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RESEARCH ARTICLE

Receptor Recycling by Retromer

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ABSTRACT The highly conserved retromer complex controls the fate of hundreds of receptors that pass through the endolysosomal system and is a central regulatory node for diverse metabolic programs. More than 20 years ago, retromer was discovered as an essential regulator of endosome-to-Golgi transport in yeast; since then, significant progress has been made to characterize how metazoan retromer components assemble to enable its engagement with endosomal membranes, where it sorts cargo receptors from endosomes to the *trans*-Golgi network or plasma membrane through recognition of sorting motifs in their cytoplasmic tails. In this review, we examine retromer regulation by exploring its assembled structure with an emphasis on how a range of adaptor proteins shape the process of receptor trafficking. Specifically, we focus on how retromer is recruited to endosomes, selects cargoes, and generates tubulovesicular carriers that deliver cargoes to target membranes. We also examine how cells adapt to distinct metabolic states by coordinating retromer expression and function. We contrast similarities and differences between retromer and its related complexes: retriever and commander/CCC, as well as their interplay in receptor trafficking. We elucidate how loss of retromer regulation is central to the pathology of various neurogenerative and metabolic diseases, as well as microbial infections, and highlight both opportunities and cautions for therapeutics that target retromer. Finally, with a focus on understanding the mechanisms that govern retromer regulation, we outline new directions for the field moving forward.

KEYWORDS retromer, *VPS35*, endosome, neurodegeneration, cell trafficking

ENDOSOMAL CARGOES – SHOULD I STAY, OR SHOULD I GO?

Three major fates await receptors following internalization by endocytosis: (1) degradation within lysosomes; (2) secretion; or (3) recycling/retrieval back to the plasma or *trans*-Golgi network (TGN) (Fig. 1A).[1,2] The degradative route involves K63-linked ubiquitylation of endosomal membrane proteins for detection by the endosomal sorting complexes required for transport (ESCRT) machinery.[3] ESCRT-0 recognizes ubiquitin earmarks on target proteins and concentrates them to form a "degradative" domain on the endosomal surface.[4–7] Following this, ESCRT-I, -II and -III are recruited to the degradative domain via ubiquitin chain recognition.[4–8] This process can also occur in a ubiquitin-independent fashion that requires the endosomal protein ALIX.[9,10] These receptors are then deubiquitylated, and ESCRT-III polymerizes around the target proteins to generate localized membrane tension which causes budding of the endosomal membrane in the luminal direction.[8] Finally, these buds undergo scission in a VPS4-dependent manner to

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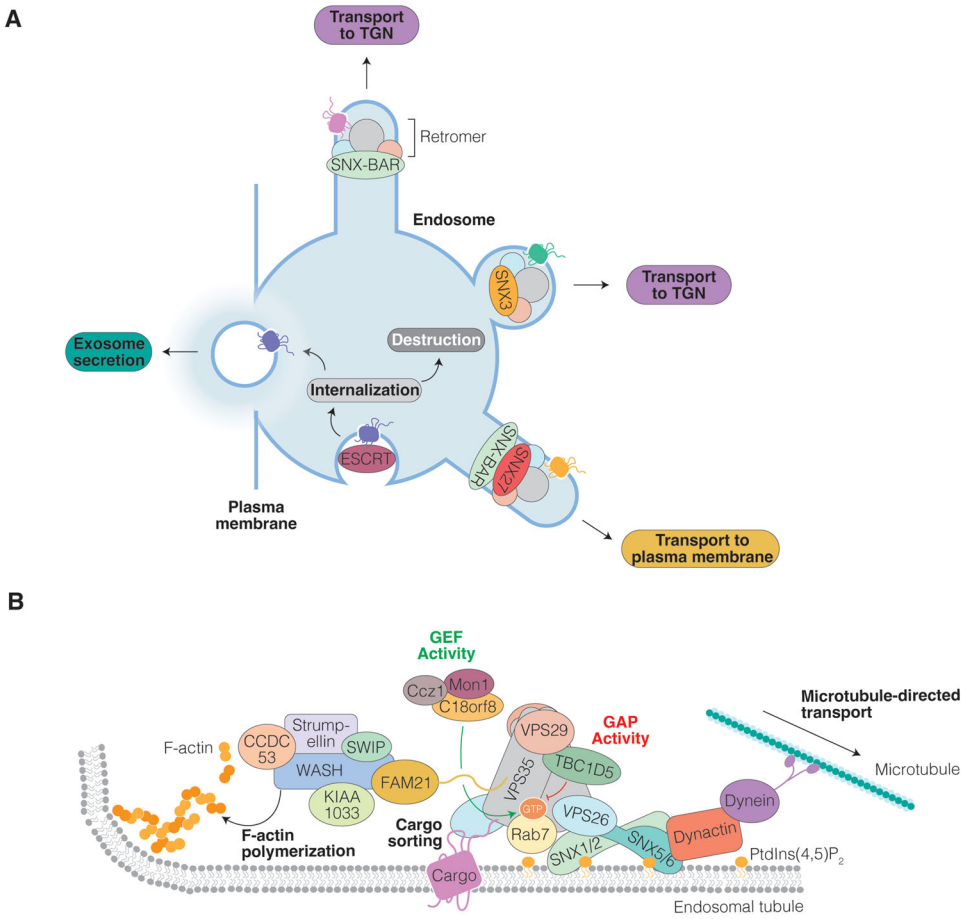

FIG 1 Receptor recycling by retromer. (A) Illustration contrasting the potential fates of cargo receptors that reside on endosomes following endocytosis. Cargo receptors may be recycled to the Golgi by distinct SNX-BAR- or SNX3-retromer pathways or to the plasma membrane by the SNX27-retromer pathway. Alternatively, receptors may bypass sorting and undergo internalization where the resulting intraluminal vesicle is destroyed; alternatively, the endosome may fuse with the plasma membrane leading to release of the intraluminal vesicle as an exosome. (B) Illustration of how many regulatory components assemble with retromer to shape the processes of endosomal recruitment, cargo sorting, tubulation, and trafficking. The SNX-BAR-retromer models is used in this example.

