Reitz et al (2011)(Reitz et al. 2011c)	SORCS1	rs4918274, rs2900717, rs11193137, rs12571141, rs17277986, rs6584777	AD
Reitz et al (2011)(Reitz et al. 2011c)	SORCS1	rs10884402, rs7078098, rs950809	memory retention
He et al (2012)(He et al. 2012)	SORCS1	haplotype (rs601883/rs7907690/rs600879/rs17277986/rs2900717/rs10884399/rs11193170/rs4918280)	AD
Wang et al (2102)(Wang et al. 2012)	SORCS1	rs12571141, rs17277986, rs6584777	AD
Xu et al (2013)(Xu et al. 2013)	SORCS1	haplotype (rs17277986, rs6584777, rs10884402, rs7078098, rs950809)	AD
Reitz et al (2013)(Reitz et al. 2013)	SORCS2	various SNPs in introns 1,2,3,7,23	AD
Lionel (2011) (Lionel et al. 2011)	SORCS3	CNV	ADHD
Reitz et al (2013)(Reitz et al. 2013)	SORCS3	various SNPs in introns 12,5,20,23 and UTR-3	AD

Author (year)	gene	polymorphism/haplotype	phenotype
Carrasquillo et al. (2010) (Carrasquillo et al. 2010)	SORT1	rs646776	Progranulin levels
Nicholson et al. (2014) (Nicholson et al. 2014a)	SORT1	rs646776	Plasma PRGN levels
McMillan et al. (2014) (McMillan et al. 2014)	SORT1	rs646776	FTD neuroanatomic endophenotypes