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Review

Endosome-to-Golgi transport pathways in physiological processes

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Summary. The trans-Golgi network (TGN) is a major traffic hub of the cell, as it regulates membrane transport in the secretory pathway as well as receiving protein cargo by retrograde transport from endocytic compartments. Retrograde transport between endosomes and the TGN is essential for the recycling of membrane proteins which regulate a range of cellular and development functions. In addition, retrograde transport pathways are exploited by many bacterial toxins to mediate cytotoxicity and by some viral proteins to promote pathogenicity. Recent advances using a range of molecular cell biological strategies have identified multiple retrograde transport pathways each regulated by a distinct set of molecular machinery. Here we review recent advances in this field and highlight the importance of these transport pathways in a range of physiological processes.

Key words: Retrograde transprot, Trans-Golgi network, Endosomes, Golgins

Introduction

Membrane transport pathways were traditionally divided into the outward-bound or secretory pathway and the inward-bound or endocytic pathway. However, it is now clear that intracellular membrane transport pathways form a complex network and the two traditional pathways converge at a variety of locations (Derby and Gleeson, 2007). The trans-Golgi network (TGN), located at the exit face of the Golgi stack (Griffiths and Simons, 1986) represents a trafficking hub at the intersection of the outward-bound and inward-bound pathways. The TGN sorts a plethora of cargo proteins and lipids into membrane carriers destined for the plasma membrane, endosomes, secretory granules, or other locations (Keller and Simons, 1997; Traub and Kornfeld, 1997; Di Fiore and De Camilli, 2001; Sannerud et al., 2003; Young et al., 2005). In addition, the TGN receives cargo from various endosomal locations by a process known as retrograde transport (Derby and Gleeson, 2007; Johannes and Popoff, 2008). Initially of interest in understanding how bacterial toxins are internalised and transported within the cell, retrograde transport is now recognised as playing a key role in many physiological and cellular processes (Bonifacino and Rojas, 2006; Johannes and Popoff, 2008). Here we review the key features of retrograde transport pathways, summarise the range of cargo that use these pathways, and discuss machinery components that regulate the different endosome-to-TGN transport routes.

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Function of retrograde trafficking in development, cell function and disease

The retrograde transport route is a highly selective pathway that transports some molecules from endosomal compartments to the TGN, bypassing alternative routes from endosomes back to the plasma membrane or onward to the late endocytic-lysosome pathway (Fig. 1). Efficient transport of endogenous proteins from the early endosomes to the TGN is limited to a specific set of transmembrane proteins (Table 1). As indicated in Table 1 the cargos that use this retrograde transport pathway have a wide variety of functions. These functions include the recycling of membrane proteins such as the sorting receptors, mannose-6-phosphate receptors (M6P-R), sortilin and Wntless, transmembrane peptidases such as furin and ß-amyloid cleaving enzyme (BACE),

SNAREs, as well as ion and glucose transporters (Ghosh et al., 1998; Lewis et al., 2000; Ghosh et al., 2003; Shewan et al., 2003; Sandvig and van Deurs, 2005; Bonifacino and Rojas, 2006). In addition, bacterial and plant toxins, such as Shiga toxin, cholera toxin, pertussis toxin and ricin (Table 1), are internalized by endocytosis then undergo retrograde transport to the TGN as an essential step in mediating cytotoxicity (Sandvig and van Deurs, 2000; Utskarpen et al., 2006; Plaut and Carbonetti, 2008). Furthermore, the HIV accessory protein, Nef, enhances viral infectivity by downregulating CD4 and MHC class I through interactions with transport machinery and perturbing retrograde transport (Johannes et al., 2003).

The importance of retrograde transport in the regulation of copper transport in mammalian cells by the Menkes protein (Petris et al., 1996), and of glucose transport in adipocytes and skeletal muscle by the glucose transporter GLUT4 (Shewan et al., 2003) has been appreciated for some time. More recently, a plethora of papers has demonstrated a novel function for retrograde transport in the secretion of signalling molecules. The secretion of Wnt signalling proteins is dependent upon a transmembrane sorting receptor, Wntless, which recycles between the TGN and the cell surface via the retrograde transport pathway (Franch-Marro et al., 2008; Pan et al., 2008; Port et al., 2008; Yang et al., 2008). Loss of Wntless, or a block in retrograde transport, results in impairment of Wnt secretion and defects in development and homeostatis in *Drosphilia* and *C. elegans*. These exciting findings have highlighted the relevance of retrograde transport in development.

