HHS Public Access

Author manuscript

Mol Psychiatry. Author manuscript; available in PMC 2019 May 24.

Published in final edited form as:

Mol Psychiatry. 2019 June ; 24(6): 857–868. doi:10.1038/s41380-018-0221-3.

Endosomal sorting and trafficking, the retromer complex and neurodegeneration

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Abstract

The retromer is a highly conserved multimeric protein complex present in all eukaryotic cells whose activity is essential for regulating the recycling and retrieval of numerous protein cargos from the endosome to trans-Golgi network or the cell surface. In recent years, molecular and genomic studies have provided evidence that aberrant regulation of endosomal protein sorting and trafficking secondary to a dysfunction of the retromer complex could be implicated in the pathogenesis of several neurodegenerative diseases. Thus, deficiency or mutations in one or more protein components of the retromer leads to increased accumulation of protein aggregates as well as enhanced cellular neurotoxicity. In this review, we will discuss the structure and function of the retromer complex and its neurobiology, its relevance to key molecules involved in neurodegeneration and the potential role that it plays in the development of two major neurodegenerative disorders, Parkinson's disease and Alzheimer's disease. Lastly, we will discuss the viability of targeting the retromer via pharmacological chaperones or genetic approaches to enhance or restore its function as a novel and unifying disease-modifying strategy against these diseases.

Introduction

A common feature of a large variety of neurodegenerative diseases is the progressive accumulation of protein aggregates inside neurons and glial cells as well as their extracellular deposition within distinct brain regions, which ultimately is responsible for the clinical phenotype of that particular disorder. In most cases, these inclusions can be formed by the mutant version of a particular protein, or a wild type but abnormally modified protein, which in both cases, by becoming misfolded, loses its natural solubility and becomes highly

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Conflict of interest

The authors declare that they have no conflict of interest to disclose.

cytotoxic. These series of events are thought to occur in many neurodegenerative diseases and are considered as the biochemical signature of a significant alteration in protein homoeostasis, which characterize them. Among the systems in place to maintain the integrity of a functional proteome, or proteostasis, recent studies have demonstrated that efficient sorting and trafficking of different proteins, (i.e, membrane proteins, cytosolic proteins, receptors, transporters) via the endosomal-lysosomal system within cells, plays a crucial role.

The system is an intricate but interconnected network designed to traffic cargos, such as proteins and lipids to be recycled or degraded for proper cellular function [1–3]. Some of the cargo can enter the system via the plasma membrane, others via the ribosomal pathway, but in both scenarios cargo follows three major routes: the degradation pathway to the lysosomes, the recycling pathway to the cell surface, or the endocytic pathway to the trans-Golgi network (TGN).

Physiologically, protein recycling and degradation is crucial for cell homeostasis. Molecules at the plasma membrane destined for degradation are trafficked via three distinct pathways in the endosomal-lysosomal network: endocytosis, autophagy, or phagocytosis [4,5]. For the purposes of this review, we will focus only on the endocytic pathway and its prevalence in neurodegenerative diseases, specifically through an evolutionary conserved, multimeric protein system known as the retromer complex. We will discuss the evidence linking dysregulation of this endosomal-lysosomal pathway to the pathogenesis of neurodegenerative diseases and the relevance of studying the retromer complex both from a molecular and pharmacological point of view with the ultimate goal to exploit the system as a novel therapeutic target against those diseases.

Endosomal-lysosomal trafficking: role of the retromer complex

The endocytic pathway is crucial for uptake of nutrients, cell surface receptor signaling, and several other key cellular processes [5–7]. According to their specific roles in the system, distinct compartments, such as early endosome, recycling endosome, late endosome, and lysosome, all function in tandem to support protein recycling and degradation [8]. The early endosome functions as a major sorting hub, permitting receptor recycling back to the cell surface or to the late endosome for reuse and eventually to the lysosome, the final destination for protein degradation and host organelle for key hydrolases [9]. Similarly, protein cargo is transported between the endosome and the TGN, thereby bypassing cell surface recycling. For example, many of the hydrolases stationed in the lysosome are recycled via this endosome-TGN transport system [10,11]. Newly synthesized hydrolases are trafficked from the TGN to endosome for eventual transport to the lysosome, while hydrolase receptors travel from endosome to TGN for reuse. This retrograde transport of cargo between endosome and TGN is mediated by a highly conserved eukaryotic complex, called the retromer complex [12,13]. Whether genetic or sporadic, alterations or dysfunctions of this protein sorting machinery have been tightly associated with neurodegenerative diseases. For the purposes of this review, we will focus on retrograde recycling of proteins via the retromer complex and its potential link to neurodegeneration.

