CHAPTER FIVE

Formation of Tubulovesicular Carriers from Endosomes and Their Fusion to the *trans*-Golgi Network

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Abstract

Endosomes undergo extensive spatiotemporal rearrangements as proteins and lipids flux through them in a series of fusion and fission events. These controlled changes enable the concentration of cargo for eventual degradation while ensuring the proper recycling of other components. A growing body of studies has now defined multiple recycling pathways from endosomes to the *trans*-Golgi network (TGN) which differ in their molecular machineries. The recycling process requires specific sets of lipids, coats, adaptors, and accessory proteins that coordinate cargo selection with membrane deformation and its association with the cytoskeleton. Specific tethering factors and SNARE (SNAP (Soluble NSF Attachment Protein) Receptor) complexes are then required for the docking and fusion with the acceptor membrane. Herein, we summarize some of the current knowledge of the machineries that govern the retrograde transport from endosomes to the TGN.

1. INTRODUCTION

Eukaryotic cells exchange material and communicate with their surrounding environment primarily through their endomembrane system. This system is composed of a diverse group of specialized membrane-enclosed compartments that are intimately related. In the secretory pathway, proteins and lipids destined for secretion or intracellular distribution are synthesized in the endoplasmic reticulum (ER) and pass through the Golgi apparatus and the *trans*-Golgi network (TGN) where they undergo additional modifications before being delivered to their final destination. This forward (anterograde) flow of material is counterbalanced by the internalization of proteins and lipids from the plasma membrane (PM) for delivery to lysosomes or recycling through retrograde transport routes. The continuous exchange of material between compartments in a directional and controlled manner regulates many cellular processes such as nutrient uptake, cell migration, cell polarity, development, signaling and immunity, to name but a few. Not surprisingly, aberrant transport between compartments contributes to many human diseases. Likewise, many pathogenic organisms, or their toxins, have evolved ways to reach their cytoplasmic targets, establish intracellular replicative niches and escape the host cell by subverting and exploiting these pathways.

Each compartment of the endomembrane system has a particular composition that is responsible for its function. Yet, the massive flow of proteins and lipids through these compartments makes them far from static. This transport is mainly driven by vesicular and tubular transport carriers (TCs)

that bud from one compartment and fuse with another, thereby delivering soluble and membrane-bound components (Bonifacino and Glick, 2004). Budding, transport, and fusion of TCs requires a complex molecular machinery including protein coats, molecular motors, tethering factors, and SNAREs (SNAP (Soluble NSF Attachment Protein) Receptor) working in strict coordination to achieve specificity and directionality. The spatiotemporal control of these events is most often orchestrated by small GTPases of the Ras superfamily (Cai et al., 2007).

2. ENDOSOME MATURATION: OVERVIEW

Endosomes are intracellular compartments where the endocytic and secretory pathways intersect. They receive cargo from the cell surface, as well as from the Golgi complex, and then reroute molecules back to the PM, to the TGN, to intraluminal vesicles (ILVs), or to lysosome-related organelles (LROs) such as melanosomes, making endosomes one of the most dynamic intracellular compartments. Because of the constant exchange of materials, endosomes constitute a rather heterogeneous population that is roughly divided into early, late, and recycling endosomes according to their protein and lipid composition, morphology, and function. Early endosomes (EEs) are the first endocytic compartments that collect cargo from the cell surface. Many internalized molecules are either transported back to the PM from recycling endosomes (REs) through fast Rab4-dependent or slow Rab11-dependent pathways, or retained in late endosomes (LEs) for their delivery to lysosomes (Spang, 2009; Ullrich et al., 1996; van der Sluijs et al., 1992). During the transition from EE to LE, there is a continuous interplay of fusion and budding events that is accompanied by a progressive compositional reorganization involving numerous cytosolic proteins that transiently associate with the limiting membrane (Figure 1).

A hallmark of endosome maturation is the replacement of Rab5 with Rab7 (Rink et al., 2005). Rab GTPases function as molecular switches cycling between an inactive GDP-bound state with predominantly cytosolic distribution and an active GTP-bound state that is associated with specific membranes. This feature makes Rab GTPases important determinants of organelle identity. Their GTPase cycle is regulated by guanine nucleotide exchange factors (GEFs) that activate Rabs by promoting GDP-to-GTP exchange, and GTPase-activating proteins (GAPs) that deactivate Rabs by promoting GTP hydrolysis. The GTP-bound Rabs exhibit structural

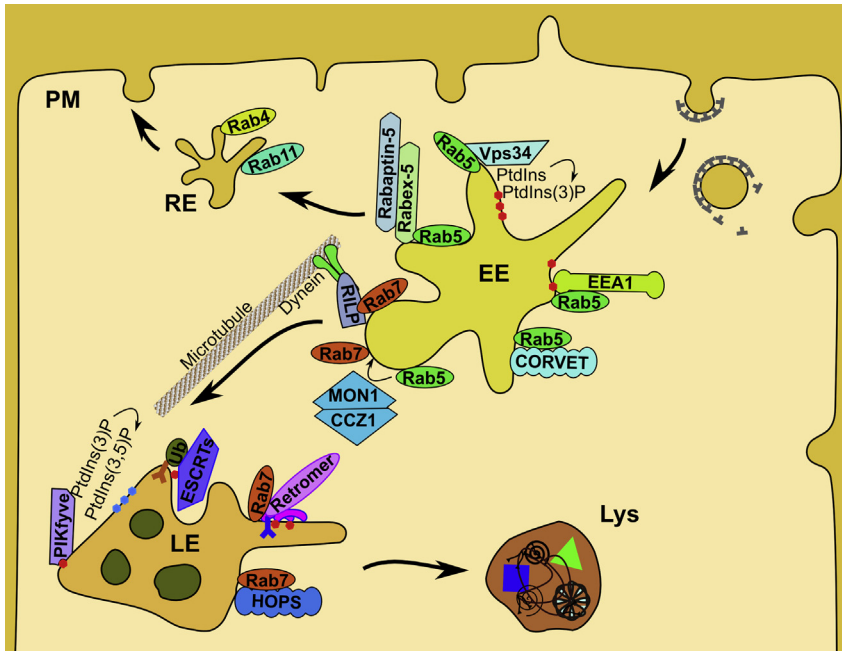

Figure 1 Schematic representation of the principal components during endosomal maturation. PM, plasma membrane; RE, recycling endosome; EE, early endosome; LE, late endosome; Lys, lysosome.

differences from the GDP-bound forms in two flexible regions known as switch I and switch II. In particular, the switch II region becomes more tightly packed upon GTP binding through extra contacts established by the γ-phosphate of the nucleotide. These conformational differences in the switches create distinct recognition surfaces that enhance the recruitment of downstream effectors (Barr and Lambright, 2010; Eathiraj et al., 2005).

Many proteins that show GEF activity for Rab5 share a conserved vacuolar protein sorting 9 (Vps9) domain that is required for binding and nucleotide exchange (Carney et al., 2006). Rabex-5 is a Vps9 domain-containing protein with GEF activity for Rab5 and Rab21 (Delprato and Lambright, 2007; Delprato et al., 2004; Horiuchi et al., 1997) that can be recruited to EEs by interaction with ubiquitinated transmembrane cargo (Mattera and Bonifacino, 2008). Rabex-5 enhances Rab5 activation through interaction with Rabaptin-5, which in turn is a Rab5 effector (Horiuchi et al., 1997). This positive feedback loop promotes further Rab5 binding and contributes to the recruitment of other Rab5 effectors including p150, which directly binds to Vps34, a class III phosphatidylinositol-3 kinase that produces

PtdIns(3)P (Christoforidis et al., 1999; Huotari and Helenius, 2011). Phosphatidylinositols can be reversibly phosphorylated at different positions of their D-*myo*-inositol head group to generate seven different possible compounds with unique subcellular distributions. PtdIns(3)P is predominantly found on the cytosolic leaflet of early endosomal membranes where it serves as a platform for the recruitment of additional effectors through specific binding domains. These include the FYVE (Fab1/YOTB/Vac1/EEA1) domain (Misra and Hurley, 1999; Stenmark et al., 1996) and the phox-homology (PX) domain (Hiroaki et al., 2001; Ponting, 1996). It is well established that PtdIns(3)P, together with Rab5, regulates homotypic fusion of EEs. For this, the EEA1 protein establishes a dual interaction with PtdIns(3)P through an FYVE domain and with Rab5 to act as a tethering factor (Dumas et al., 2001; Mills et al., 1998). Rab5 also recruits the Class C core vacuole/endosome tethering (CORVET) complex to the membrane of EEs (Balderhaar et al., 2013). The yeast CORVET complex consists of four conserved core subunits (Vps11, Vps16, Vps18, and Vps33) and two additional subunits (Vps3 and Vps8) that directly interact with activated Rab5/Vps21 (Balderhaar et al., 2013; Peplowska et al., 2007).