deposit intraluminal vesicles enriched with target proteins within the endosomal lumen.[8] By this point, the endosome has matured and is referred to as a late endosome/multivesicular body. Further maturation into—or fusion with—lysosomes ensures that the target proteins are broken down by hydrolase enzymes.[11] Intraluminal vesicles may bypass lysosomal destruction if late endosomes fuse with the plasma membrane where they are secreted as exosomes which serve a variety of cell autonomous and noncell autonomous signaling functions.[12]

Recycling is an alternative fate for endocytosed plasma membrane receptors that bypass degradation or secretion. Following endocytosis, early endosomes may rapidly—and nonselectively—deliver their content back to the plasma membrane in a process termed "bulk membrane flow."[13,14] Similarly, yet selectively, transmembrane proteins on endosomes may undergo cargo sorting and clustering on tubulovesicular profiles that undergo scission to generate carriers that are targeted to the plasma membrane or TGN[15–17] (Fig. 1A). Importantly, even on the same endosomes, the opposing degradative and recycling pathways may occur in parallel via spatial separation of distinct "degradative" and "recycling" domains[18,19] (Fig. 1A). These receptor rerouting processes are orchestrated by various endosomal coat complexes which participate in cargo selection based on specific sorting motifs present in the cytoplasmic tails of cargo proteins.[15–17,20,21]

RETROMER—THE IMMEDIATE FAMILY

Retromer is a highly conserved assembly of VPS35, VPS26, and VPS29 that was discovered as a regulator of endosome-to-Golgi receptor trafficking in *Saccharomyces cerevisiae* (Fig. 1A).[2,22] Apart from this, in metazoan species retromer also regulates endosome-to-plasma membrane trafficking (Fig. 1A).[16,17] These receptor recycling itineraries depart from endosomes and prevent the lysosomal destruction of retromer cargoes including IGF2R/CI-MPR, sortillin, DMT1-II, GLUT1, and the β_2 adrenergic receptor.[17,23]

Structurally, VPS26 contains an arrestin fold and has a mobile loop within its C-terminus (amino acids 235–246) that binds to the N-terminus of VPS35.[24,25] VPS26 exists as two paralogues (VPS26A and B) that compete for binding to VPS35, forming mutually exclusive retromer complexes.[26,27] Indeed, VPS26 paralogues display unique preferences for decorating endosomes at different stages of maturation: for example, VPS26B shows a greater preference for associating with late endosomes than VPS26A.[26] VPS26A- and B-containing retromer also have different cargo specificities: for example, VPS26A binds to and traffics the CI-MPR, whereas VPS26B does not.[26] These spatiotemporal differences in endosomal localization and cargo specificity are encoded by the divergent C-terminal tail of VPS26B.[26] In mice testis, an alternatively spliced VPS26A isoform interacts with VPS35, suggesting that retromer may form distinct tissue-specific complexes which may enable retromer to traffic cargoes that are expressed in a tissue-specific fashion.[28] VPS35 forms a right-handed α-solenoid structure and engages with VPS26 and VPS29.[24,29,30] The conserved PYLRL motif on VPS35 is necessary for its interaction with VPS26.[31–34] VPS26 and VPS29 bind independently to the N- and C-terminal regions of VPS35, respectively, however, each component is necessary to enable maximal stability of the others.[32,35] Incorporation of VPS26 into the retromer complex induces conformational changes in VPS35 and VPS29.[31,32] VPS29 has a metallophosphoesterase fold which acts as a scaffold for binding to the C-terminus of VPS35.[29,30] Its metallophosphoesterase fold weakly binds Mn^{2+} and Zn^{2+} ions, and the residues involved with metal binding appear to be important for its stability.[30,36] Catalytic activity against a phosphoserine peptide corresponding to the CI-MPR sorting signal by the retromer complex in vitro was initially reported, and this function was abolished by mutation of key residues in VPS29 or with Zn^{2+} chelators.[37] However, a conserved histidine "trigger" is thought to be required for metallophosphoesterase activity in similar proteins but is replaced by phenylalanine at position 63 suggesting that VPS29 is catalytically inactive.[29,30] In agreement with this, it was subsequently found that VPS29 does not display metallophosphoesterase activity against generic substrates in vitro.[29,36]

Recently, the structural organization of retromer on membranes has been described.[38] Retromer expressed in *Chaetomium thermophilium* co-assembles with recombinant Vps5 homodimers in vitro to enable engagement with liposome membranes. Retromer is organized into dimer complexes (i.e., dimers of VPS29-VPS35-VPS26 trimers) with arch-like architecture. VPS26 binds to Vps5 at the membrane-proximal base, with VPS35 extending away to form an arch "leg" that contacts a second copy of VPS35 on the opposite leg at the apex. VPS29 positioned on the membrane-distal end engages with VPS35 on the opposite side of the apex. This general architecture enables solvent exposure of distinct retromer surfaces that are known to engage with transmembrane cargoes. The VPS35 dimer interface is flexible and stabilized through electrostatic interactions.[38,39] Retromer also appears to organize into tetramers (i.e., tetramers of VPS29-VPS35-VPS26 trimers), flat chains, as well as a monomeric complex (i.e., a monomer of VPS29-VPS35-VPS26 trimer).[39,40] It is important to note considerable variation in the reported retromer structures.[38–40] These reflect diverse conformations and assemblies which may exist in eukaryotes or may arise from technical differences in the approaches used. For instance, the reported arch-like architecture of retromer might have been influenced by the Vps5 homodimer on Folch lipid liposomes and may differ from that assembled on a Vps5-Vps17 heterodimer.[38]

ITINERARY-SPECIFIC RETROMER ADAPTORS—THE EXTENDED FAMILY

Retromer interacts with a variety of adaptors that participate in cargo selection, endosomal recruitment, dictate trafficking itineraries, and serve other regulatory functions. By and large, retromer forms higher order functional complexes by associating with SNX1/2 and SNX5/6 (SNX-BAR-retromer) or with SNX3 (SNX3-retromer) to regulate endosome-to-Golgi retrieval pathways via tubular or vesicular endosomal carriers, respectively (Fig. 1A and B).[41–44] In contrast, endosome-to-plasma membrane recycling is mediated by a complex of retromer with SNX27 (SNX27-retromer) that generates tubular endosomal carriers (Fig. 1A).[17,45] These carriers are trafficked, then tether and fuse with target membranes.[46]