The retromer complex: structure and function

Retromer was first discovered in yeasts in 1998 and was aptly named due to its function in transporting protein cargo in the retrograde direction from the endosome to the TGN [13]. Retromer is a hetero-pentameric protein complex, comprised of a sorting nexin (SNX) and a cargo-recognition core composed by the vacuolar protein sorting 35 (Vps35)/ Vps26/ Vps29 trimer, which sorts cargo for delivery to the TGN [14–16]. Cargo are sorted via the retromer in three distinct pathways: 1) the recycling pathway involves transporting cargo from endosome to plasma membrane, which is particularly important in neurons, as for example, synaptic plasticity is dependent on proper delivery of glutamatergic receptors to the plasma membrane, 2) the retrograde transport of proteins to the TGN, which is critical for proper delivery of lysosomal proteases and hydrolases, and 3) the degradation pathway which involves internalization of cargo from the plasma membrane or the cytosol into the early endosome, which eventually fuses with lysosomes [17,18]. Under physiological conditions, there is a balanced coordination between the three above mentioned sorting pathways; however, if any of these mechanisms are dysregulated, aberrant protein sorting in the endosomal-lysosomal pathway could lead to cell toxicity and ultimately neurodegeneration [19,20].

Among the central components of retromer complex is the cargo-recognition core composed of trimeric Vps35/Vps26/Vps29 proteins, which binds to transmembrane endosomal proteins to be transported **(Figure 1)**. Vps35 serves as structural backbone for Vps26 and Vps29 [14]. Second, the ‘tubulation’ component of the retromer, which bind to the cargo recognition core, consists of the sorting nexin (SNX) family of proteins characterized by the inclusion of a carboxy-terminal BIN–amphiphysin–RVS (BAR) domain. Such proteins include SNX1, SNX2, SNX3, SNX5 and SNX6, which are recruited to the endosomal membrane by Rab5-GTP and Rab7-GTP proteins [21]. Third, retromer complex contains a recruitment module for stabilizing the cargo recognition core once it reaches the plasma membrane. Such proteins include SNX3, the RAS-related protein RAB7A, and TBC1 domain family member 5 (TBC1D5), which is a member of the TRE2–BUB2–CDC16 (TBC) family of RAB GTPase-activating proteins (GAPs) [22,23]. Recently, studies have found that another sorting nexin, SNX27, is linked to retromer and functions to recognize and select specific cargo, such as beta adrenergic receptor, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs) and N-methyl-D-aspartate receptors (NMDARs), to be transported to the plasma membrane [24–26]. Lastly, the WAS protein family homologue 1 (WASH1), FAM21, strumpellin, coiled-coil domain-containing protein 53 (CCDC53) and KIAA1033 (also known as WASH complex subunit 7) collectively called the WASH complex, and function to direct cargo to the retromer pathway instead of the degradative pathway **(Figure 1)** [27]. Cargo for the retromer include cation-independent mannose 6-phosphate receptor (CIMPR), Vps10-member sortilin, sortilin-related receptor 1 (SORL1; also known as SORLA), glutamate receptors, phagocytic receptors that mediate the clearing function of microglia, and the Wnt transport protein, Wntless [21, 28–30]. Retromer binding specific cargo and implementing proper protein sorting is essential to cellular homeostasis. For example, CIMPR-recycling via retromer influences delivery of lysosomal hydrolases to the endosomal-lysosomal system, whereas beta-adrenergic receptor recycling affects synaptic transmission [31].

Retromer dysfunction has recently been linked to several neurodegenerative diseases. Deficiency or mutations in one or several components of the retromer complex has been shown to be directly involved in the pathogenesis of these disorders, implicating the regulation of endosomal trafficking and protein recycling as a crucial molecular target in their pathogenesis [32]. For this review, we will discuss the relevance and potential mechanisms of retromer complex dysfunction and dysregulation in two neurodegenerative conditions: Parkinson's disease and Alzheimer's disease, as well as therapeutic implications of using pharmacological intervention to target this complex for their treatment.

Retromer complex and Parkinson's disease

Parkinson's disease (PD), marked by accelerated loss of dopaminergic neurons in the substantia nigra and accumulation of alpha synuclein-containing Lewy Bodies, is the second most common human neurodegenerative disease following Alzheimer's disease. Predominantly, PD manifests as a sporadic disease, with aging as a primary risk factor; however in 10% of cases, autosomal dominant and recessive transmission of familial PD occurs [33,34].

PD was first linked to the retromer complex in 2011 when exome sequencing revealed a mutation in residue 620 (D620N) in the Vps35 orthologue **(Figure 2A)** [35]. Additionally, post-mortem analysis of brain tissues revealed decreased protein levels of Vps35 in the substantia nigra of PD patients [36]. Although this disease-associated mutation suggests that retromer dysfunction may be a contributing factor to PD development, the exact role of the retromer in the disease pathogenesis is incomplete.

Nevertheless, data from cellular and *in vivo* models have begun to tease apart the relationship between Vps35 dysfunction and endosomal-trafficking perturbations in PD. First, global genetic knockout of Vps35 causes early death in embryonic stages in mice [37]. However, using a Drosophila model, one study found that RNAi-mediated Vps35 knockdown led to aberrant alpha-synuclein degradation in the lysosome, specifically, via impaired CIMPR recycling and subsequently, improper delivery of its ligand, cathepsin D, to the lysosome **(Figure 2A)** [38]. Importantly, accumulation of insoluble alpha-synuclein in the lysosome was concurrent with PD-associated locomotor deficits, suggesting that defects in retromer sorting may decrease proper degradation of aggregated alpha-synuclein in the Lewy Bodies. In cellular models, studies indicate that D620N Vps35 mutation resulted in defective CIMPR sorting as well as altered localization of the AMPA glutamate receptor, Glu1, indicating a link between retromer and post-synaptic transmission [39]. Collectively, the majority of studies suggests that the D620N mutation in VPS35 associated with late-onset PD, causes a loss of function in the retomer complex **(Table 1)** [40,41]. Notably, mutations in Vps35 do not disrupt its association with the cargo recognition core; i.e. Vps26 and Vps29, nor alters Vps35 localization, but rather seems to affect the affinity of retromer cargo to associate with their respective complexes. Specifically for PD, studies suggest that mutations in Vps35 reduce the Vps35-WASH complex association leading to deficient trafficking of autophagy protein (Atg9A) in addition to impacting the retrograde transport of CIMPR to the TGN [34].