The homotypic fusion and protein sorting (HOPS) complex shares the same four core subunits with the CORVET complex, but has Vps39 and Vps41 as effectors for Rab7/Ypt7 (Price et al., 2000). Vps39 and Vps41 locate on opposing sides of the HOPS complex (Brocker et al., 2012), which is consistent with its role in regulating tethering and fusion of LEs with the lysosome/vacuole. Rab7 is a key player in endolysosomal maturation and rerouting cargos away from degradation. The SAND1/Mon1-Ccz1 complex blocks the positive feedback loop between Rab5 and its GEF Rabex-5 and then promotes the recruitment of Rab7 to the membrane (Kinchen and Ravichandran, 2010; Poteryaev et al., 2010). The concentration of PtdIns(3)P is also important for the recruitment of SAND/Mon1 to EEs so that it can bind to Rab5 (Poteryaev et al., 2010). Two GEFs for Rab7/Ypt7 have been proposed in this process; the first one is the Vps39 subunit of the HOPS tethering complex (Rink et al., 2005) which binds to Mon1 in vitro (Nordmann et al., 2010) but does not have GEF activity in mammalian cells (Peralta et al., 2010), and the second is the Mon1-Ccz1 complex itself whose GEF activity in vitro is greatly enhanced when Ypt7 is placed on membranes (Cabrera et al., 2014). Active Rab7 then continues recruiting its own effectors, like Rab-interacting lysosomal protein (RILP), which interacts with the dynein–dynactin motor complex to move LEs along microtubules toward the perinuclear region of the cell (Jordens et al., 2001), the

retromer complex that retrieves receptors and other cargoes from lysosomal degradation (Arighi et al., 2004; Seaman, 2004) and the HOPS tethering complex that participates in lysosomal fusion events (Balderhaar and Ungermann, 2013; Solinger and Spang, 2013). Parallel to the Rab5/Rab7 exchange is the conversion from PtdIns(3)P to PtdIns(3,5)P2. The lipid kinases Fab1 in yeast and PIKfyve in mammals, bind to PtdIns(3)P through their FYVE-domains and catalyze its conversion to PtdIns(3,5)P2 (Gary et al., 1998; McCartney et al., 2014; Zolov et al., 2012). Optimal activity of these kinases requires the formation of a complex with other regulatory proteins including Vac14 and Fig4/Sac3 (Botelho et al., 2008; Duex et al., 2006). Paradoxically, Fig4 can also convert PtdIns(3,5)P2 to PtdIns(3)P (Gary et al., 2002). The production of PtdIns(3,5)P2 by Fab1/PIKfyve causes a concomitant depletion of PtdIns(3)P, which in turn promotes the release of its binding effectors and the recruitment of different ones for PtdIns(3,5)P2.

Another event connected to endosomal maturation is the formation of ILVs. In this process, ubiquitinated transmembrane cargo is sorted into ILVs with the help of the ESCRT (endosomal sorting complex required for transport) complexes 0, I, II, and III (Babst et al., 2002a,b; Hurley and Emr, 2006; Katzmann et al., 2001). The Hrs and STAM proteins conform the ESCRT-0 complex in metazoans. Hrs binds to PtdIns(3)P on EEs (Raiborg et al., 2001b) and, together with STAM, interacts with clathrin and ubiquitinated cargo for its clustering into membrane microdomains (Mizuno et al., 2003; Raiborg et al., 2001a, 2002, 2006). Following ESCRT-0 assembly, the ubiquitinated cargo is further concentrated through ESCRT-I and ESCRT-II into membrane invaginations (Babst et al., 2002b; Bilodeau et al., 2003). Then, ESCRT-III mediates the abscission of the inward bud to complete ILV biogenesis (Wollert et al., 2009). Finally, the AAA ATPase VPS4 releases all the ESCRT complexes back into the cytosol (Babst et al., 1998; Lata et al., 2008). During the transition from EEs to LEs, the lumen of these organelles not only is filled with ILVs but also becomes increasingly acidic. This acidification is primarily determined by the activity of the vacuolar ATPase (V-ATPase), a large multisubunit complex that pumps protons from the cytosol to the lumen. This proton transport generates a voltage difference across the membrane that is dissipated through the transport of chloride ions by the ClC-7 Cl^-/H^+ antiporter (Ishida et al., 2013). The luminal pH of EEs decreases from ~6.2 to less than 5.0 in LEs/lysosomes, promoting a number of biological events such as the dissociation of ligand—receptor complexes, activation of lysosomal enzymes and receptor sorting (Mindell, 2012). Eventually, fully matured LEs fuse with

lysosomes and the digested products are reused by the cell or secreted to the extracellular milieu. Endolysosomal hydrolyses together with lysosomal membrane proteins are then loaded into tubulovesicles that bud off and acidify, thus becoming available to fuse with additional LEs in a cyclic process known as lysosome reformation (Bright et al., 1997).

3. COAT COMPLEXES IN ENDOSOMAL SORTING

The fate of transmembrane cargo delivered to endosomes by endocytosis or biosynthetic trafficking is determined by either the ESCRT pathway for its sorting into ILVs and subsequent degradation in lysosomes, or by recycling pathways that retrieve material for its reuse. The first crucial step during the recycling process is the recruitment of cargo into a TC. To ensure correct cargo packaging, the nascent TC is coated with unique protein complexes and regulatory factors that recognize signals in the cytosolic domains of the transmembrane proteins. The sorting process at endosomes can be carried out by different protein complexes such as clathrin and its adaptors, the sorting nexins (SNXs), and the retromer complex (Figure 2).

3.1 Adaptor Protein Complexes

The heterotetrameric adaptor protein (AP) complexes are components of protein coats that mediate cargo selection and vesicle formation at various stages of the endomembrane system. While the clathrin-associated AP-2 complex mediates rapid internalization from the PM, other APs mediate sorting events at different endosomal compartments or the TGN. AP-1 also functions in association with clathrin to mediate TGN-to-EE as well as EE-to-TGN transport. AP-3 has been shown to exist as part of clathrin and non-clathrin coats that participate in the biogenesis of lysosomes and LROs (Dell'Angelica, 2009). Finally, AP-4 and AP-5 are components of non-clathrin coats associated with the TGN and LEs, respectively (Dell'Angelica et al., 1999; Hirst et al., 1999, 2011).

All AP complexes consist of two ear domains connected to a core through long unstructured hinge segments, except for AP-5, which lacks the hinge segments. While the hinge and ear domains recruit scaffolding and accessory proteins, the core domains interact with the cytosolic tails of cargo and mediate the recruitment to membranes by binding to specific Arf GTPases and/or phosphoinositides (Park and Guo, 2014). AP complexes confer specificity on membrane trafficking through recognition of

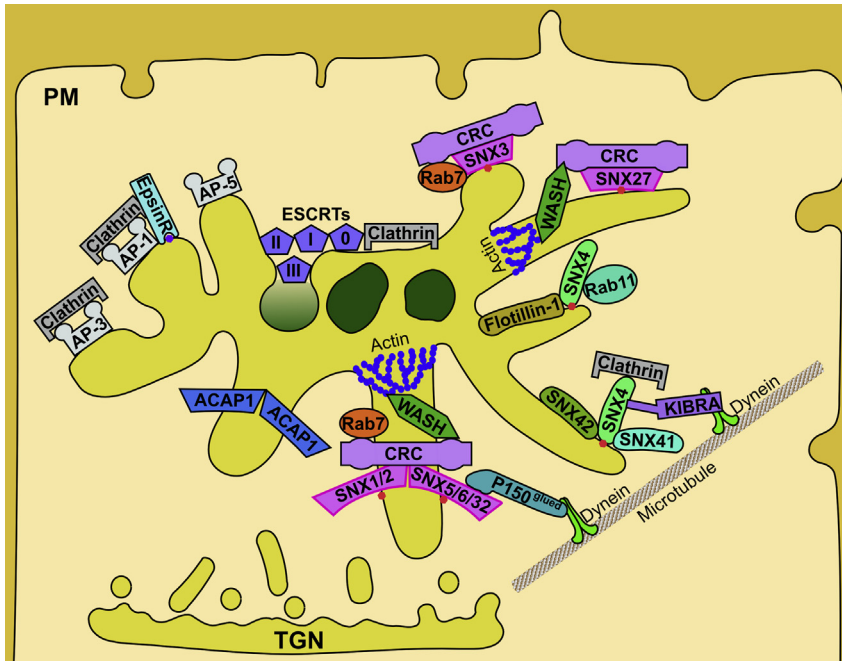

Figure 2 Overview of the major protein complexes required for selective cargo sorting at endosomes. PM, plasma membrane; TGN, *trans*-Golgi Network.

sorting signals of transmembrane cargo. The best-characterized sorting signals are tyrosine-based YxxØ and dileucine-based [D/E]xxxL[L/I] motifs, where Ø is a bulky hydrophobic amino acid and x is any amino acid. X-ray crystallographic analyses have revealed that these two signals bind to different sites on the AP core domain and that a conformational change that exposes both binding sites is required for their simultaneous recognition (Jackson et al., 2010; Kelly et al., 2008). In addition to these well-known sorting motifs there are also noncanonical signals that can be recognized by AP complexes. For example, the basolateral sorting signal GDNS is different from the endocytic signal YTRF (a YxxØ motif) of the transferrin receptor (TfR) (Odorizzi and Trowbridge, 1997). Similarly, the low-density lipoprotein receptor contains a noncanonical bipartite basolateral signal that is different from the endocytic signal FDNVPY which is a ([Y/F]xNPx[Y/F]) motif (Guo et al., 2013; Matter et al., 1992). The repertoire of signals recognized by AP complexes can be expanded through the use of alternative subunit isoforms (Guo et al., 2013; Mattera et al., 2011). Thus, the combinatorial assembly of different subunit isoforms

through specific gene expression can produce multiple AP heterotetramers, each of them with the potential to perform unique functions (Bonifacino, 2014; Mattera et al., 2011).