SNX-BAR-retromer. SNX-BAR-retromer was first identified in *S. cerevisiae*, where the retromer trimer stably interacts with Vps5 and Vps17 (SNX1/2 and SNX5/6 orthologs, respectively).[2,22,47] Although metazoan retromer functionally associates with SNX1/2 and SNX5/6, these interactions appear to be somewhat transient or of low affinity, as these components do not consistently co-immunoprecipitate together.[15,21,26,48,49] However, their association is largely appreciated by colocalization to the same endosomes. Initial reports showed that Vps5 and Vps17 interact, and their deficiency resulted in enhanced secretion of the vacuolar hydrolase carboxypeptidase Y.[47] Vps10 is a receptor that targets hydrolases from the Golgi to the vacuole.[2,47] Vps10 must undergo endosome-to-Golgi retrograde transport to enable subsequent delivery of carboxypeptidase Y to the vacuole.[2] When this process is inhibited, hydrolases such as carboxypeptidase Y are aberrantly secreted.[2,47] Indeed, this occurs in Vps29-, Vps35-, and Vps10-deficient yeast strains.[2] In mammalian systems, the CI-MPR performs a similar task and couriers hydrolases to the lysosome.[50] Similarly, retromer depletion impairs endosome-to-Golgi trafficking of the CI-MPR and enhances secretion of the lysosomal hydrolase cathepsin D, thus reducing the degradative capacity of lysosomes.[15,16,46] Depletion of either SNX1, -5 or -6 leads to CI-MPR mis-trafficking; strikingly, SNX2 depletion does not, suggesting that its loss may be functionally compensated for by SNX1.[44,51,52] Consistent with this, codepletion of SNX1 and SNX2 limit the endosomal recruitment of VPS26.[42] The PX domains of SNX1/2 show a strong preference for binding to phosphatidylinositol (PtdIns)(3,4)P_2 on membranes.[53] In contrast, SNX5/6 do not exhibit appear to bind to phospholipid membranes, and likely are recruited to endosomes by binding to the cytoplasmic tails of receptor cargoes.[44,53,54] SNX1 interacts with SNX6, and SNX5 and -6 are required for the stability of SNX1.[44] SNX1/2, along with the SNX1 interacting protein RME8 segregate recycling domains on endosomes from degradative ones that are decorated with ESCRT machinery.[18] SNX1/2 contain BAR domains that sense and mediate local membrane curvature to generate endosomal tubules in a clathrin-independent fashion.[43,51,55] SNX6/5 bind to the $p150^{glued}$ component of the dynactin-dynein motor complex to elicit minus-end microtubule transport of tubular carriers loaded with the CI-MPR to the TGN following scission.[56,57] In an SNX1/2-dependent manner, endosomal carriers containing the CI-MPR are tethered to the Golgi by golgin 245.[46] A pool of PtdIns(4)P at the TGN antagonizes the $p150^{glued}$-SNX6 interaction and enables carrier-to-Golgi cargo transfer.[58] EHD1 stabilizes SNX1-positive endosomal tubules and may regulate fission to produce tubular carriers.[59] The nucleotide-binding P-loop of EHD1 is necessary for its interaction with VPS26, and when in complex with ANKFY1, collectively ensures the recruitment of retromer to endosomes rather than the Golgi.[59,60] Moreover, both SNX1 and -2 can be cleaved by initiator caspases 8, -9 and -10, whereas only SNX2 is cleaved by the executioner caspase 6 during apoptosis.[61] SNX2 cleavage impairs the SNX2-VPS35 interaction and reduces the endosomal recruitment of VPS26.[61] In addition, independent of its catalytic activity, the apoptosis initiator, caspase 9, regulates CI-MPR endosome-to-Golgi transport.[62] Caspase 9 interacts with VPS35 as well as SNX1, -2, -5 and -6, and elicits an inhibitory action against the ESCRT pathway.[62] Together, these findings suggest that apoptotic signalling may communicate with retromer to modulate

receptor trafficking and homeostasis. However, these actions may be less coordinated than expected given the wide array of proteins cleaved by caspases during apoptosis.

Genetic screens to analyze CI-MPR trafficking have been incredibly valuable tools for the identification of retromer modulators and/or endosome-to-Golgi pathway modifiers in general.[44,63] The rationale for their use was tied to early reports which independently showed that CI-MPR trafficking required retromer.[15,16] Recognition and sorting of the CI-MPR and sortilin by retromer were mapped to a canonical [F/L/W]x[L/M/V] (where x is any amino acid) sorting motif in their cytoplasmic tails.[21] However, several established cargoes lack this sorting motif, leading to the discovery of variable bipartite sorting signals in cargoes including Vps10 and Ear1 in yeast.[64] Importantly, most of what we understand about retromer stems from its role in CI-MPR trafficking. The recent demonstrations that retromer was dispensable for CI-MPR trafficking, and that SNX-BAR components carried out this function independently of retromer was both surprising and controversial.[48,49] Particularly, because this work by the Steinberg and Cullen labs seems to contradict their earlier findings.[44,54] In their recent work, genetic deletion of retromer components or their depletion by RNA interference did not affect CI-MPR trafficking in an array of cell lines.[48,49] In broad disagreement with others,[15,21,26] their studies demonstrated that the CI-MPR did not directly bind to retromer but rather engaged with SNX1/2 and SNX5/6 in a manner that was abolished by mutation of the WLM sorting motif within its cytoplasmic tail.[48,49] Further, the CI-MPR did not reside on the same tubular endosomal domains as retromer, but rather with SNX1/2 and SNX5/6.[48,49] These observations are difficult to square with previous findings and call into question our current understanding about SNX-BAR-retromer.[65]