Some studies suggest that Vps35 deficiency or mutation can cause loss of dopaminergic neurons due to impaired retrieval of lysosome associated membrane glycoprotein 2a (LAMP2a) and thus impaired alpha-synuclein degradation, while other studies suggest that this Vps35 deficit causes impaired dopaminergic neuronal function via mitochondrial fusion [42,43]. More recently, in vivo analysis using a mutated Vps35 knock-in mouse model demonstrated impairment in dopamine release at an early age time-point, before classical PD neuropathology arises [44]. Taken together, these studies support the concept that D620N mutation in Vps35 is indicative of a loss-of-function of the retromer complex pathway; however, conflicting reports of neurodegeneration by a gain-of-function mechanism following Vps35 mutation indicate the need for further elucidation of the exact role that Vps35 deficiency or mutation could play in the pathogenesis of this disease [45]. For a complete list of the papers published so far on the retromer complex and PD see Table 1.

Retromer complex and Alzheimer's disease

Alzheimer's disease (AD) is the leading cause of dementia worldwide and is characterized by progressive accumulation of amyloid beta (Aβ) peptides and hyper-phosphorylated tau protein deposition leading to eventual development of Aβ plaques and tau neurofibrillary tangles, respectively [46]. Toxic Aβ formation and subsequent accumulation is produced via sequential cleavage of the Aβ precursor protein (APP) by the β-secretase 1 (BACE1) enzyme, followed by the gamma secretase complex cleavage [3]. It is important to note that Aβ conversion from APP usually occurs in the Golgi, while continuous production of Aβ occurs in organelles such as the early/late endosomes and lysosomes [7]. While the non-amyloidogenic pathway leads to release of soluble APP from the plasma membrane, under pathological conditions, APP may be sequestered in the endosomes, where BACE1 and gamma secretase cleavage induce formation of Aβ 40 and Aβ42 peptides, which are the precursors to Aβ plaque deposition **(Figure 2B)** [47].

As mentioned previously, endosomal trafficking vulnerability in neurons is vastly prevalent in neurodegenerative disordered such as AD. The first indication of this fact stemmed from post-mortem brain tissue analysis from AD patients, indicating aberrant enlargement of early endosomes, a phenotype now considered prototypical of endosomal trafficking dysfunction [48]. Specifically, the retromer complex was first implicated in AD in 2005, when microarray profile analysis revealed that Vps35 and Vps26 are reduced in the entorhinal cortex, a region particularly vulnerable to AD and neurodegeneration even in the preclinical stages, indicating an early perturbation in retromer function [49]. Guided by this finding, studies have investigated several transmembrane proteins that display correlative expression levels with Vps35, including SNX3 and Rab7 [50], but the most promising of which, was SORL1 also known as SORLA, a member of the VPS10-containing receptor family, now known to bind APP in the endosome [51–53]. Transcriptionally, SORLA expression is downregulated in AD and likely is a molecular mediator between APP and BACE1, inhibiting the interaction between the two in the Golgi, thereby reducing APP cleavage. While *in vivo* and *in vitro* studies confirm that SORLA is essential for APP trafficking from endosome to TGN, disruption of its cytoplasmic binding motif results in increased APP localization in the endosome and subsequent increased APP processing into Aβ peptides. SORLA has additionally been shown to affect APP exiting from the early endosome and the

oligomerization state of APP, which influences the affinity of this protein to interact with secretases [54]. It is important to point out that some human studies also have provided conflicting data on SORLA and AD, with some papers showing an inverse correlation between Aβ levels and SORLA, whereas others reporting no differences between AD and controls **(Table 2)** [55,56]. Another member of the VPS10-containing receptor family is SORCS1 which has also been associated with late-onset AD and reported to be decrease in AD brains [57]. Additionally, genome wide analysis studies have associated SORCS1 with type 2 diabetes [58]. Supporting an involvement of the system in APP sorting and metabolism, initial studies reported that endogenous murine Aβ1–40 and Aβ1–42 were increased in the brains of females but not males SORCS1 knock-out mice, and this effect involved an interaction with the Vps35 component of the retromer complex [59]. However, in a recent paper by Knight and colleagues the authors did not find significant changes in brain levels of total and oligomeric Aβ peptides [60]. While no obvious explanation exist for this unexpected biologic effect, we believe that the observation reported in this paper is very important since it clearly underscore the complexity of the mechanisms that regulate such an important cellular function: membrane protein sorting and trafficking. To this end further studies are warranted to better understand this aspect of the cell biology of the retromer complex.