Epsin proteins also function as adaptors providing a platform for recruitment of clathrin coat components. While the three canonical epsins 1, 2, 3, can interact with AP-2, clathrin, ubiquitin, and PtdIns(4,5)P2, and are involved in clathrin-mediated endocytosis (Sen et al., 2012), a fourth non-canonical epsin, epsinR, can interact with AP-1, clathrin, PtdIns(4)P but not with ubiquitinated proteins (Mills et al., 2003; Saint-Pol et al., 2004). EpsinR distribution overlaps with that of AP-1 at the TGN and endosomes, yet its localization does not depend on AP-1 expression (Hirst et al., 2003). Instead, Epsin recruitment appears to depend on the presence of PtdIns(4)P (Mills et al., 2003; Wang et al., 2003), which might be derived from the activity of the oculocerebrorenal syndrome of Lowe protein 1 (OCRL1) (Lowe, 2005), an inositol polyphosphate 5-phosphatase. Whereas disruption of epsinR inhibits the retrograde trafficking of the model cargoes CI-MPR and Shiga toxin B-subunit (STxB) to the TGN, AP-1 is not required for retrograde transport of STxB despite its colocalization on EE/RE (Mallard et al., 1998; Saint-Pol et al., 2004). This is in contrast to the functional interaction between AP-1 and epsinR in budding of vesicles carrying mannose 6-phosphate receptors (MPRs) and acid hydrolase precursors from the TGN (Mills et al., 2003). One explanation for this variation in function might be the existence of distinct AP-1 isoforms with distinct properties or tissue-specific expression. In this regard, while an AP-1 variant containing a μ1A subunit isoform is expressed ubiquitously, an AP-1 variant containing another subunit isoform, μ1B, is preferentially expressed in polarized epithelial cells (Folsch et al., 1999; Gan et al., 2002; Ohno et al., 1999) thus providing for isoform-specific functions. Given the variety of accessory proteins reported to function with AP-1 and clathrin, it is tempting to consider a regulated transport achieved by modulation of coat components. The detailed interplay between AP-1, clathrin, and accessory proteins, however, remains largely unknown.

3.2 Sorting Nexins SNX4–SNX41–SNX42

SNXs constitute a diverse family of proteins that possess a PX domain for binding to phosphoinositides, in most cases PtdIns(3)P, and thus are predominantly found in the endosomal system. Numerous SNX proteins contain additional domains flanking the PX module that contribute to other

functions including membrane remodeling, cargo selection, signaling, or scaffolding.

In yeast, retrieval of the v-SNARE Snc1 from EEs to the TGN is dependent on SNX4, SNX41, and SNX42 (Hettema et al., 2003). In contrast, the SNARE Pep12, which is retrieved from LEs to the TGN, depends on Grd19p/SNX3 (Hettema et al., 2003). SNX4 can bind either SNX41 or SNX42 and is associated with tubular structures on RE that are independent of other SNX proteins (Hettema et al., 2003). SNX4 has been reported to interact with other proteins implicated in the formation of membrane microdomains such as flotillins and clathrin. Flotillins are considered lipid raft proteins for their propensity to coassemble into discrete microdomains in the PM, thus defining a specific type of endocytic pathway (Glebov et al., 2006). Flotillins can translocate from the PM to endosomes from which they are recycled back to the PM. SNX4 binds to Flotilin-1 and Rab11 in tubulovesicular RE, and mediates sorting and recycling of TfR and E-cadherin (Solis et al., 2013). Also, the transport of the plant toxin ricin from endosomes to the Golgi is significantly reduced upon SNX4 or flotillin knockdown (Pust et al., 2010; Skanland et al., 2007) suggesting a role in retrograde traffic. Interestingly, SNX4 through its binding to KIBRA associates with the minus end-directed microtubule motor dynein and is required for the long-range transport of TfR from the peripheral EE to the juxtanuclear recycling compartment (Traer et al., 2007). The PX domain of SNX4 can bind to clathrin through an inverted clathrin box sequence (Skanland et al., 2009). The association of SNX4 with clathrin and dynein can be inhibited by wortmannin, a PI3-kinase inhibitor, thus indicating that the interaction occurs when SNX4 is associated with PtdIns(3)P on the membrane (Skanland et al., 2009). It has been proposed that flotillins at the PM could function as platforms that concentrate cargo, which is then handed over to clathrin-coated pits for subsequent endocytosis (Otto and Nichols, 2011). It is unclear whether SNX4—SNX41—SNX42 is part of a coat. It will be important to dissect how SNX4 interacts with flotillins and clathrin in the regulation of these novel and intriguing cargo sorting events within endosomes.

3.3 Arf-GAP with Coiled-Coil, ANK Repeat, and PH Domain-Containing Protein 1

Another putative adaptor reported to be part of a clathrin complex on endosomes is ACAP1 (Arf-GAP with coiled-coil, ANK repeat, and PH domain-containing protein 1). ACAP1 is a GAP for Arf6 that promotes recycling of

the glucose transporter Glut4 and the adhesion molecule integrin β1 (Bai et al., 2012; Li et al., 2007). When overexpressed in cells, ACAP1 is found on the surface of tubular carriers emanating from RE (Li et al., 2007). Similar to the SNX-BARs, ACAP proteins contain a BAR (Bin/amphiphysin/Rvs) domain and a pleckstrin homology (PH) domain for binding to phosphoinositides. Remarkably, the BAR domain in ACAP1 cannot bind or bend membranes by itself. Instead, it functions as a multimerization module that allows membrane deformation through the neighboring PH domain (Pang et al., 2014). Membrane curvature is induced by a positively charged patch on the PH domain that promotes membrane binding and a flexible hydrophobic loop that inserts into the membrane to promote its bending. Moreover, the ACAP1 dimer lines up on the membrane asymmetrically using only one of its PH domains to contact the phospholipids, while the other PH domain establishes lateral contacts along the tubule (Pang et al., 2014). The tandem arrangement of BAR and PH domains is not unique to ACAP proteins, thus the mechanism described for membrane tubulation by ACAP1 may be relevant for other related PX domains such as the SNX-BAR proteins.

3.4 Retromer

3.4.1 Retromer composition

In addition to SNX4−SNX41−SNX42, other SNXs have been implicated in retrograde transport as part of the retromer complex. Retromer was first described in yeast as a heteropentameric complex required for retrieval of the sorting receptor Vps10 (vacuolar protein sorting 10) from endosomes to the TGN. Vps10 and its functional equivalent MPRs in mammals are type-I integral membrane proteins that deliver newly synthesized hydrolase precursors from the TGN to endosomes. Then, upon luminal acidification, the hydrolase precursors are released and the receptors are recycled back to the TGN to mediate additional rounds of sorting. The initial characterization of yeast retromer showed functional division into two subcomplexes: a heterodimer of the SNX proteins Vps5 and Vps17, and a heterotrimer of Vps26-Vps29-Vps35 (Horazdovsky et al., 1997; Seaman et al., 1998). The Vps5-Vps17 subcomplex contains, in addition to the PX domain, a membrane-curvature-sensing BAR domain whose intrinsic self-assembly activity appears to contribute to membrane tubulation (Carlton et al., 2004; van Weering et al., 2012).