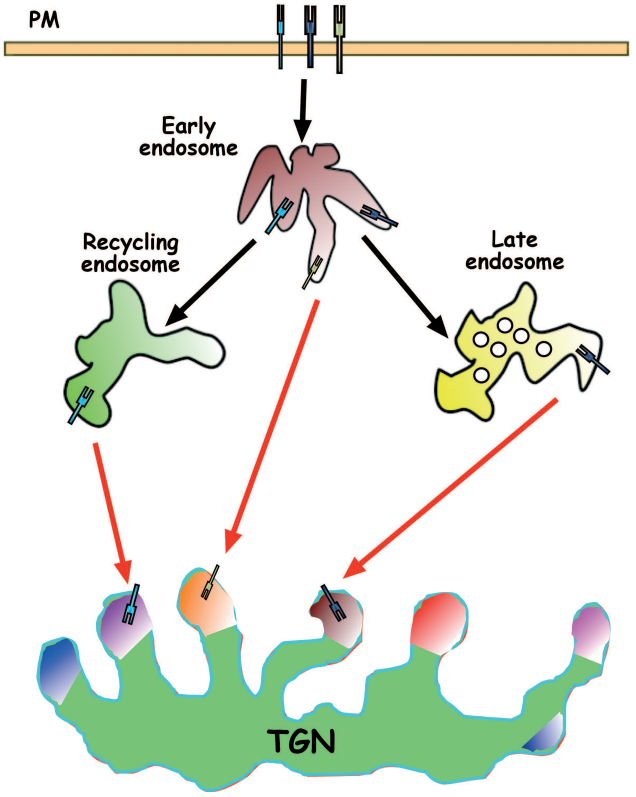

Fig. 1. Endosome-to-TGN retrograde transport pathways. The retrograde transport of cargo proteins to the TGN can occur from the early endosome, recycling endosome and late endosome (indicated by red arrows). Each of these three pathways is selective for a distinct cohort of cargo and requires distinct machinery components. See text for details

Table 1. Cargo proteins that undergo endosome to trans-Golgi network transport steps.

Cargo protein	Functional information	Reference
CI-M6PR/CD-M6PR	Cation-independent and -dependent mannose-6-phosphate receptors that are involved in TGN to endosome transport of lysosomal enzymes	Riederer et al., 1994; Ghosh et al., 2003
TGN38/TGN46	Rat TGN38 and human TGN46 recycling protein of unknown function	Banting et al., 1998; Ghosh et al., 1998
Furin	Membrane associated subtilising-like eukaryotic endoprotease that is involved in proteolytic cleavage	Mallet and Maxfield, 1999; Teuchert et al., 1999
Sortilin	Multi-ligand receptor that is involved in trafficking of proteins from the TGN to the lysosomes	Seaman, 2004; Canuel et al., 2008; Mari et al., 2008
Shiga toxin	Exotoxins produced by Shigalla like bacteria	Johannes et al., 1997; Mallard et al., 1998
Cholera toxin	Exotoxins produced by Vibrio cholera	Lencer, 2004
Ricin	Plant related exotoxins	Iversen et al., 2001; Sandvig and van Deurs, 2005; Stechmann et al., 2010
Wntless	Sorting receptor required for Wnt secretion	Hausmann et al., 2007; Belenkaya et al., 2008; Eaton, 2008; Franch-Marro et al., 2008; Port et al., 2008; Yang et al., 2008
ATP7A (Menkes protein)	P type ATPase involve in regulation of copper levels in mammalian cells	Petris et al., 1996; Lane et al., 2004
VAMP4	v-SNARE associated with the early/recycling endosome	Tran et al., 2007
Syntaxin 6	t-SNARE localised to the TGN for efficient retrograde transport of TGN38 and Shiga toxin	Kasai and Akagawa, 2001; Wendler and Tooze, 2001; Lieu et al., 2007
GLUT4	Major glucose transporter involved in uptake of glucose under insulin stimulated conditions	Shewan et al., 2003; Hou and Pessin, 2007; Blot and McGraw, 2008
BACE (ß-amyloid cleaving enzyme)	Alzheimer related enzyme that is involved in processing of amyloid precursor protein	von Arnim et al., 2004; Wahle et al., 2005

The membrane protein TGN38/46 and the non-toxic receptor-binding B-subunit of bacterial Shiga toxin have played key roles in the discovery, and the molecular dissection, of membrane trafficking at the early/recycling endosomes-TGN interface. Over the past few years, a number of retrograde transport pathways from the endosomal compartments to the TGN have been identified in mammalian cells (Sannerud et al., 2003; Bonifacino and Rojas, 2006; Johannes and Popoff, 2008). Multicellular organisms have a greater complexity in their retrograde transport pathways, both in components and number of pathways, than single cell yeast (Bonifacino and Rojas, 2006; Johannes and Popoff, 2008) and the evolution of these pathways is likely to reflect specialised functions associated with development and physiology of multicellular organisms.