Similarly, Vps35 hemizygous deletion in the Tg2576 mouse model of brain amyloidosis resulted in increased BACE1 activity in the hippocampus, whereas downregulation of Vps26 as well as Vps35 decreased BACE1 localization to the TGN [37]. Furthermore, deletion of sortilin, which is required for retromer-mediated delivery of BACE1 from the endosome to TGN, increased localization of BACE1 in the endosome. Additionally, SNX27, an important module for retromer recruitment, binds to gamma-secretase, the key enzyme involved in pathogenic cleavage of APP and inhibits its effect on APP proteolysis [37]. Thus, dysregulation of SNX27 could result in increased pathogenic APP cleavage via this secretase. Together, these data implicate the retromer as a crucial player in Aβ production by mediating secretase localization/affinity as well as time-dependent sequestration of APP to the endosome. Interestingly, our group has recently shown that the expression levels of the retromer system are reduced in an age- and brain region-dependent manner in a mouse model expressing human mutant APP, the Tg2576 mice [61].

Akin to Aβ neuropathology, another key characteristic of AD, as well as a subset of other neurodegenerative disorders known as tauopathies, is the pathogenic accumulation of highly phosphorylated microtubule-associated protein tau (MAPT) and progressive neurofibrillary tangle formation [62]. Although a clear link between tau pathology and endosomal dysfunction has yet to be elucidated, recent advances in tau neurobiology has revealed several plausible hypotheses worth addressing further. Tau protein was originally thought to reside only intracellularly; however, studies as recent as 2013, have demonstrated that tau can be released via endocytosis and enter the neuronal endosome [63, 64]. Notably, pathogenic tau processing may initiate upon tau sequestration in the endosome, although it is still unclear whether tau cleavage or tau aggregation necessitates tauopathy neurotoxicity.

Since tau can be transported via endocytosis, it follows that a dysfunction in any of the endocytic trafficking mechanisms could initiate pathogenic tau production. As mentioned

previously, the retromer complex functions to deliver cathepsin D (CTSD), a lysosomal protease, through the endosomal-lysosomal system via sortilin or CIMPR. Interestingly, alterations in CTSD protein and mRNA level is apparent in AD and other lysosomal storage diseases [65,66]. Indeed complete loss of cathepsin D results in the lysosomal storage disorder, neuronal ceroid lipofuscinosis, characterized by accelerated neurodegeneration and abnormal storage material in the lysosome. CTSD deficiency was shown to elevate tau neurotoxicity in several animal models, likely through a mechanistic defect in endosomal-lysosomal trafficking. However, The question if abnormal processing of tau is occurring in the endosome or downstream of aberrant caspase activation remains still unanswered [67]. Interestingly, a recent study by Rodriguez et al. suggests that Rab7A may regulate tau secretion. Rab7A, a small GTPase, is implicated in lysosome biogenesis as well as regulation of endosome, autophagosome, and lysosome trafficking [68, 69]. Importantly, Rab7 as well as Rab5 are required for proper retromer complex recruitment to endosomes [70]. *In vitro* data demonstrate partial co-localization of tau and Rab7A in neurons and suggests a potential role of the late endosome in tau secretion [68]. For a complete list of the papers published so far on the retromer complex and PD see Table 2.

Retromer and neurodegeneration: influence on synaptic plasticity

Retromer complex has also been implicated in neuronal health, cell polarity, and synaptic plasticity, such that deficits in the retromer complex function may result in reduced integrity at the synapse level. Knockdown of Vps35 may influence presynaptic neurotransmitter release by reducing both NMDA and AMPA excitatory currents [71]. Vps35 also contributes to AMPA receptor (AMPAR) trafficking and localization on the synapse. Specifically, D620N-mutated Vps35 in murine neurons results in altered synaptic transmission and AMPAR recycling, with a selective effect on excitatory but not inhibitory transmission. Additionally, a recent study suggests that retromer is essential in regulating AMPAR delivery to synapses during long-term potentiation in mature neurons [72]. This finding reiterates the importance of understanding retromer complex neurobiology in pathological conditions as its dysfunction may directly influence synaptic activity in association with the typical hallmark protein aggregation. This fact suggests a possible biologic and mechanistic link between disruption of early endosomal trafficking events and subsequent cognitive decline in AD, PD, and other neurodegenerative disorders.

Retromer and neurodegeneration: influence on glia

Compelling evidence supports the concept that not only neurons but also glial cells are highly vulnerable to neurodegenerative insults. For example, astrocytes function as metabolic support for neurons, but also modify synaptic signaling, recycling of neurotransmitters, and regulation of the blood brain barrier. Also, astrocytes respond to pathological situation by converting to a reactive and pro-inflammatory state, referred to as astrogliosis [73–75]. Astrocytes are particularly essential for protein clearance by ingesting large amounts of dead cells, synapses, and accumulated protein aggregates, especially under pathological conditions [76]. However, excess accumulation of aggregated proteins, such as toxic Aβ, can alter their phagocytic function resulting in dysfunctional lysosomal machinery and enlargement of endosomes in the astrocytes. While the contribution of endosomal/lysosomal mechanisms of clearance within the astrocyte in the context of neurotoxic protein

fragments has only recently been appreciated, it is plausible that defects in endosomal trafficking, potentially through the retromer complex system, may not only influence neuronal physiology but also astrocytes neurobiology.