On the other hand, the Vps26-Vps29-Vps35 subcomplex lacks any membrane-binding activity and requires the interaction with the SNX

dimer and Rab7/Ypt7 for recruitment to the membrane (Haft et al., 2000; Liu et al., 2012; Rojas et al., 2008; Seaman et al., 1998). The interaction of Vps35 with the cytosolic tail of Vps10 and A-ALP cargo proteins led to the hypothesis that it is involved in cargo selection (Nothwehr et al., 1999, 2000); thus, the Vps26-Vps29-Vps35 trimer is frequently referred to as the cargo-recognition (or selective) complex (CRC). In this sense, retromer combines cargo-recognition properties and membrane association and deformation capabilities in two subcomplexes. Retromer is well conserved from yeast to mammals. In vertebrates, gene duplications have produced two orthologs for Vps26 (represented by Vps26A and Vps26B) (Haft et al., 2000), another two for Vps5 (represented by SNX1 and SNX2) and various Vps17 homologs represented by SNX5, SNX6, and possibly SNX32 (Cullen and Korswagen, 2012; Griffin et al., 2005). The yeast Vps5, Vps17, and their mammalian orthologs belong to the SNX-BAR protein subfamily as they contain C-terminal BAR domains (Carlton et al., 2004; Habermann, 2004; van Weering et al., 2010). The intrinsic self-assembly activity of the BAR domains is crucial for membrane remodeling. The dimerization propensity is thought to sense and induce positive curvature on the membrane through electrostatic interactions between the positively charged concave surface of the two BAR domains and the negatively charged phospholipids (Peter et al., 2004). In addition, all SNX-BAR proteins contain an amphipathic helix, equivalent to the one observed within the N-BAR family, that following a similar mechanism could be inserted into the cytosolic membrane leaflet, favoring the formation of positive curvature (Bhatia et al., 2009; Pylypenko et al., 2007; van Weering and Cullen, 2014; van Weering et al., 2012). The yeast Vps5-Vps17 SNX-BAR heterodimer is also conserved in mammals as one Vps5 ortholog dimerizes with one Vps17 homolog (Koumandou et al., 2011; Wassmer et al., 2007). Interestingly, a recent analysis of homo- and hetero-oligomerization of the human SNX-BAR protein family using a cell-free protein coexpression coupled to a fluorescence proximity assay showed that while several SNX-BAR proteins are able to form homodimers, the retromer-associated SNX1, SNX2, and SNX5 require heteromeric interactions for dimerization (Sierecki et al., 2014). Notably, the formation of heterodimers in the SNX-BAR-retromer complex parallels the capacity of remodeling liposomes into tubules in vitro (van Weering et al., 2012).

Using yeast two-hybrid screens and immunoprecipitation experiments, various studies have mapped the binding sites of the yeast Vps5 and its mammalian ortholog SNX1 for the CRC to their amino (N)-terminal

domains whereas Vps17 seems not to interact directly with the CRC (Rojas et al., 2007; Seaman and Williams, 2002). Here, it is important to consider that, although some SNX-BAR proteins have a propensity to participate in promiscuous interactions that could indicate nonspecific binding, the recent pairwise map of retromer-interacting SNX-BAR proteins with other members of the SNX-BAR family (Sierecki et al., 2014) hints at the possibility that the number of SNX-BAR combinations potentially associated with retromer could be significantly larger than initially anticipated. This possibility merits further exploration to understand the complexity of the mammalian retromer.

Recent data indicate that the CRC can interact with SNX proteins other than SNX-BAR members, specifically, the multidomain SNX27 (which lacks the BAR module for inducing/sensing membrane curvature) (Gallon et al., 2014) and SNX3 (consisting solely of a PX domain) (Harterink et al., 2011; Zhang et al., 2011). There is limited overlap between cargo recycled by the SNX-BAR-CRC, SNX3-CRC, and SNX27-CRC, suggesting that these complexes function independently (Burd and Cullen, 2014; Cullen and Korswagen, 2012). Indeed, the SNX27-CRC mediates the recycling of cargo proteins from EEs to the PM rather than the TGN (Steinberg et al., 2013; Temkin et al., 2011). Despite the phylogenetic conservation of retromer subunits, the exact composition of SNXs and the nature of their interactions with the CRC remain not well established as compared to the more straightforward yeast model. The association of the CRC with SNX components in mammals is much more transient that in yeast (Rojas et al., 2007; Swarbrick et al., 2011), possibly to facilitate the integration and coordination of a more intricate recycling network. Taking into account the numerous SNXs associated with the CRC and the precedents set by other coats, it has been hypothesized the existence of multiple retromer complexes. These might be formed by the CRC as a central core and distinct adaptors, such as SNXs, to allow the recycling of specific cargo through different trafficking pathways (Cullen and Korswagen, 2012).

Retromer and clathrin are key players in retrograde trafficking; however, their precise relationship still remains unclear. The interaction and colocalization of clathrin with retromer components is controversial. While retromer components such as VPS35, SNX1, SNX2, SNX5, and SNX6 have been identified within isolated clathrin-coated vesicles (Borner et al., 2006) and ultrastructural analysis indicates a partial colocalization between Vps26 and clathrin on EE/RE (Popoff et al., 2007), a recent report by McGough and Cullen failed to observe a significant colocalization between

the SNX-BAR-CRC and clathrin on the same endosomes (McGough and Cullen, 2013). Similarly, the identification of an inverted clathrin-binding box within the PX domains of SNX1, SNX2, and SNX3 that directly associates with clathrin (Skanland et al., 2009) has been challenged by McGough and Cullen who failed to observe such interactions (McGough and Cullen, 2013). Nonetheless, depletion of VPS26 or clathrin results in an almost complete block of STxB and MPRs retrograde trafficking (Popoff et al., 2007), suggesting that they may act in tandem, as opposed to separate, retrograde pathways. In this regard, it has been observed that the retromer subunit SNX1 interacts with RME-8, a DNA-J domain-containing protein localized to endosomes that recruits the clathrin chaperone Hsc70 and stimulates its ATPase activity to promote clathrin disassembly (Chang et al., 2004; Shi et al., 2009). This suggests that retromer may regulate endosomal clathrin dynamics. Remarkably, retromer also interacts with the clathrin scaffolding protein Hrs through the Vps35 and SNX1 components (Chin et al., 2001; Popoff et al., 2009). Hrs has been implicated in clustering ubiquitinated cargo into flat clathrin microdomains on the endosome membrane prior to its sorting (Raiborg et al., 2002, 2001a). Thus, the opposing activities of RME-8 and Hrs on clathrin accumulation might articulate downstream antagonistic processes driven by retromer and the ESCRT machinery for cargo recycling or degradation.

3.4.2 Structure and cargo recognition

Over the past few years, several X-ray structural analyses of single subunits and binary assemblies of retromer core components have provided important insights into their functional architecture and structural relationships with other trafficking proteins. The crystal structure of Vps29 shows that this subunit has a metallophosphoesterase fold (Collins et al., 2005; Hierro et al., 2007; Wang et al., 2005). Despite this similarity and the initial exciting idea that retromer might regulate retrograde trafficking by controlling cargo dephosphorylation (Damen et al., 2006), recent biochemical evidence suggests that Vps29 serves as a scaffold for the assembly of additional subunits rather than as an active phosphatase (Collins et al., 2005; Hierro et al., 2007; Swarbrick et al., 2011). Indeed, the crystal structure of the C-terminal half of Vps35 in complex with Vps29 shows an α-helical solenoid structure that masks the catalytic metal binding site (Hierro et al., 2007). Opposite to the binding face for Vps35 there is an exposed hydrophobic patch on Vps29 that can interact with TBC1D5, a potential Rab7 GAP (Harbour et al., 2010; Hesketh et al., 2014; Seaman et al., 2009), and with VARP, a

Rab32/38 effector that binds to VAMP7 and participates in the delivery of GLUT1 to the cell surface (Hesketh et al., 2014). Thus, the scaffolding function of Vps29 appears to engage the CRC with additional regulatory factors. The remaining N-terminal half of Vps35 is predicted to continue as an α-helical solenoid, so that the entire Vps35 structure is expected to form an elongated structure with some degree of flexibility around the midsection (Hierro et al., 2007). Such an α-solenoid arrangement is reminiscent of that found in components of the AP complexes, clathrin, COPI, and COPII coats involved in trafficking. Indeed, this α-solenoid architecture is likely derived from an early membrane-curving module known as the "protocoatomer" (Devos et al., 2004; Field et al., 2011). While the C-terminal part of Vps35 binds to Vps29, the first 150 residues harbor a binding site for Vps26 (Hierro et al., 2007). Although no structure exists for the Vps35-Vps26 subcomplex, mutational analyses in yeast have identified the ^{97}PRLYL^{101} sequence within the N-terminal region of Vps35 as being required for interaction with Vps26 (Gokool et al., 2007a; Restrepo et al., 2007; Zhao et al., 2007). The structure of both human Vps26 orthologs revealed a bilobed structure formed by two β-sandwich subdomains linked by a polar core with strong similarity to arrestins, a protein family with a general scaffolding role in trafficking of membrane proteins (Aubry and Klein, 2013; Collins et al., 2008; Shi et al., 2006). Arrestins are well known for binding to phosphorylated GPCRs, phosphoinositides, clathrin and its AP-2 adaptor during endocytosis. However, despite the overall structural similarity with arrestins, Vps26 lacks key functional surface residues present in the arrestin family, interacts with different ligands and participates in distinct trafficking pathways (Kang et al., 2014). Thus, the significance of the arrestin fold in Vps26 and its mechanistically relevance within retromer remain to be determined. Interestingly, a recent crystallographic analysis has solved the structure of Vps26A bound to the amino-terminal PSD95, Dlg1, zo-1 (PDZ) domain of SNX27. The interaction is mediated by the insertion of an exposed β-hairpin loop of the PDZ domain into a conserved pocket between the two lobes of the arrestin fold of Vps26A (Gallon et al., 2014). The PDZ domain of SNX27 interacts with cargo proteins containing a class I PDZ-binding motif ([S/T]-x-Ø) (Joubert et al., 2004; Lauffer et al., 2010; Lunn et al., 2007), which in turn shows a positive cooperative effect when the PDZ domain is bound to the retromer subunit VPS26A (Gallon et al., 2014). SNX27 contains an additional C-terminal 4.1/ezrin/radixin/moesin (FERM)-like domain that binds to (NPxY) motifs of transmembrane proteins (Ghai et al., 2013). Thus, SNX27 might bind concomitantly to PtdIns(3)P at