SNX3-retromer. SNX3 can recruit retromer onto the endosomal surface, and from here SNX3-retromer regulates the endosome-to-Golgi trafficking of its cargoes through the generation of vesicular endosomal carriers.[41,66] SNX3 contains a PX domain, similar with SNX1/2.[67] The PX domain of SNX3 binds more strongly to PtdIns(3)P than does the PX domains of SNX1/2, which may account for their spatial separation on endosomes.[53,68] Similarly, SNX3 is recruited to other compartments enriched with PtdIns(3)P such as phagosomes sequestering *Salmonella enterica* or *Escherichia coli*.[69,70] Control of the SNX3-PtdIns(3)P interaction, and thus its endosomal recruitment, is opposed by phosphorylation of $SNX3^{S72}$ within its PX domain.[71] This residue is conserved across the PX domains of other proteins such as SNX1 and -2 and may represent a common mode of regulation.[71] However, the kinase responsible for SNX3 phosphorylation at this site awaits discovery. Endosomal recruitment of SNX3 is reduced following exposure to wortmannin, an inhibitor of phosphoinositide 3-kinase.[72] On the endosomal surface, SNX3 docks onto the VPS26-VPS35 interface to induce a conformational change in VPS26 to enable recognition of the [−/+]ψØψ[L/M] (where, −/+ denotes any charged amino acid, Ø denotes a bulky aromatic residue, and ψ denotes a residue with a hydrophobic or long aliphatic hydrocarbon tail) sorting motif on its cargo DMT1-II.[73] SNX3 engages with the MON2-DOPEY2-ATP9A endosome remodelling complex and is required for proper sorting of its cargo Wntless.[74] Indeed, akin to SNX3 or VPS35 depletion, silencing MON2 and DOPEY2 expression perturbs Wntless trafficking and enhances its turnover.[74] SNX3 is also critical for endosomal maturation and the formation of multivesicular bodies, a function thought to be distinct from its role in cargo retrieval.[72] In a SNX3-dependent manner, endosomal carriers containing the CI-MPR carriers are tethered to the Golgi by GCC88.[46]

SNX27-retromer. SNX27 lacks a BAR domain, akin to SNX3, but a key difference between the two is that SNX27-retromer interacts with SNX1, -2, and -5 which mediate tubular carrier formation for the endosome-to-plasma membrane trafficking pathway.[17] However, SNX1/2 or SNX5/6 depletion only partially phenocopies the degradation of SNX27-retromer cargoes, indicating that a degree of functional redundancy exists in the pathway.[17] SNX27 contains a PX domain and a FERM domain that collectively bind to PtdIns(3,4)P_2, PtdIns(3,5)P_2, PtdIns(4,5)P_2, and PtdIns(3,4,5)P_3 on membranes.[75,76] The FERM domain is not required for the general endosomal recruitment of SNX27 but rather for recruitment to transferrin-positive recycling endosomes.[76]

The PX domain of SNX27 and SNX1/2 have distinct preferences for binding to PtdIns(3)P and PtdIns(3,4)P_2, respectively, suggesting that SNX27 recruitment to SNX1/2-decorated endosomes, or vice-versa, may occur indirectly via the SNX27-SNX1/2/5 interaction or at distinct stages throughout endosomal maturation.[17,53] A surface-exposed β-hairpin within the PDZ domain of SNX27 binds to a groove in the arrestin fold of VPS26A.[77] The PDZ domain of SNX27 binds to transmembrane cargoes that contain a PDZ binding motif on their cytoplasmic tails.[17] The SNX27-VPS26A interaction increases the affinity of SNX27 for PDZ binding motifs, suggesting that incorporation of SNX27 into the retromer complex plays an important role in cargo sorting.[77] Similarly, an acidic clamp upstream of the PDZ binding motif on SNX27 cargoes is important for cargo selection.[78] SNX27-retromer cargoes, including the β_2 adrenergic receptor, lack an acidic clamp which is compensated for by phosphorylation of residues that occupy these positions, thus providing an analogous negative charge.[78] In contrast, phosphorylation of the β_2 adrenergic receptor^{S411} within its PDZ binding motif abolishes its interaction with SNX27 and enhances its turnover.[78,79] The FERM domain of SNX27 also participates in cargo sorting through recognition of NPxY/NxxY sorting motifs (where x is any amino acid).[80] The VPS26-SNX27 interaction is critical for GLUT1 recycling but is antagonized by the PTEN-SNX27 interaction.[81] Most oncogenic PTEN mutations impair its lipid phosphatase activity; however, the T401I mutation, which does not affect its catalytic function, fails to inhibit the VPS26-SNX27 interaction and leads to enhanced glucose uptake and glycolysis.[81] Similarly, the deubiquitinase OTULIN binds to SNX27 via its PDZ binding motif and OTU domain which inhibits the VPS26-SNX27 interaction in a manner that is independent of its catalytic function.[82] In response to a variety of stressful stimuli (e.g., nutrient starvation, ER stress, mitochondrial depolarization, lipopolysaccharide, pro-inflammatory cytokines, and high ATP levels), phosphorylation of SNX27^{S51} by MAPK11/14 inhibits the selection and recycling of cargoes to the plasma membrane.[83] This indicates that SNX27 controls the density of receptors at the plasma membrane as a way of adapting to environmental fluctuations.

ADDITIONAL RETROMER ADAPTORS—FRIENDS WITH BENEFITS

WASH complex. The Wiskott–Aldrich syndrome and scar homologue (WASH) complex nucleates branched chains of F-actin on the endosomal surface and coordinates endosomal tubule scission/fission.[84–86] The WASH complex consists of WASH, FAM21, KIAA1033, strumpellin, SWIP, and CCDC53.[84–86] Retromer recruits the WASH complex to endosomes which, together, form a supercomplex via *VPS35* binding to the unstructured tail of FAM21.[87–89] The tail of FAM21 contains 21 copies of an unstructured LF[D/E]$_{2-10}$LF motif that can simultaneously bind to multiple copies of VPS35, suggesting that FAM21 senses the concentration of cargo-engaged retromer to coordinate F-actin nucleation on tubulating endosomes.[88,89] Depletion of WASH, strumpellin or KIAA1033 leads to uncontrolled endosome tubulation and CI-MPR mis-trafficking, indicating that endosomal F-actin polymerization is a prerequisite for scission.[87,90] A complex of MAGEL2 and TRIM27 binds to VPS26 and VPS35 and controls K63-linked ubiquitination of WASH^{K220} to promote F-actin nucleation and CI-MPR trafficking.[91] Apart from endosomes, the retromer-WASH supercomplex docks onto macropinosomes and phagosomes to regulate sorting of p25 and the integrin SibC in *Dictyostelium discoideum*.[92] SNX27 interacts with WASH complex components FAM21, strumpellin, and WASH via its FERM domain.[17] This interaction suppresses PtdIns 4-kinase β activity and thus PtdIns(4)P production at the Golgi.[93] PtdIns(4)P regulates cargo disengagement from retromer at the Golgi; limiting its production enhances the targeting of SNX27-retromer cargoes to the plasma membrane.[93] In addition, ANKRD50 incorporation into the SNX27-retromer-WASH supercomplex is required for the endosome-to-plasma membrane trafficking of GLUT1.[94] Importantly, the VPS35^{D620N} mutation causes autosomal dominant Parkinson's disease and impairs the VPS35-FAM21 interaction.[54,95] This mutation reduces the endosomal recruitment of the WASH