Further validation for this hypothesis stems from the link between the retromer complex and microglial abnormalities, particularly supported by the observation that microglia isolated from AD brain tissue show significant deficiency in Vps35 [30]. Under physiological conditions, retromer regulates the delivery of phagocytic receptors to the microglial surface, specifically the triggering receptor expressed on myeloid cells 2 (TREM2), which is found in the CNS exclusively in microglia [77]. Mutations in TREM2 are linked to late onset AD pathogenesis as well as frontotemporal-lobar degeneration with dementia and other neurodegenerative disorders and result in reduced delivery of the receptor to the cell surface, indicating a potential dysfunction of the recycling mechanism [78]. Importantly, TREM2 function seems to be Vps35-dependent, such that, a loss-of-function or an AD-linked mutation in TREM2 results in an improper recycling of TREM2 back to the plasma membrane as well as its accelerated degradation in the lysosome [79]. TREM2 receptors function to clear protein debris from the extracellular space; however, it is becoming more clear that TREM2 neurobiology is rather complex. For example, inflammatory stimuli decreases TREM2 expression *in vitro*; however, *in vivo*, expression is increased. Moreover, in the context of AD, studies have found contradictory results regarding the role of TREM2 deficiency and Aβ pathology progression, while a recent study suggests that this phenomenon could be explained by a disease-progression dependent mechanism [77,80]. Likewise, TREM2 neurobiology has recently been investigated in the context of tau pathology, though also producing conflicting results. Bemiller, *et al.* found that TREM2 deficiency in a model of tauopathy, the Htau mice, worsens tau pathology via increased tau phosphorylation and aggregation [81]. Contrastingly, another group found that TREM2 deficiency in another model of tauopathy, the P301S transgenic mouse model, does not alter tau phosphorylation or levels of insoluble tau [82]. Additionally, they posit that TREM2 deficiency, in fact, is protective and attenuates tau-induced neuroinflammatory responses. Taken together, these studies implicate TREM2 in the pathogenesis of both Aβ and tau neuropathology, suggesting a potential role for Vps35 and the retromer complex in both these proteinopathies, though greater detail regarding the mechanisms of these interactions is necessary.

Therapeutic implications of the retromer: use of pharmacological chaperones

A novel approach to dissect the mechanism surrounding the retromer complex neurobiology and its involvement in neurodegenerative processes has recently turned to the use of pharmacological chaperones to stabilize this complex. As we alluded to above, increasing the levels of one or several components of the retromer complex enhances its stability and trafficking function. On the other hand, it is now also clear that from a molecular point of view down-regulation of just one of the three components of the core (Vps35, Vps29, or Vps 26) results in a significant decrease in the other members, further supporting the idea that the interaction of these 3 elements is important both for the function as well as the stability of the complex. To this end, a chaperone is a molecule that typically stabilizes a folded macromolecule (i.e., protein) by directly binding to it and protecting it against degradation

and denaturation [83, 84]. Recently, Mecozzi et al. by performing a computerized virtual in silico screen identified a group of small molecules that the analysis predicted to bind at the level of the retromer core complex [85]. Among them, they have identified and characterized two thiophene thiourea derivatives that selectively bind, stabilize the retromer complex against thermal denaturation and increase the retromer levels in hippocampal neurons [85]. Importantly, the increase in retromer function was associated with enhanced APP trafficking out of endosomes and less neurotoxic Aβ fragments in neurons. Small pharmacological chaperons present a novel, interesting and potentially viable therapeutic strategy to target retromer since several studies confirm that increasing retromer levels does not lead to any toxic events in cellular models as well as animal models [31,61]. Since retromer complex dysfunction has been implicated in a variety of neurodegenerative diseases, small molecules targeting this system represent a viable therapeutic niche for these diseases.

Conclusions

The neurobiology of the retromer complex represents a novel area of research in the neurodegenerative field. Several diseases, such as AD and PD, have been linked to a dysfunction in retromer trafficking and overall, abnormalities in the endosomal-lysosomal transport system. While studies have mainly focused on the role of the retromer complex system in the development of amyloidosis, it is essential to also understand the relationship between retromer dysfunction and other aspects of neurodegeneration such as tau pathology, synaptic dysfunction and neuroinflammation, particularly in the context of microglial clearance of aggregated proteins. Enhancement or restoration of retromer complex function using pharmacologic probes has recently been investigated as well and has provided us with very exciting new therapeutic opportunities.

Interestingly, these small molecule chaperones present a novel and viable therapeutic avenue substantially different from the current ones in the field that typically target a specific molecule (a secretase such as BACE1, or a kinase such as cdk5 kinase), or aim at neutralizing Aβ/tau toxicity. Thus, by contrast with those approaches, the pharmacologic retromer chaperones by targeting a defect in the cell biology would modulate a common and unifying cellular mechanism in the context of neurodegeneration and for this reason could be a more desirable and at the same time reliable strategy for targeting these diseases at the core of their pathogenesis.

Acknowledgment

Domenico Praticò is the Scott Richards North Star Charitable Foundation Chair for Alzheimer’s research. The work from the author’s lab presented in this paper was in part supported by grants from the National Institute of Health (AG055707, AG056689).