the endosomal membrane through the PX domain, and interact with both PDZ-ligands and NPxY sorting motifs while associated with the retromer subunit VPS26 for recycling cargo to the PM. Indeed, a recent global proteomics analysis has identified more than 150 transmembrane proteins that require the CRC for their retrieval to the cell surface and nearly half of them rely on SNX27 for such recycling pathway (Steinberg et al., 2013). For some cargoes, the recycling pathway could be direct to the cell surface but for others it might involve an intermediate passage through the TGN. The ability of retromer to recruit cargoes relies on its association with the cytosolic tails of different transmembrane receptors; however, the absence of strong binding motifs and the implication of distinct retromer subunits in cargo recognition make the mechanism to discriminate cargo selection something of a Cryptex puzzle. In addition to the PDZ ligand and NPxY sorting motifs recognized by SNX27, many other retromer cargoes are recognized through hydrophobic tripeptide motifs that have been long presumed to interact directly with Vps35 (Seaman, 2007, 2012). For example, the ^{42}WLM^{44} sequence of the CI-MPR, the ^{9}FLV^{11} sequence of sortilin (a mammalian Vps10 homolog), and the ^{555}YLL^{557} sequence of the divalent metal transporter 1 isoform II (DMT1-II) interact with Vps35 for their retrograde transport to the TGN (Seaman, 2007; Tabuchi et al., 2010). Interestingly, Vps26 can also bind directly to short hydrophobic sequences, as is the case for the ^{12}FANSHY^{17} motif in the cytoplasmic tail of the SorL1/SorLA receptor (Fjorback et al., 2012), which not surprisingly is similar to the ^{1456}FYVFSN^{1461} motif present in the yeast Vps10 receptor and is required for retrograde transport (Cereghino et al., 1995). For some cargoes, effective recruitment may not be restricted to a single binding motif within the cytosolic tail; indeed, Vps10 and CI-MPR present additional sequences that contribute to the binding with Vps35 (Arighi et al., 2004; Nothwehr et al., 2000) and could involve subtle fine-tuning regulation.

3.4.3 Functional diversity

In recent years, a burst of studies has identified numerous retromer-dependent cargos. These new data have significantly enlarged the number of physiological roles of retromer. For example, retromer complexes are involved in plant development through the secretion of the phytohormone auxin by PIN-FORMED (PIN) transporters (Jaillais et al., 2007) as well as sorting of soluble proteins to the plant vacuole via an interaction with vacuolar sorting receptors (Oliviusson et al., 2006), the establishment of developmental morphogen gradients in metazoans through trafficking of the Wnt receptor

Wntless (Harterink et al., 2011; Zhang et al., 2011), intracellular iron uptake through interaction with the TfR (Chen et al., 2013), and the divalent metal transporter DMT1 (Tabuchi et al., 2010) during the transferrin cycle. Additional processes are the establishment of cell polarity through trafficking of Crumbs (Pocha et al., 2011; Zhou et al., 2011), maintenance of tissue homeostasis associated with basolateral PM location of the transforming growth factor beta (TGF-β) receptor (Yin et al., 2013), transcytosis of the polymeric immunoglobulin receptor (Verges et al., 2004), apoptotic cell clearance through sorting of the phagocytic receptor CED-1 (Chen et al., 2010) and recycling of the β2-adrenergic receptor, and the glucose transporter GLUT1 to the PM (Choy et al., 2014; Steinberg et al., 2013; Temkin et al., 2011).

Recently, it has been found that retromer also mediates the rapid local delivery of postsynaptic receptors from endosomes to the shaft domain of neuronal dendrites (Choy et al., 2014). Retromer malfunction has been linked to the pathogenesis of neurodegenerative disorders such as Alzheimer's disease (Carlo et al., 2013; Fjorback et al., 2012; Nielsen et al., 2007; Willnow et al., 2011), because of its role in localization and processing of the amyloid precursor protein (APP) via interaction with sortilin and SorL1/SorLA, and late-onset Parkinson's disease caused by a point mutation (D620N) within the Vps35 subunit (Vilarino-Guell et al., 2011; Zimprich et al., 2011).

Retromer function is also hijacked by numerous pathogens to facilitate host invasion, establish intracellular replicative niches and promote survival. So far, numerous pieces of evidence indicate that retromer contributes to papillomavirus entry (Lipovsky et al., 2013), HIV-1 assembly (Groppelli et al., 2014), and induced T cell immortalization by herpesvirus saimiri (Kingston et al., 2011). Similarly, bacterial pathogens including *Coxiella burnetii*, *Legionella pneumophila*, and *Salmonella enterica* alter retromer function to facilitate intracellular survival and growth (Bujny et al., 2008; Finsel et al., 2013; McDonough et al., 2013).

3.4.4 Coupling budding and scission to cytoskeleton

It is well established that actin filaments, microtubules, and their associated motors assist in membrane deformation during TC formation (Anitei and Hoflack, 2012). The Arp2/3 complex, through its intrinsic F-actin polymerization activity, generates branched actin networks that are thought to push on the membrane and provide part of the force to create a tubular neck on the nascent TCs (Anitei and Hoflack, 2012; Pollard, 2007). Arp2/3 activity is

regulated by nucleation-promoting factors (NPFs) that localize to defined membrane microdomains. The WASH (WASP and SCAR homolog) complex is the major Arp2/3 NPF at endosomes (Derivery et al., 2009; Gomez and Billadeau, 2009), and retromer contributes to its membrane recruitment (Gomez and Billadeau, 2009; Harbour et al., 2010, 2012). Not surprisingly, WASH is required for the retrieval of CI-MPR from endosomes to the TGN (Gomez and Billadeau, 2009) and for the recycling of TfR and GLUT1 from endosomes to the PM (Derivery et al., 2009; Piotrowski et al., 2013), supporting the functional cooperation between WASH and retromer in both trafficking pathways. The WASH complex comprises five proteins: FAM21, WASH1, SWIP, strumpellin, and CCDC53, and the association with the CRC is through direct binding of FAM21 to Vps35. FAM21 is central to WASH function. While the N-terminal part of FAM21 associates with SWIP and WASH1 and provides stability to the complex, a large unstructured tail of the remaining sequence (~1100 residues) binds to Vps35 via multiple (~20) Leu—Phe (LF) motifs (Harbour et al., 2012; Jia et al., 2012, 2010). Although FAM21 interacts directly with Vps35, it has been observed in vivo that this interaction depends on the presence of Vps29 (Helfer et al., 2013), which might be required to strengthen its scaffolding function. In addition, the FAM21 tail interacts with the CapZ alpha/beta heterodimer, a capping protein that is presumed to block actin filament elongation and promote additional branching (Derivery et al., 2009; Hernandez-Valladares et al., 2010). The regulation of the capping activity by FAM21, however, remains poorly understood (Edwards et al., 2014).

During clathrin-mediated endocytosis, it has been proposed that actin polymerization may promote constriction and fission of the tubular neck to separate the vesicle from the PM (Collins et al., 2011). In fact, it has been described a positive feedback loop between actin and dynamin during the constriction of the neck (Taylor et al., 2012). Not surprisingly, dynamin also interacts with WASH; however, this interaction is not regulated by the activity of dynamin, indicating a role downstream of WASH (Derivery et al., 2009). It is worth noting that several SNX proteins possess a dynamin-binding SH3 (Src Homology 3) domain that might promote the recruitment of dynamin at scission sites (Cullen, 2008). The EHD (Eps15 homology domain) proteins are structurally similar to dynamin and constitute another family of membrane-remodeling enzymes essential for the fission of TCs (Naslavsky and Caplan, 2011). EHD proteins can induce tubulation of membranes in vivo and in vitro, and regulate dynamin activity in vivo (Jakobsson et al., 2011). EHD1, a member of the family, interacts with

Vps26 and Vps35 and is required for retrieval of CI-MPR (Gokool et al., 2007b). However, the underlying mechanism by which retromer regulates dynamin and/or dynamin-like proteins, such as members of the EHD family to elicit tubule scission remains to be elucidated.