complex and perturbs the endosome-to-Golgi itineraries but not the plasma membrane ones.[54,95] The direct interaction between SNX27 and the WASH complex via its FERM domain—independently of the VPS35-FAM21 interaction—might explain why the recycling pathway is somewhat resistant to the defects caused by the VPS35^{D620N} mutation.[17,54] This mutation, similar with WASH depletion, leads to mis-trafficking of ATG9A and impedes autophagosome formation.[95] Following endosomal tubulation the scission and liberation of carriers occurs at endoplasmic reticulum (ER)-endosome contacts.[96,97] Indeed, the ER is recruited to FAM21-positive sorting domains on endosomes prior to fission.[97] ER-endosome contacts are coordinated in *trans* by an interaction between SNX2 on tubular endosomes and the ER-resident protein VAMPA/B.[96] In *trans*, VAMPA/B regulate endosomal PtdIns(4)P levels, WASH complex activity, and thus scission dynamics.[96] At the ER-endosome interface, spastin drives tubule fission and its depletion impedes CI-MPR trafficking.[98] Altogether, the WASH complex is an important retromer adaptor that assists in the formation of tubular endosomal carriers for the efficient retrieval and recycling of receptors. It is interesting to note that the WASH complex is not conserved in yeast and is therefore not necessary for endosome-to-Golgi trafficking in simple eukaryotes.

Rab7 GTPase and TBC1D5. The small GTPase Rab7 regulates endosomal maturation, fusion, and lysosome biogenesis.[99,100] Apart from these functions, in a GTP-nucleotide-bound state Rab7 loads retromer onto the endosomal membrane.[87,101,102] The Mon1-Ccz1-C18orf8 complex is a guanine nucleotide exchange factor that switches Rab7 from a GDP- to GTP-bound state, an upstream requirement for the recruitment of retromer to the endosomal surface.[101–104] Rab7 depletion, as well as expression of a GDP-locked mutant, result in the disassociation of VPS26 from endosomes.[87,101,102] Rab7 depletion also impairs the endosome-to-Golgi trafficking of the CI-MPR.[101,102] In yeast, the conserved α-helix$^{\#6}$ of Vps35 is required for binding to the Rab7 ortholog Ypt7.[105] Deletion of α-helix$^{\#6}$ in VPS35 leads to mis-trafficking of the CI-MPR in mammalian cells, suggesting that the VPS35-Rab7 interaction is important for receptor trafficking.[105] The VPS26-Rab7 interaction is enhanced by Rab7 palmitoylation, and the VPS35-Rab7 interaction is abolished by a RAB7A mutation that causes Charcot–Marie–Tooth 2B disease.[102,106]

VPS29 and VPS35 interact with two loops in TBC1D5 to form a complex of similar affinity to the VPS35-VPS26 interaction ($K_D \sim 220$ nM).[102,107] Importantly, VPS29 binds to TBC1D5 far more strongly than VPS35 does. The retromer-TBC1D5 interaction has been highly conserved for over one billion years despite TBC1D5 lacking a clear homologue in yeast.[108] TBC1D5 contains a TBC/GTPase-activating protein (GAP) domain that catalyzes the GTP-to-GDP hydrolysis of Rab7 in vitro, a catalytic function that is enhanced when it is bound to retromer.[107,109] Indeed, over-expression of TBC1D5, but not mutants lacking the TBC/GAP domain or GAP activity, reduces the endosomal recruitment of VPS26.[87,102] TBC1D5 depletion also enhances the Rab7-retromer interaction.[110] The loss of TBC1D5 or retromer components promotes Rab7 hyperactivation and its relocalization to nonendosomal membranes such as mitochondria and ER.[111] In *Drosophila*, Tbc1d5 deficiency enhances the endosomal retention of retromer.[112] TBC1D5 depletion augments some but not all retromer-dependent trafficking itineraries. In cells overexpressing VPS35 or its D620N mutant, TBC1D5 depletion increases CI-MPR delivery to the TGN; however, this fails to occur in non-overexpressing cells.[110] Similarly, TBC1D5 depletion modestly enhances GLUT1 trafficking to the plasma membrane.[113] However, a VPS29^{L152E} mutant that fails to bind to TBC1D5 has the opposite effect and reduces GLUT1 trafficking.[108,114] This mutant also fails to bind to VARP/ANKRD27 making this finding difficult to interpret. Likewise, loss of TBC1D5 impairs the endosome-to-plasma membrane trafficking of CI-MPR.[107] These inconsistencies indicate that the relationship between TBC1D5 and retromer is not strictly of an inhibitory nature.

TBC1D5 has at least two Atg8/LC3-interacting regions (LIR): its C-terminal LIR is primarily responsible for binding to Atg8 proteins in vitro;[115] its N-terminal LIR is required for binding to VPS29 in vitro but can be outcompeted by increasing amounts of LC3A.[115] Mutant TBC1D5 lacking its N-terminal LIR retains its interaction with LC3A/B but does not recruit to autophagosomes, suggesting that the TBC1D5-retromer interaction may be required for targeting to autophagosomes.[115] The VPS29-TBC1D5 interaction is antagonized during autophagy, with TBC1D5 favoring interaction with components of the autophagy initiation machinery including ATG9 and ULK1.[116] ATG9 is critical for autophagosome formation and its trafficking to the phagophore is regulated by retromer and WASH, as well as TBC1D5 in an AP2-dependent manner.[95,116,117] Control of ATG9A trafficking by the retromer-TBC1D5 complex also regulates Rab7-dependent mitophagy.[111] In an autophagy-dependent manner, TBC1D5 preferentially binds to LC3A over retromer during glucose deprivation.[113] This weakens the inhibitory effect of TBC1D5 for retromer, enhancing the endosomal recruitment of retromer and GLUT1 trafficking to augment glucose uptake.[113] This mode of regulation may be limited to autophagy triggered by glucose deprivation, hypoxia, and KRAS transformation, as autophagy activation following mTOR inhibition with rapamycin does not produce the same effect.[113] The retromer-TBC1D5 complex activates mTORC1 signaling and thus suppresses autophagy by restricting Rab7 hyperactivation.[118] Hyperactivated Rab7 outcompetes RagC for lysosomal domains leading to defective lysosomal recruitment of mTORC1 and reduced mTORC1 signaling even under amino acid replete conditions.[118] Moreover, retromer deficiency confers sensitivity to mTORC1 inhibition with rapamycin.[119] Indeed, similar to caloric restriction or exposure to rapamycin, vps-35 and vps-29 deficiency extends lifespan in *Caenorhabditis elegans* but this is not the case for Vps29 deficiency in *Drosophila*.[112,118]