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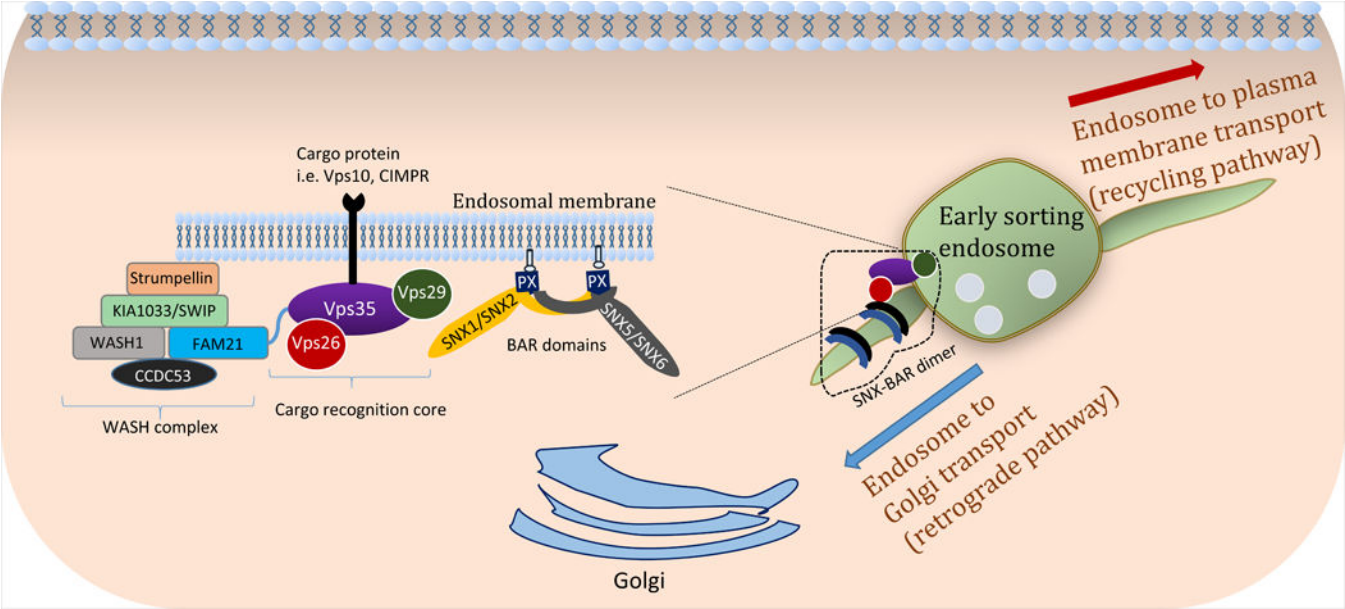

Figure 1. Structure and function of the retromer complex in the endocytic system.

Intracellular trafficking of endocytosed material can follow two distinct pathways via the retromer complex: the *recycling pathway* (indicated by the red arrow) which shuttles cargo from the endosome to the plasma membrane for reuse, or the *retrograde pathway* (indicated by the blue arrow), which transports material from the endosome to the Trans-Golgi Network (TGN). The mammalian retromer consists of two major subdomains: a vacuolar protein sorting-associated protein 35 (VPS35)-VPS26-VPS29 trimeric complex, known as the cargo-recognition core, and a membrane-associated sorting nexin (SNX) dimer, known as the tubulation component. Intracellular transport of many transmembrane proteins and cargo depend on proper function of the retromer complex such as VPS10 receptors and cation-independent mannose 6-phosphate receptor (CIMPR). The SNX dimer is composed of SNX1, SNX2, SNX5, and SNX6, which all have a SNX-phox-homology (SNX-PX) domain and a C-terminal Bin/Amphiphysin/Rvs (BAR) domain and function as a binding partner to the cargo recognition core. The WASH complex consisting of WAS protein family homologue 1 (WASH1), FAM21, strumpellin, coiled-coil domain-containing protein 53 (CCDC53) and KIAA1033, directs cargo to the retromer complex and away from the degradation pathway.