The association of a TC to the cytoskeleton through microtubule motors not only allows its long-range movement but also provides an additional longitudinal force that, coupled with the activity of dynamin and/or EHD proteins, facilitates the fission process. The well-established retromer members SNX5 and SNX6 bind directly to the dynactin component $p150^{glued}$, an activator of the microtubule motor dynein to mediate the retrograde movement of TCs toward the centrosome (Hong et al., 2009; Wassmer et al., 2009). Consistent with this, inhibition or knockdown of $p150^{glued}$ results in altered retromer distribution and impaired CI-MPR recycling from endosomes to the TGN (Hong et al., 2009; Wassmer et al., 2009). Thus, by coupling SNX-BARs to the CRC and the dynein-dynactin motor, retromer can coordinate membrane deformation and cargo selection with long-range retrograde transport along microtubule tracks to the TGN. Furthermore, a recent study has demonstrated that SNX1, SNX4, and SNX8 couple to distinct combinations of dynein and kinesin motors within discrete sorting domains from a single endosome (Hunt et al., 2013). As such, the mobility of SNX1 and SNX8 relays on dynein-1/kinesin-1 whereas SNX4 relays on dynein-1/kinesin-2 microtubule motors (Hunt et al., 2013). In this respect, it is tempting to speculate that by using different SNXs combinations it might be possible to engage distinct subsets of microtubule motors and ensure vectorial transport.

4. TUBULOVESICLE ARRIVALS AT TGN

4.1 First Contact: Tethers

The retromer-mediated delivery of membrane-spanning proteins is often assumed to be mediated by the retromer tubules themselves. There is the possibility, however, that the tubules bud from the endosome and then break up into further intermediates. In any event, the final carrier likely fuses to the TGN. All the evidence in support of proteins playing a role in this process is indirect as the fusion event itself has not been directly observed or reconstituted. Tethering factors are thought to capture the retrograde TCs and then engage in a stepwise fusion process involving classical fusion machinery such as SNAREs. There are limited experimental data that

demonstrate the overall relationship between all the components of this system and it is not known which of these components act redundantly and which act in symphony. There is the additional possibility that some of these factors are involved in the tethering of other non-retromer vesicles.

Tethering factors can be divided into two broad categories: long coiled-coil proteins and multisubunit tethering complexes (MTCs) (Yu and Hughson, 2010). MTCs can be further subdivided into the complex associated with tethering containing helical rods (CATCHR) family, the TRAPP family and the HOPS/CORVET complexes. There are five tethering factor complexes associated with fusion events at the TGN.

4.1.1 Long coiled-coil tethering factors

Long coiled-coil tethering factors (LCTFs) are likely to be the first point of contract for incoming retrograde TCs. They protrude into the cytosol from the membrane and are proposed to 'catch' incoming cargo. Despite not having conserved sequence homology, there are LCTFs associated with a number of organelles suggesting that they have a conserved and necessary role in vesicle tethering or organelle morphology. Golgins are a class of extensively coiled-coil proteins that associate with the Golgi apparatus. They are broadly defined by their localization and thus have been implicated in a number of processes dependent on their suborganelle localization and interacting partners (Barr and Short, 2003). Generally, they function as long tethers that indirectly associate with the membrane of the Golgi apparatus and extend into the cytosol. A number of Golgins have been localized to the TGN and are thus potentially involved either directly or indirectly in receiving cargo from the endosomes. These TGN-associated Golgins include a subclass containing the GRIP domain (Kjer-Nielsen et al., 1999; Munro and Nichols, 1999), a cross-kingdom-conserved stretch of ~44 amino acids that is necessary and sufficient to recruit fusion proteins to the *trans*-Golgi (Kjer-Nielsen et al., 1999; Munro and Nichols, 1999). There are four GRIP domain-containing Golgins conserved in mammals: Golgin-245, Golgin-97, GCC88, and GCC185. Experimental evidence indicates that all four GRIP domain-containing Golgins are involved in retrograde trafficking, and ectopic overexpression of a conserved GRIP domain alone is enough to inhibit retrograde trafficking (Lu et al., 2004). Depletion of GCC185 leads to accumulation of STxB in endosomes and deficiencies in MPR trafficking (Derby et al., 2007; Reddy et al., 2006). GCC88 seems to function as part of a slightly different pathway, as its depletion does not affect STxB trafficking but does inhibit MPR trafficking and TGN38

recycling (Lieu et al., 2007). Golgin-97 has been shown to be necessary for STxB trafficking using inhibitory antibodies to Golgin-97 (Lu et al., 2004). In addition, Golgin-97 is part of a complex with Rab11a/b and its effector FIP1/RCP, which localizes to the Golgi apparatus and is essential for retrograde trafficking of STxB and TGN38, but not MPR (Jing et al., 2010). Finally, Golgin-245 depletion also prevents recycling of STxB; however, it also causes disruption of the TGN structure, so this effect could be pleiotropic (Yoshino et al., 2005). A recent study took the elegant approach of reversibly tethering Golgins to the mitochondria. This approach showed that Golgin-97, Golgin-245 and GCC88 were sufficient to reroute the retrograde cargos TGN46, CD-MPR, CI-MPR, and Vti1a to the mitochondria (Wong and Munro, 2014). However, GCC185 was not sufficient to reroute any of these cargos.

4.1.2 CATCHR tethering factors

The CATCHR tethering factors are a category of MTCs classified on the basis of sequence homology. It comprises four complexes: GARP, COG, Dsl1, and exocyst—23 proteins in total. Available structural data suggest that the majority of these proteins are derived from a common ancestral protein (Yu and Hughson, 2010). The higher order structures seem to be comparable too; three of the four complexes are tetrameric or octameric, the outlier being the trimeric Dsl1 complex. Three of these four complexes, GARP, COG, and Dsl1, play a role at the Golgi apparatus and are discussed below; the fourth complex, the exocyst, is implicated in exocytosis at the PM.

4.1.2.1 Golgi-associated retrograde protein

One of the more established MTCs implicated in endosome-to-TGN trafficking is the Golgi-associated retrograde protein (GARP) complex. GARP is a cross-kingdom-conserved heterotetrameric complex that was originally characterized in yeast. Genetic evidence supported by biochemical data identified four subunits of yeast GARP: VPS51, VPS52, VPS53, and VPS54 (Conibear and Stevens, 2000; Siniossoglou and Pelham, 2002). The mammalian orthologs were readily identified aside from VPS51, which has less sequence homology. The previously uncharacterized Ang2 was later identified as the mammalian VPS51 ortholog (Bourgoignie et al., 1986; Perez-Victoria et al., 2010). Ang2, VPS52, VPS53, and VPS54 all comprise tandem helical rods, a hallmark of CATCHR domain containing proteins (Bonifacino and Hierro, 2011; Yu and Hughson, 2010). The yeast GARP complex was originally implicated in Golgi transport processes by a

combination of biochemical protein trafficking defects and localization (Conibear and Stevens, 2000). In addition, it was demonstrated that the recycling SNARE Snc1p was mislocalized in GARP mutants (Siniossoglou and Pelham, 2002). This evidence, coupled with the Golgi apparatus localization, led to the hypothesis that GARP plays a direct role in retrograde vesicle tethering. This concept was further supported by work in mammalian cells, which showed that retrograde transport of MPRs, TGN46, and STxB was dependent on GARP (Perez-Victoria et al., 2008). Additionally, the GARP complex was directly associated with other proteins essential for membrane association and fusion as discussed below.