Approaches to dissect retrograde transport

Traditionally, cell lines have provided the model systems to explore and dissect retrograde trafficking using both microscopic and biochemical approaches. The ability to define retrograde transport pathways has been dramatically enhanced over the past decade by the use of defined organelle markers, such as EEA1 for early endosomes, Rab11 for recycling endosomes, Rab7 and LAMP1 for late endosomes and a range of markers for the Golgi apparatus including the TGN (Derby and Gleeson, 2007). Tracking the movement of cargo from the cell surface back to the Golgi apparatus can be readily accomplished by use of fluorescently labelled ligand molecules, such as fluorescently labelled toxins, or antibodies which recognise an extracellular epitope of a membrane cargo molecule or modified cargo containing an exofacial tag. Tracking the internalisation and transport of cargo usually is performed by tagging the cell surface molecules of intact cells at 0°C, warming to 37°C and then monitoring the internalisation of the labelled complexes through intracellular compartments. The availability of software packages for quantifying fluorescent intensities in defined regions of cells has allowed these fluorescence-based studies to move from a qualitative cell based analysis to a quantitative analysis within a population of cells. Given the range of fluorochromes now commercially available, multiple organelle markers can be labelled simultaneously with the cargo to determine the distribution of the cargo in different compartments at any one time-point. Coupled with interference RNA (RNAi) to deplete components of the trafficking machinery, transport routes and the regulatory components can be identified for each cargo. Microscopic analyses can also be supplemented with powerful biochemical assays to determine the kinetics of arrival at the Golgi apparatus; such assays were pioneered in the 1990s and which exploited post-translational modifications that occur specifically in the TGN such as protein sulphation (Johannes et al., 1997).

With the identification of molecular components which regulate retrograde transport, the importance of retrograde transport pathways is now under investigation in a range of organisms such as *C. elegans* and *Drosphilia* by the silencing and knock-out of machinery components. In addition, the advent of two photon imaging, RNAi and advances in stem cell technology will now provide avenues to explore retrograde trafficking in a very wide range of specialised cells in the whole organism.

Retrograde transport routes

Retrograde pathways include pathways from the late endosome to the TGN as well as from the early/recycling endosomes to the TGN (Fig. 1). Retrograde transport pathways arising from endocytic compartments have been dissected by tracking the transport of not only bacterial toxins but also cargos such as M6P-R, TGN38/46, furin, and the glucose transporter, GLUT4 (Table 1). One of the first components identified to define one of the retrograde transport pathways was Rab9 (Lombardi et al., 1993). Rab9 is a small GTPase localised to the late endosome and was shown to be important for the transport of M6P-R from the late endosome back to the TGN (Lombardi et al., 1993; Soldati et al., 1995). Over-expression of a dominant-negative mutant of Rab9, and the RNAi silencing of Rab9 in cultured cells, resulted in a block in recycling of M6P-R from the late endosome (Soldati et al., 1993; Carroll et al., 2001). The Rab9 effector, TIP47 binds to a phenylalanine/tryptophan motif present in the cytoplasmic tail of M6P-R (Diaz et al., 1997) and is required for late endosome to Golgi transport of M6P-R (Diaz et al., 1997; Carroll et al., 2001).

On the other hand, other cargos using endosome-to-Golgi transport such as TGN38 or Shiga toxin were shown to be independent on Rab9 (Mallard et al., 1998). Early studies showed that internalised TGN38 and Shiga toxin co-localised with transferring-positive early/recycling endosomes, rather than Rab9-positive late endosomes, en route to the TGN, indicating that both these cargos used a retrograde transport pathway arising from the early/recycling endosome (Mallard et al., 1998). Subsequently, recycling of TGN38 and Shiga toxin was shown to be Rab6 dependent (Mallard et al., 2002). Recent studies in our laboratory tracking the itinerary of TGN38 have indicated that this cargo is transported to the Golgi directly from early endosomes bypassing the recycling endosome (Lieu and Gleeson, 2010), a pathway for TGN38 previously proposed by Banting and colleagues (Banting and Ponnambalam, 1997). In contrast, Shiga toxin is transported from the early endosomes to the Golgi via the recycling endosomes. By RNAi depletion of a range of machinery components, Shiga toxin and TGN38 were shown to require different trafficking components for efficient retrograde transport (Lieu and Gleeson, 2010). Therefore, collectively these studies indicate the existence of at least three distinct trafficking routes from the early endosomes to the TGN (Fig. 1). Given the

identification of an increasing number of components for the sorting of cargo in the early endosome, and for the generation of transport carriers and the fusion of the carriers at the TGN, future studies should now be able to accurately define the precise number of retrograde transport pathways.