VARP. VARP interacts with retromer and regulates the endosome-to-plasma membrane trafficking itineraries of some but not all cargoes.[120] The N-terminal region of VARP is required for its interaction with retromer; this interaction is also conserved for its related protein in yeast Vrl1.[120,121] VARP is a Rab32/38 effector; however, VPS29 but not Rab32 is required for its endosomal recruitment.[114] The VARP-VPS29 interaction is required for the proper sorting of GLUT1 to the plasma membrane.[108,114] However, in one study, VARP depletion did not lead to appreciable GLUT1 degradation.[120] VARP has a Zn^{2+} "fingernail" that binds to VPS29 at the same site as TBC1D5.[108] In cells, VARP and TBC1D5 directly compete for binding to VPS29 and thus their incorporation into the retromer supercomplex.[108] A retromer binding switch from TBC1D5-to-VARP may serve a regulatory function given that VARP also associates with VAMP7, a SNARE protein involved in vesicle fusion.[108,114] VARP displays a preference for binding to retromer dimers suggesting that arrangement of retromer coats may affect the TBC1D5-to-VARP switch.[108]

DIRECT CONTROL OF RETROMER—FAMILY POLITICS

Post-translational modifications to retromer components may impact its localization, cargo selection, and trafficking functions (Table 1). These modifications may modulate retromer function in response to environmental and metabolic changes. Insulin promotes glucose uptake into peripheral tissues by augmenting AKT-dependent trafficking of GLUT4 to the plasma membrane.[125] However, prolonged insulin exposure results in GLUT4 degradation in a similar manner to VPS26 depletion.[122] Downstream of the insulin receptor, this effect appears to be driven by CK2 rather than phosphoinositide 3-kinase or ERK.[122] Following insulin stimulation, VPS35 attachment to endomembranes is modestly reduced; however, this is abolished by the expression of a phosphodeficient mutant of $VPS35^{S7A}$.[122] The residues that immediately flank $VPS35^{S7}$ conform to the consensus phosphorylation motif of CK2, although it is currently unknown if it actually phosphorylates VPS35.[122] The DNA damage responsive kinase NEK1 phosphorylates the C-terminal tail of $VPS26B^{S302/304}$.[124] A

TABLE 1 Post-translational modifications that regulate retromer function

Protein	Site and PTM type	Regulated by	Outcome	Effect on trafficking	Reference
Vps35	S7 phosphorylation	Unknown kinase (likely CK2)	↓ endosome recruitment of retromer	Likely ↓ endosome-to-Golgi/plasma membrane trafficking	122
Vps35	K515/555/701 ubiquitination	Parkin	Unclear May ↑ WASH and FAM21 stability	Likely ↑ endosome-to-Golgi/plasma membrane trafficking	123
Vps26B	S302/304 phosphorylation	NEK1	↓ binding of *VPS26B* to SNX27 ↑ binding of *VPS26B* to SNX2	↑ endosome-to-plasma membrane trafficking	124
SNX2	D84 Cleavage	Caspase 6, 8, 9 and 10	↓ binding of SNX2 to retromer	Likely ↓ endosome-to-Golgi/plasma membrane trafficking	61
SNX3	S72 phosphorylation	Unknown kinase	↓ binding of SNX3 to PtdIns(3)P ↓ endosome recruitment of SNX3-retromer	Likely ↓ endosome-to-Golgi trafficking	71
SNX27	S51 phosphorylation	MAPK11/14	↓ binding of SNX27 to PDZ motif-containing cargoes	↓ endosome-to-plasma membrane trafficking	83
WASH	K220 ubiquitylation	MAGEL2-TRIM27 complex	↑ actin nucleation at endosomal surface to promote tubule formation	↑ endosome-to-Golgi trafficking Likely ↑ endosome-to-plasma membrane trafficking	91
Rab7	GTP-bound	Mon1-Ccz1-C18orf8 (GEF)	↑ endosome recruitment of retromer	Likely ↑ endosome-to-Golgi/plasma membrane trafficking	102,101,104
Rab7	GDP-bound	TBC1D5 (GAP)	↓ endosome recruitment of retromer	↓ endosome-to-Golgi transport	87,102,110

phosphomimetic mutant of VPS26B$^{S302/304D}$ displays impaired binding to SNX27, yet increased delivery of its cargo GLUT1 to the plasma membrane.[124] Interestingly, a phosphodeficient mutant of VPS26B$^{S302/304A}$ has reduced ability to bind to SNX2.[124] Together, this suggests that phosphorylation of the C-terminus of VPS26B coordinates the extent to which endosome-to-plasma membrane, or -Golgi trafficking itineraries are activated by VPS26B-containing retromer. It may also enable retromer to sense and adapt to stressful situations (e.g., DNA damage). In yeast, phosphorylation of residues that comprise loop$^{\#6}$ of Vps26 are critical for cargo selection and trafficking, and is antagonized by Mih1, a member of the CDC25 phosphatase family.[126] However, it is unclear whether a similar regulatory mechanism exists in metazoa.