4.1.2.2 COG

The COG complex, composed of Cog1-8 subunits is broadly associated with the Golgi apparatus (Willett et al., 2013b). The subunits are arranged as a two-lobed, eight-protein complex that interacts with multiple partners (Fotso et al., 2005; Ungar et al., 2005). Traditionally, the COG complex was thought to be involved with vesicle tethering and fusion between the cisternae of the Golgi stack. However, more recent evidence has also implicated COG in the fusion of retrograde vesicles to the TGN. Yeast mutants for the COG subunits 2 and 3 are defective in the sorting of the soluble vacuolar cargo CPY (Wuestehube et al., 1996); independently, a Cog3 mutant was shown to missort and degrade the TGN protease Kex2p (Spelbrink and Nothwehr, 1999). Cog1 depletion by siRNA in mammalian cells stops effective retrograde recycling of STxB (Zolov and Lupashin, 2005) as well as another retrograde cargo, subtilase cytotoxin (Smith et al., 2009). Experiments with mammalian cells transiently depleted of Cog6 showed abnormal localization and trafficking of not only STxB, but also TGN46 (or its rat ortholog TGN38), CI-MPR, and the γ-adaptin subunit of AP-1 (Laufman et al., 2011). Cog4-depleted cells showed the same for TGN38/46, and CI-MPR (Laufman et al., 2011). Thus, the COG complex is not only responsible for intra-Golgi transport, but also for endosome-to-TGN transport; this is supported by recent evidence that the COG complex associates with multiple SNARE complexes (Laufman et al., 2011), discussed below, and 12 different Rab GTPases (Fukuda et al., 2008; Miller and Ungar, 2012; Suvorova et al., 2002; Willett et al., 2013b).

4.1.2.3 Dsl1 complex

Recent evidence suggests that also participating at the TGN with the COG complex is the trimeric Dsl1 complex (Arasaki et al., 2013). Like GARP and

COG (above), the Dsl1 complex falls into the CATCHR family. In yeast, the Dsl1 complex is well characterized and consists of Dsl1, Tip20, and Sec39/Dsl3 (in mammals the homologous subunits are ZQ10, RINT1, and NAG respectively). The complex is thought to extend laterally from the ER surface and to promote fusion of COPI vesicles that bud from the Golgi with the ER (Schmitt, 2010). However, the mammalian Tip20 ortholog RINT1 has recently been implicated in tethering of endosome-derived vesicles in a mechanism dependent on direct interaction with a COG complex component, Cog1 (Arasaki et al., 2013). This proposal was based on the observation that *trans*-Golgi proteins seem more disrupted than *cis*-Golgi proteins when RINT1 has been depleted. This was followed up by demonstrating that the endocytic route of cholera toxin is also disrupted. Immunoprecipitation experiments supported a specific interaction of RINT1 with Cog1, perhaps implying that the complexes collaborate to tether incoming vesicles.

4.1.3 Other multisubunit tethering complexes

In addition to the CATCHR complexes, there are two other MTCs: the HOPS/CORVET and TRAPP (I, II, and III) complexes. HOPS and CORVET are related complexes implicated in endosome maturation and fusion, and to date have not been shown to participate in endosome-to-TGN transport. The TRAPP family of complexes are primarily involved with tethering and fusion at the Golgi stack (Barrowman et al., 2010). There are three TRAPP complexes. The best characterized is the seven-subunit TRAPPI complex (Trs20p, Trs31p, Bet3p, Trs33p, Bet5p, Trs85p, and Trs23p), which is implicated in the fusion of COPII vesicles at the *cis*-Golgi (Kim et al., 2006; Sacher et al., 2000, 2001, 1998). Functionally, TRAPPI directly binds to and acts as the exchange factor for the Rab1 GTPase, initiating a cascade of further interactions (Sacher et al., 2001). The TRAPPII complex contains all seven subunits of TRAPPI plus Trs130p, Trs120p, and Trs65p (Sacher et al., 2001). TRAPPII has been associated with multiple processes including Rab1 GEF activity and interactions with COPI (Yamasaki et al., 2009). It was suggested that the recruitment of Trs85p to the TRAPPI complex makes a functionally distinct complex referred to as the TRAPPIII complex. TRAPPIII is the most recently described of the TRAPP complexes, with a proposal that Trs85p does not interact with the canonical TRAPPI machinery, but instead exists as a free pool in the cytosol (Lynch-Day et al., 2010). The core TRAPPI and, therefore, TRAPPIII structure containing Bet3p, Bet5p, Trs23p, and Trs33p, has been solved revealing a flat complex with bet3 and bet5 in the middle.

Both of the central proteins interact with the tightly packed helices of Trs33p as well as a domain each of Trs23p. A central groove is formed between Bet3p and Bet5p making the overall topology similar to a flattened torus. TRAPPIII was shown in yeast to be essential for macroautophagy through interactions with Rab1 (Lynch-Day et al., 2010). Recent findings suggest that this is a secondary effect due to TRAPPIII deficiency causing a trafficking deficiency of the autophagy factor ATG9 (Shirahama-Noda et al., 2013).

In mammalian systems, there are homologs for almost all TRAPP subunits aside from TRS65, which seems to lack a direct homolog (Sacher et al., 2008). In addition, there are three extra subunits designated TRAPPC11, TRAPPC12, and TRAPPC13 (Bassik et al., 2013; Scrivens et al., 2011). It has been proposed that there are two mammalian TRAPP complexes (Bassik et al., 2013). One complex is the direct functional homolog of the yeast TRAPPII, consisting of the TRAPP core as well as TRAPPC9 and TRAPPC10, the Trs120 and Trs130 homologs. The second complex, TRAPPIII, includes the Trs85 homolog TRAPPC8 as well as the three mammalian specific members, TRAPPC11, TRAPPC12, and TRAPPC13. It is not known if the core TRAPP complex (TRAPPI) functions in a similar way to the yeast complex.

4.2 Rabs and Arls

Vesicle tethering and fusion at the TGN appears to be dependent on at least two independent GTP regulated events. Firstly, recruitment of some of the tethering complexes seems to be dependent on the Arl1 GTPase. Secondly, Rab GTPases independently mediate the final steps before membrane fusion.

4.2.1 Arl1

The sequentially first GTP-regulated event requires an Arf-like GTPase, Arl1. Arl1 was identified in *Drosophila* due to its genomic proximity to an unrelated gene that was being cloned. Arl1 is related to, but different from, Arf GTPases (Tamkun et al., 1991). The mammalian ortholog was localized to the Golgi apparatus, but later shown to also be enriched at the TGN, and to be necessary for retrograde transport of STxB (Lowe et al., 1996; Lu et al., 2001; Tai et al., 2005; Van Valkenburgh et al., 2001). Additionally, it was demonstrated that overexpression of a dominant-negative form of Arl1 caused aberrations in Golgi structure and function (Lu et al., 2001). Arl1 was shown to interact with three of the four GRIP domain-containing *trans*-Golgi golgins, Golgin-245, GCC185, and

Golgin-97 (Burguete et al., 2008; Jackson, 2003; Lu et al., 2004; Pfeffer, 2009; Setty et al., 2003; Van Valkenburgh et al., 2001), a finding supported by an interaction of the yeast Arl1 ortholog and the single yeast GRIP domain-containing protein, IMH1 (Panic et al., 2003b). An Arl1-GRIP domain complex was crystallized and the structure solved in two independent studies, which both showed the GRIP domain homodimerizes to interact with the interswitch region of Arl1 (Panic et al., 2003a; Wu et al., 2004). This homodimerization would recruit to Arf1 monomers either side of the GRIP dimer. In the context of the full Golgin this would position the C-terminus next to the membrane, complexed with the Arl1 monomers, and the large N-terminal tether extending laterally into the cytosol. Interestingly, yeast Arl1 has also been shown to interact with the GARP subunits VPS53 and VPS54 (Panic et al., 2003b). This interaction has yet to be followed up by supporting studies in mammalian cell types. Perhaps Arl1 bridges the gap between these two complexes, acting as an intermediate. In an additional layer of complexity, Arl1 recruitment to the Golgi was shown to depend on Arl3 using yeast knock-out strains, suggesting that Arl3 regulates a cascade of Golgi-related recruitment events (Setty et al., 2003).

4.2.2 Rab GTPases

The role of Rab GTPases as regulators of both tethering and membrane fusion mediators is well established. There appears to be Rab GTPases involved with almost every membrane fusion event characterized thus far. Accordingly, there have been Rab GTPases implicated in the fusion of retrograde vesicles. Three Rab GTPases have been widely implicated in fusion events at the TGN: Rab1, Rab6, and Rab2. Rab1 is primarily involved with the tethering of ER-derived COPII vesicles to the *cis*-face of the Golgi (Plutner et al., 1990; Schmitt et al., 1986; Tisdale et al., 1992). However, there are suggestions that it is also involved in events at the TGN. Trs85p, the defining factor of the TRAPPIII complex, recruits Rab1 to the membrane (Lynch-Day et al., 2010; Shirahama-Noda et al., 2013). In addition, in yeast, the Cog2 and Cog3 orthologs interact with the Rab1 ortholog, suggesting that it might have a role at the *cis*-Golgi as well as the *trans*-Golgi (Suvorova et al., 2002). Alternatively, these interactions could represent additional roles for the tethering complexes (Figure 3).