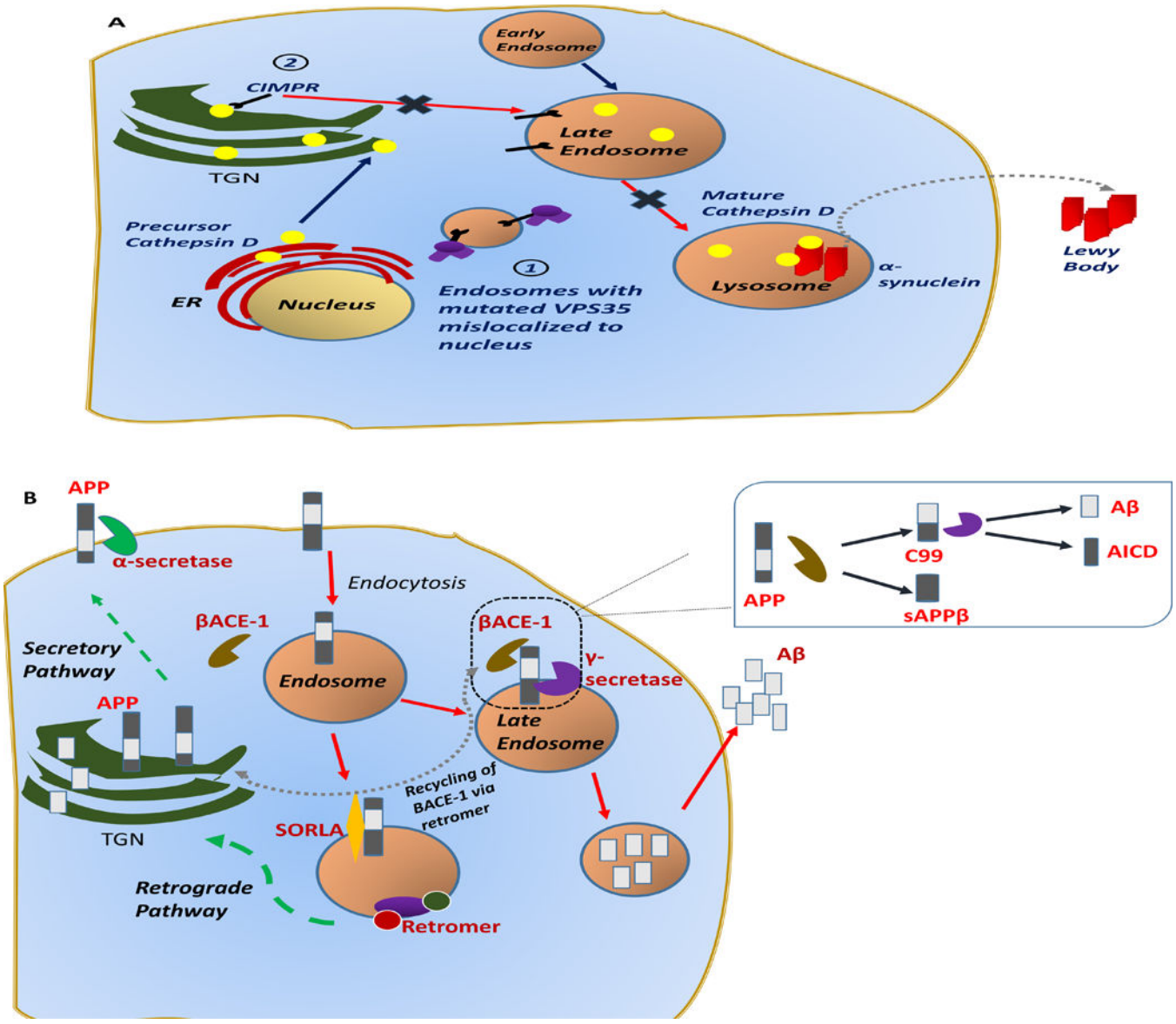

Figure 2. A. The retromer complex in Parkinson's disease.

Here we present two ways in which retromer has been linked to Parkinson's disease (PD). 1) A mutation in VPS35, the p.D620N mutation, occurs in around 1% of familial autosomal inherited PD. Mutated VPS35 causes endosomes to enlarge and mislocalize to the nucleus. 2) Alpha-synuclein is normally degraded by lysosomal protease cathepsin , a known cargo of the CIMPR receptor involved in retromer-mediated trafficking. Precursor cathepsin D is synthesized in the ER and then transported to the Golgi, where it binds to cathepsin D. At the endosome, cathepsin D releases from CIMPR and is targeted to the lysosome in its mature form, while CIMPR recycles back to the Golgi. A dysfunction in the retromer complex causes improper or inefficient binding of CIMPR to cathepsin D, thereby reducing the degradation of alpha synuclein in the lysosome. This allows for the generation of accumulated alpha synuclein and eventual Lewy Body aggregates. **B. Retromer-mediated sorting of APP in Alzheimer's disease.** Amyloid precursor protein (APP) is normally

transported to the Golgi and ultimately targeted to the plasma membrane via the secretory pathway. Upon cell internalization, APP is cleaved sequentially by alpha secretase and gamma secretase in the endosome, then trafficked to the Golgi via the retromer and its binding partner, SORLA. This is known as the non-amyloidogenic pathway. In amyloidogenic or pathological conditions, BACE1, a known retromer cargo recycled between endosome and Golgi, cleaves APP at the endosome prior to gamma secretase cleavage. If retromer dysfunction occurs, BACE1 and APP are improperly recycled, allowing residual APP to remain in the endosome and increasing APP processing via BACE1. This leads to generation of toxic amyloid beta fragments (Aβ, AICD) and eventual amyloid plaques.

Table 1.

Clinical and animal studies on the retromer complex in Parkinson's disease.