The ubiquitin ligase Parkin mediates ubiquitylation of three C-terminal lysine residues on VPS35$^{K515/555/701}$.[123] A similar notion was supported by an unbiased screen for Parkin substrates in the *Drosophila* eye.[127] VPS35 ubiquitylation does not affect its stability.[123] However, WASH and FAM21 are reduced in the mid-brain of Parkin-deficient mice, and Parkin depletion leads to mis-trafficking of ATG9A.[123] These observations hint that VPS35 ubiquitylation may affect the stability of the WASH complex and cargo trafficking, although further investigation is required to understand how VPS35 ubiquitylation truly affects retromer.[123]

The transcription factor TFEB promotes VPS26A and VPS35 expression following amino acid depletion.[128] Phosphorylation of TFEB^{S211} by mTORC1 antagonizes its entry into the nucleus and inhibits transcription of its target genes.[129] Thus, one way that cells may attempt to adapt to amino acid withdrawal is to augment retromer function given that the glutamine transporter ASCT2 is an SNX27-retromer cargo.[128,130] Remarkably, cells lacking VPS35 or VPS29 display reduced mTORC1 signalling and increased nuclear localization of TFEB, suggesting that their relationship may be bidirectional.[118]

RELATED ENDOSOMAL SORTING COMPLEXES—LONG LOST COUSINS

Retromer shares a high degree of structural and functional homology with newly identified endosomal sorting complexes. By contrasting various targeted interactomics datasets the evolutionarily conserved commander/CCC complex was identified to consist of ~14 putative subunits, including COMMD1–10, CCDC22, CCDC93, VPS26C, and VPS35L.[131] VPS26C and VPS35L share predicted structural homology to VPS26 and VPS35, respectively.[20,131] Retriever is a stable trimer consisting of VPS26C, VPS35L, and VPS29 with predicted similarity in overall architecture to retromer.[20] Retriever is incorporated into a supercomplex with SNX17 and the other CCC components.[20] Retromer and retriever exist as distinct complexes.[20] It is likely that most VPS29 is incorporated within retromer rather than retriever as loss of *VPS35* markedly depletes VPS29 levels.[46] Similar to SNX27, SNX17 has PX and FERM domains that dock onto PtdIns(3)P and participate in selection of NPxY/NxxY sorting motifs, respectively (where x is any amino acid).[53,80] CCDC22 and CCDC93 engage with the WASH complex by binding to FAM21, and therefore commander/CCC complex components may have a common role in the coordination of retromer and retriever functions.[132] Through their C-terminal COMM domains, the COMMD subunits form heterodimers.[133] COMMD3 is required for endosomal recruitment of VPS35L.[134] The SNX17-retriever-WASH supercomplex regulates the endosome-to-Golgi and -plasma membrane trafficking of a diverse array of receptors including integrin α5.[20] Similar to retromer, retriever controls the steady-state abundance of >120 cell surface proteins as well as copper and low-density lipoprotein homeostasis.[20,132,135] Depletion of CCDC93, COMMD3 or VPS26C elevates PtdIns(3)P levels and impairs the plasma membrane trafficking of integrin α5, a defect that can be rescued by inhibition of the phosphoinositide 3-kinase VPS34.[134] The lipid phosphatase MTMR2 interacts with CCDC22 to restrict its phosphorylation at serine 58, which in turn suppresses PtdIns(3)P levels and ensures proper retriever-dependent trafficking.[132,134]

RETROMER AND HUMAN DISEASE—A DYSFUNCTIONAL FAMILY

Parkinson's disease. Parkinson's disease is a progressive motor disorder that is characterized by the degeneration of dopaminergic neurons in the substantia nigra pars compacta.[136] With this, the Parkinson's disease brain displays Lewy body pathology within neurons, which are insoluble deposits of α-synuclein, as well as mitochondrial dysfunction.[136] The VPS35^{D620N} missense mutation causes a rare form of autosomal dominant Parkinson's disease.[137,138] Similarly, other VPS35 variants are associated with Parkinson's disease, albeit from a mechanistic perspective: pathology arising from the D620N mutation has been the most thoroughly characterized.[137] The D620N mutant of VPS35 impairs its interaction with FAM21, and thus the WASH complex, and impairs receptor trafficking, lysosomal function, and autophagosome formation.[54,95] The autophagy-lysosome axis is critical for suppressing α-synuclein aggregation.[139] The VPS35^{D620N} mutation increases α-synuclein aggregation, its toxicity, and neuronal loss.[140–142] Retromer also supports healthy neuronal function by other means such as dendritic spine maintenance, and recycling of neuromodulator and neurotransmitter receptors.[143,144] Indeed, retromer regulates the recycling of the dopamine receptor D_1 and AMPA receptor components GluR1 and -2, all of which undergo mis-trafficking upon VPS35^{D620N} expression.[143–145] Retromer is important for mitochondrial dynamics, function, and quality control. The VPS35^{D620N} mutant confers enhanced sensitivity to mitochondrial inhibitors.[146,147] Similar to VPS35 deficiency the D620N mutant promotes aberrant mitochondrial fragmentation in dopamine neurons via enhancement of MUL1-dependent ubiquitylation and turnover of MFN2.[148] A similar effect occurs via enhanced lysosomal turnover of DLP1 complexes following VPS35^{D620N} expression.[149] Through control of ATG9A trafficking, the retromer-TBC1D5 complex also regulates mitophagy.[111] Moreover, RME8 is interacts with SNX1 and FAM21 and mutation of this protein causes autosomal dominant Parkinson's disease that are phenotypically similar to VPS35 mutations.[150]