A stronger candidate for a Rab GTPase involved in retrograde transport is Rab6. Depletion of Rab6 causes fragmentation of the Golgi apparatus in both yeast and mammals (Li and Warner, 1996; Sun et al., 2007). In addition, Rab6 depletion causes a slight processing defect of Cathepsin D in

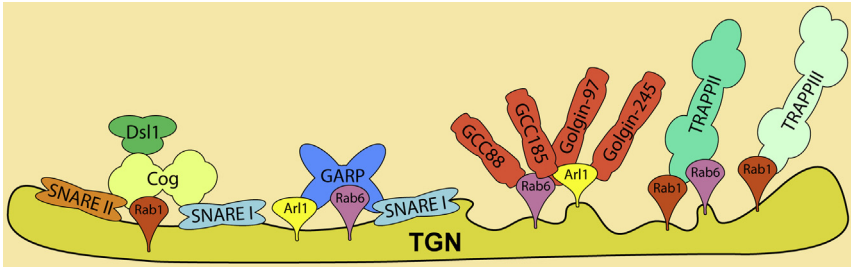

Figure 3 Proteins implicated in retrograde vesicle fusion at the TGN. An overview of the components demonstrably involved in metazoan retrograde trafficking at the TGN. In some cases, metazoan data are not available, in which case data from yeast studies have been used (e.g., Rab6/Arl1 interaction with GARP). For clarity, the SNARE complexes have been labeled as I and II; SNARE I corresponds to Stx6/Stx10, Vti1a, Stx16, VAMP3/VAMP4, and SNARE II corresponds to Stx5, GS28, Ykt6, GS15. TGN, *trans*-Golgi Network.

mammalian cells (Perez-Victoria et al., 2008), and interference with antibodies prevents STxB trafficking (Mallard et al., 2002) and CD-MPR recycling (Medigeshi and Schu, 2003). In yeast, Rab6 depletion caused mis-sorting of carboxypeptidase Y and affected secretion of α-factor and sorting of Kex2p (Bensen et al., 2001; Tsukada et al., 1999). The presence of Rab6 is reported to increase the affinity of the previously described interaction between the Golgin GCC185 and Arl1 (Burguete et al., 2008; Ganley et al., 2008). Protein–protein interaction studies in *Drosophila* demonstrated that Rab6 interacts with the TGN Golgins GCC97 and GCC88; however, this study did not identify an interaction with GCC185 (Sinka et al., 2008). Additionally, a study identifying mutant-Rab6 repressors in yeast discovered the GRIP domain- containing protein, IMH1 (Li and Warner, 1996). Rab6 was shown to interact with both the yeast and human GARP complex (VPS52, VPS53, and VPS54) when in the GTP-bound state (Liewen et al., 2005; Siniossoglou and Pelham, 2001). Expression of a dominant-negative form of Rab6 or siRNA knock-down inhibits retrograde transport of STxB (Del Nery et al., 2006; Monier et al., 2002), and knock-down of Rab6 inhibits retrograde transport of Subtilase cytotoxin, a pathway partially dependent on retromer (Smith et al., 2009). Finally, in a recent Drosophila Rab GTPase interaction screen, Rab6 was shown to interact specifically with metazoan TRAPPII and not TRAPPIII (Gillingham et al., 2014).

A recent study provided an additional candidate Rab GTPase at the TGN, Rab2. Yeast-two-hybrid experiments showed that the *Drosophila*

ortholog of GCC185 interacts with Rab2 and Arl1 but not Rab6 (Torres et al., 2014). The hypothesis that Rab2 is involved in this step is supported by data demonstrating that the *trans*-Golgi-localized Golgin-245 interacts with Rab2 (Sinka et al., 2008).

4.3 SNAP (Soluble NSF Attachment Protein) Receptors

Once tethered to the donor compartment, vesicles or tubules need a SNARE protein complex to mediate the membrane fusion, allowing mixing of the membranes as well as the lumenal contents. Two groups of SNAREs are involved, in seemingly related, but independent pathways of fusion of endosome-derived carriers with the TGN: the Stx6, Stx10, Stx16, Vti1a, VAMP3, VAMP4 group and the Stx5, GS28/GS27, Ykt6, GS15 complex.

Interactions between the Habc domain of the t-SNARE Tlg1 with the GARP complex demonstrated a potential conserved interacting partner (Conibear et al., 2003; Siniossoglou and Pelham, 2002). This region is homologous to the Syntaxin 6 (Stx6) Habc domain, which mediates the analogous interaction between Stx6 and the mammalian GARP complex (Abascal-Palacios et al., 2013; Liewen et al., 2005; Perez-Victoria and Bonifacino, 2009). Immunoprecipitation studies showed that Stx6 interacts in a complex with the t-SNAREs Stx16 and Vti1a and the v-SNAREs VAMP3 and VAMP4 (Mallard et al., 2002). The same study showed that interfering with this complex causes defects in STxB trafficking. Inhibiting the activity of Vti1a and Stx16 with antibodies affects recycling of CD-MPR, a known retromer cargo (Medigeshi and Schu, 2003). The assembled complex appears to involve not only the GARP complex but also the RINT complex, as RINT-1 was shown to interact with VAMP4, Stx16, Vti1a and weakly with VAMP3 (Arasaki et al., 2013). Golgins also appear to participate, as GCC185 binds directly to Stx16 (Ganley et al., 2008). In this study, Stx10 was involved in recycling of CI-MPR and Stx6 was not, suggesting that Stx10 might replace Stx6 in a related complex responsible for CI-MPR recycling. Stx6 seems to play a role in TGN38 trafficking, as depletion causes defects in TGN38 recycling, but not retrograde transport of STxB (Lieu et al., 2007), whereas Stx16 is necessary for retrograde transport of STxB as well as TGN38 (Lieu and Gleeson, 2010). Finally, the COG complex also seems to interact with this SNARE complex. Cog6 interacts with Stx6 (Laufman et al., 2011), Cog8 interacts with Stx16 (Willett et al., 2013a), and Cog4 enhances the assembly of the Stx6 SNARE complex (Laufman et al., 2013). In addition, the Sec1/Munc18 (SM) protein VPS45 might regulate this fusion event. VPS45 is the only SM family member found at

the Golgi in mammalian cells (Tellam et al., 1997) and in yeast mediates the assembly of an analogous SNARE complex (Bryant and James, 2001; Shanks et al., 2012) via physical interaction with Tlg2p, the functional homolog of Stx16 (Shanks et al., 2012).

Interestingly, the COG complex also interacts with a second retrograde-associated SNARE complex (Kudlyk et al., 2013) made of Stx5, GS28/GS27, Ykt6, and GS15. This complex is necessary for the retrograde transport of subtilase cytotoxin (Smith et al., 2009), as well as STxB, as shown by antibody inhibition as well as siRNA depletion (Tai et al., 2004). The interaction between this SNARE complex and the COG complex seems to be via several of the COG subunits: Cog4 interacts with Stx5, and expression of a fragment of Cog4 disrupts the colocalization of GS15 with Stx5 (Laufman et al., 2009). Immunoprecipitation studies show that Cog3 interacts with GS28 (Zolov and Lupashin, 2005), and yeast-two-hybrid assays show that Cog6 interacts with Stx5, Stx6, GS27, and SNAP29, a series of interactions supported by coimmunoprecipitation (Kudlyk et al., 2013).

5. CONCLUDING REMARKS AND OPEN QUESTIONS

During the last decade we have seen a growing appreciation of the dynamics of the endosomal network and the molecular machineries responsible for its regulation. Depending on the cell type, it is estimated that 50% of the PM is internalized every hour (Steinman et al., 1983). This massive flow of lipids and macromolecules is counterbalanced by a continuous recycling and secretory transport maintained through dynamic molecular interactions. These interactions are essential in processes such as nutrient uptake, cell migration, cell polarity, morphogenesis, downregulation of signaling receptors, immune surveillance, antigen presentation, and in learning and memory. Recent studies have yielded a wealth of new information regarding the retrograde transport between the endosomal system and the TGN. Endosomes, as part of their maturation process, play a pivotal role for recycling, degradation, or rerouting cargoes through tubular and vesicular structures. Multiple pathways have now been defined in detail, which differ between the cargo transported and the machinery used including specific lipids, APs, coats, tethers, SNAREs, and small GTPases along with their regulators and effectors. In this review we have summarized important insights and current models for how cargo carriers are produced from endosomes, with a special emphasis on the retromer complex, and the tethering factors

on the TGN for capturing those carriers. Although the importance of the endosome-to-TGN transport is now well established, fundamental questions still remain. For example, there is still no clear model for how different types of coat lattices can be formed around tubulovesicular carriers and how different architectural configurations promote specificity towards different cargoes. Likewise, the field is still at an early stage in integrating how recycling and degradation are coordinated, and how distinct tubulovesicular carriers generated from endosomes are coordinated with different tethers or "docking stations" at the TGN. More work is also required to understand how the recycling pathways are adapted within the numerous cell types according to their different physiological needs. Efforts to address these issues will lead to a more detailed molecular roadmap of recycling pathways that ultimately might be used for therapeutical intervention.

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