	TItle	Reference
Clinical Studies		
	Mutation in the alpha-synuclein gene identified in families with Parkinson's disease	Polymeropoulos et al., 1997
	VPS35 mutations in Parkinson disease.	Vilariño-Güell et al., 2011
	Retromer binding to FAM21 and the WASH complex is perturbed by the Parkinson disease-linked VPS35(D620N) mutation.	McGough et al., 2014
	Reduced LRRK2 in association with retromer dysfunction in post-mortem brain tissue from LRRK2 mutation carriers.	Zhao et al., 2018
	A mutation in VPS35, encoding a subunit of the retromer complex, causes late-onset Parkinson disease.	Zimprich et al., 2011
	Genetic variability of the retromer cargo recognition complex in parkinsonism.	Gustavsson et al., 2015
	Genetic variation of the retromer subunits VPS26A/B-VPS29 in Parkinson's disease.	Shannon et al., 2014
	Vacuolar Protein Sorting Genes in Parkinson's Disease: A Re-appraisal of Mutations Detection Rate and Neurobiology of Disease.	Gambardella et al., 2016
Animal/ Cellular Studies		
	Parkinson Disease-linked Vps35 R524W Mutation Impairs the Endosomal Association of Retromer and Induces α-Synuclein Aggregation.	Follett et al., 2016
	Parkinson's disease-associated mutant VPS35 causes mitochondrial dysfunction by recycling DLP1 complexes.	Wang et al., 2016
	Retromer-dependent neurotransmitter receptor trafficking to synapses is altered by the Parkinson's disease VPS35 mutation p.D620N.	Munsie et al., 2015
	The Vps35 D620N mutation linked to Parkinson's disease disrupts the cargo sorting function of retromer.	Follett et al., 2014
	VPS35 dysfunction impairs lysosomal degradation of α-synuclein and exacerbates neurotoxicity in a Drosophila model of Parkinson's disease.	Miura et al., 2014
	Parkinson's disease-linked mutations in VPS35 induce dopaminergic neurodegeneration.	Tsika et al., 2014
	RAB7L1 interacts with LRRK2 to modify intraneuronal protein sorting and Parkinson's disease risk.	MacLeod et al., 2013
	Vps35 in cooperation with LRRK2 regulates synaptic vesicle endocytosis through the endosomal pathway in Drosophila.	Inoshita et al., 2017
	In Situ Peroxidase Labeling and Mass-Spectrometry Connects Alpha-Synuclein Directly to Endocytic Trafficking and mRNA Metabolism in Neurons.	Chung et al., 2017
	VPS35 in Dopamine Neurons Is Required for Endosome-to-Golgi Retrieval of Lamp2a, a Receptor of Chaperone-Mediated Autophagy That Is Critical for α-Synuclein Degradation and Prevention of Pathogenesis of Parkinson's Disease.	Tang et al., 2015
	Mutation in VPS35 associated with Parkinson's disease impairs WASH complex association and inhibits autophagy.	Zavodszky et al., 2014

Table 2.

Clinical and animal studies on the retromer complex in Alzheimer's disease.

	Title	Reference
Clinical Studies		
	Model-guided microarray implicates the retromer complex in Alzheimer's disease.	Small et al., 2005
	De novo deleterious genetic variations target a biological network centered on Aβ peptide in early-onset Alzheimer disease.	Rovelet-Lecrux et al., 2015
	Neuronal LR11 expression does not differentiate between clinically-defined Alzheimer's disease and control brains	Sager et al., 2012
	SORL1 rare variants: a major risk factor for familial early-onset Alzheimer's disease.	Nicolas et al., 2016
	Lysosomal sorting of amyloid-β by the SORLA receptor is impaired by a familial Alzheimer's disease mutation.	Caglayan et al., 2014
	Coding mutations in SORL1 and Alzheimer disease.	Vardarajan et al., 2015
	Identification of Alzheimer disease-associated variants in genes that regulate retromer function.	Vardarajan et al., 2012
Animal / Cellular Studies		
	Impaired axonal retrograde trafficking of the retromer complex augments lysosomal deficits in Alzheimer's disease neurons.	Tammineni et al., 2018
	The location and trafficking routes of the neuronal retromer and its role in amyloid precursor protein transport.	Bhalla et al., 2012
	Microglial beclin 1 regulates retromer trafficking and phagocytosis and is impaired in Alzheimer's disease.	Lucin et al., 2013
	The retromer complex system in a transgenic mouse model of AD: influence of age.	Chu and Pratico, 2017
	Vps35-dependent recycling of Trem2 regulates microglial function.	Yin et al., 2016
	Retromer deficiency observed in Alzheimer's disease causes hippocampal dysfunction, neurodegeneration, and Abeta accumulation	Muhammad et al., 2008
	SNX15 regulates cell surface recycling of APP and Abeta generation	Feng et al., 2016
	VPS35 haploinsufficiency increases Alzheimer's disease neuropathology.	Wen et al., 2011
	Overexpression of SNX7 reduces Abeta production by enhancing lysosomal degradation of APP.	Xu et al., 2018
	Neuronal sorting protein-related receptor sorLA/LR11 regulates processing of the amyloid precursor protein.	Andersen et al., 2005
	Pharmacological chaperones stabilize retromer to limit APP processing.	Mecozzi et al., 2014
	Hyperleucinemia causes hippocampal retromer deficiency linking diabetes to Alzheimer's disease.	Morabito et al., 2014
	Retromer disruption promotes amyloidogenic APP processing.	Sullivan et al., 2011
	Diabetes-associated SorCS1 regulates Alzheimer's amyloid-beta metabolism: evidence for involvement of SorL1 and the retromer complex.	Lane et al., 2010
	Unexpected partial correction of metabolic and behavioral phenotypes of Alzheimer's APP/PSEN1 mice by gene	Knight et al., 2016

Title	Reference
targeting of diabetes-Alzheimer's-related Sorcs1.	