Alzheimer's disease and neurodegerative tauopathies. Alzheimer's disease is a progressive neurological disorder resulting in cognitive decline and memory loss.[151] These clinical features coincide with brain atrophy and the deposition of extraneuronal amyloid plaques and intraneuronal neurofibrillary tangles consisting of aggregated amyloid-β and tau, respectively.[152–157] VPS35 and VPS26 are reduced in the entorhinal cortex of people with Alzheimer's disease.[158–160] In addition, an L625P missense mutation in VPS35 was identified in an individual with sporadic early onset Alzheimer's disease; this mutation perturbs the VPS35-VPS29 interaction, and therefore the stability of the retromer complex.[161] Similarly, all three retromer components are depleted in the hippocampus and frontal cortex of other neurodegenerative tauopathies which lack amyloid-β pathology, including Pick's disease and progressive supranuclear palsy.[162] In tau^{P301S} transgenic mice, Vps35 depletion exacerbates cognitive and behavioral phenotypes.[162] Retromer depletion enhances pathological tau hyper-phosphorylation, a phenotype that is antagonized by Vps35 overexpression or with retromer chaperones.[162–165] In addition, retromer is critical for autophagy-dependent clearance of tau aggregates, and limits tau-induced neurotoxicity.[166–168] Indeed, retromer depletion promotes amyloid-β production and amyloid plaque deposition via mis-trafficking of the amyloid-β precursor protein APP and its processing enzymes, β- and γ-secretase.[169–172] Endosome-to-Golgi trafficking of APP is mediated by retromer indirectly via binding to the retromer cargo SORL1.[173] Interestingly, *SORL1* is also major genetic risk factor for Alzheimer's disease.[174] Pharmacological stabilization of retromer limits amyloid-β production both in vitro and in vivo.[164,175] In a small-scale genetic study, the retromer interactors *SNX3, SNX1, KIAA1033,* and *RAB7A* were shown to be genetically linked with Alzheimer's disease, however, these "hits" failed to reach genome-wide significance in larger and more robust studies.[66,176]

Amyotrophic lateral sclerosis. The gene expression of retromer components, as well as its adaptors, is reduced in the spinal cords of humans with the motor neuron disease amyotrophic lateral sclerosis.[177] These reductions in gene expression coincide with deficiency at the protein level.[177] Retromer deficiency is also observed in stem cell-derived motor neurons from amyotrophic lateral sclerosis patients with *SOD1* mutations and in transgenic $Sod1^{G93A}$ mice.[177,178] Enhancing retromer stability with the chaperone 2a improves motor neuron survival and locomotor function in $Sod1^{G93A}$ mice.[178] However, others have reported that enforcing Vps35 expression enhances paralysis in $Sod1^{G93A}$ mice, whereas depletion of Vps35 has the opposite effect.[177] Due to these conflicting findings, it remains unclear if targeting retromer will be useful in the context of amyotrophic lateral sclerosis.

Microbial infections. Several microbes have evolved ways to hijack the retromer-TBC1D5 system for their benefit. The *Legionella pneumophila* effector RidL outcompetes TBC1D5 and VARP for binding to VPS29 and inhibits retromer-dependent trafficking to promote intracellular growth and replication of the pathogen.[179–182] *L. pneumophila* may also disrupt retromer indirectly by depleting PtdIns(3)P levels.[183] Similarly, the retromer-TBC1D5 complex is exploited by human papillomaviruses, for which TBC1D5 is a host factor required for pathogen invasion.[184] The human papillomavirus L2 capsid protein binds to retromer to promote TBC1D5-dependent GTP-hydrolysis by Rab7.[184] Interestingly, constant cycling of the Rab7 nucleotide state through a "start-stop-start" mechanism ensures that retromer preferentially traffics the virus to the TGN instead of its cargoes.[184] The influenza A virus effector protein M2 abrogates the Rab7-TBC1D5 interaction by binding to the C-terminus of TBC1D5 which inhibits autophagosome-lysosome fusion and enhances virus secretion.[185] In addition, following herpes infection, the viral M45 protein induces aggregation of NFκB and RIPK1 and their turnover via autophagy in a VPS26B- and TBC1D5-dependent manner to inhibit inflammation and cell death.[186] SARS-CoV-2 is the virus that causes the respiratory disease COVID-19. Recently, a CRISPR screen identified retromer components (VPS35, VPS26A, VPS29) and SNX27, as well as the related commander/CCC complex members (COMMD2, -3 and -4), several components of the lysosomal V-type ATPase and the lysosomal protease CTSL as host factors required for SARS-CoV2

infection.[187] Binding of SARS-CoV-2 to the ACE2 receptor on the plasma membrane of host cells enables the virus to be endocytosed and delivered to the lysosome where its enzymatic breakdown enables the release of its genetic material for viral replication.[187] Interestingly, ACE2 contains a PDZ binding motif that engages with the PDZ binding domain of SNX27 which, together with retromer, recycles ACE2 bound to SARS-CoV-2 back to the plasma membrane to inhibit delivery of the virus to lysosomes and thus its replication.[188]

Other diseases. Retromer and its adaptors are linked with several other metabolic and neurodegenerative diseases. *VPS26* is a genetic risk factor for type 2 diabetes.[189] VPS35 has a potential oncogenic function in liver cancer by augmenting the phosphoinositide 3-kinase–AKT–mTORC1 pathway.[190] SNX27 is depleted in the brains of people with Down's syndrome, which is associated with Alzheimer's disease-like pathology.[191] Mutations in *KIAA0196* which encodes the WASH complex component strumpellin cause hereditary spastic paraplegia.[192] Interestingly, mutations in *KIAA0196* as well as retriever and commander/CCC complex genes *VPS35L* and *CCDC22*, respectively, cause Ritscher-Schinzel syndrome.[193,194] In addition, *RAB7A* mutations cause the axonopathy Charcot–Marie–Tooth 2B disease.[195]

CONCLUSIONS—FAMILY HISTORY AND THE NEXT GENERATION

More than 20 years after its discovery in yeast, we have now begun to understand the function of retromer at the molecular level. The mechanisms that govern its recruitment to endosomes, engagement with adaptors, and cargo selection/sorting have been characterized in much greater detail. Loss and gain of function experimental approaches have allowed us to understand the widespread consequences of retromer dysfunction which are not limited to general perturbation of the endolysosomal and autophagy systems. Indeed, retromer dysfunction recapitulates an array of pathologies relating to neurodegenerative diseases, and retromer is commonly exploited by viruses and bacteria. From a pharmacological standpoint, targeting retromer in a variety of diseases seems promising given that its dysfunction contributes to a variety of disease-related phenotypes.[196] It will be interesting to see how these evolve as potential therapeutics and whether single or combined downstream functions of retromer account for their benefits. An important aspect of retromer biology that is poorly understood is its upstream regulation. The mechanisms by which cells fine-tune retromer function to adapt to dynamic changes in nutrient availability, growth factor stimulation, and the switching of metabolic states is only beginning to be explored. To better understand the workings of retromer at the molecular level, future efforts must seek to answer such fundamental questions.

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J.M.C. conceived the review, wrote and edited the text, and generated the figures. T.J.S., D.D. and S.K. edited the manuscript and supervised the project.

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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