Cargos that use endosome-to-TGN transport pathways

Selected examples of cargos that use endosome-to-TGN transport will be discussed which have provided the foundations for defining the machinery components and the trafficking routes.

Mannose 6-phosphate receptors

A shared function of the cation-dependent and cation-independent M6P-Rs is the delivery of newly synthesised acid hydrolyases to the lysosomes (Ghosh et al., 2003). To achieve this receptor mediated delivery system both M6P-Rs recycle between the TGN and endosomes. The steady state distribution of M6P-R includes the TGN and the early endosome, recycling endosome and the late endosome, however the precise distribution between these compartments varies with the cell type. The collective evidence indicates that the retrograde transport of M6P-R can occur from all three endocytic compartments (Diaz and Pfeffer, 1998; Arighi et al., 2004; Derby et al., 2007). Rab9 and TIP47 mediate the retrograde transport of M6P-R from the late endosomes (Lombardi et al., 1993; Carroll et al., 2001). Transport of M6P-R also occurs from early endosomes to the TGN, a pathway dependent on the sorting complex retromer, discussed below. The recycling endosome is also likely to play a role in endosome-to-TGN transport of M6P-R. The ablation of the recycling endosome using HRP-conjugated transferrin blocked retrograde transport of a chimeric M6P-R construct consisting of the cytoplasmic tail of M6P-R fused to a Tac tag in CHO cells (Lin et al., 2004), suggesting that the recycling endosome is also used for endosome to TGN transport of M6P-R.

As M6P-R uses multiple endosome-to-TGN transport pathways for its intracellular trafficking, it is not surprising that multiple SNARE complexes are required for the transport of M6PR (Amessou et al., 2007; Ganley et al., 2008). By RNAi experiments, both syntaxin 5 and syntaxin 16 have been reported to be required for retrograde transport of M6P-R from early/recycling endosomes (Amessou et al., 2007), while a syntaxin 10 mediated SNARE complex has also been recently reported to be important for transport of M6P-R from the late endosome (Ganley et al., 2008).

Protein toxins

Protein toxins exploit retrograde pathways to exert their cytoxicity (Sannerud et al., 2003; Sandvig and van Deurs, 2005; Spooner et al., 2008). Most protein toxins are composed of two subunits, which are disulphide bonded. The catalytic A subunit is responsible for cytotoxicity of the toxin while the B subunit is required for intracellular trafficking. The B subunit of protein toxins binds to glycolipid receptors on the cell surface of host cells and the receptor bound toxin complex is then endocytosed into the early endosome. From the early endosome, these toxins are transported in a retrograde manner to the TGN, through the Golgi stack and eventually reaching the ER (Sannerud et al., 2003; Sandvig and van Deurs, 2005; Spooner et al., 2008). Once in the ER, the catalytic A subunit can dissociate from the B subunit and translocate to the cytosol where it exerts it cytotoxicity by binding to the 28S ribosome to prevent translation. Using the B subunit of Shiga toxin, Cholera toxin, Pseudomonas toxin and ricin as model cargos, a variety of research groups have reported that there are differences in the retrograde transport pathways for each toxin (Sandvig et al., 1992; Johannes et al., 1997; Iversen et al., 2001; Feng et al., 2004). For instance, *Pseudomonas* exotoxin traffics to the TGN via the Rab9 dependent late endosome pathway while the retrograde transport of ricin is Rab9 independent (Iversen et al., 2001; Smith et al., 2006). Also, retrograde transport of Shiga toxin is dependent on Rab11, a small GTPase localised to the recycling endosome (Wilcke et al., 2000). Overexpression of GDP or GTP bound mutants of Rab11 can inhibit endosome to TGN transport of Shiga toxin (Wilcke et al., 2000). On the other hand, retrograde transport of ricin is Rab11 independent (Wilcke et al., 2000; Iversen et al., 2001) indicating that ricin uses a different pathway from Shiga toxin.

TGN38/46

TGN38 is a membrane protein that recycles between the TGN and the plasma membrane (Stanley and Howell, 1993). The function of TGN38 is currently unknown, although there is some evidence for its involvement in exocytic transport from the TGN (Jones et al., 1993). TGN38 was first identified as a resident of the TGN in Normal Rat Kidney (NRK) cells from a screen of cDNA clones using polyclonal serum raised against a mixture of Golgi membrane proteins (Luzio et al., 1990). Subsequently, orthologues of TGN38 such as TGN46 (human orthologue of TGN38) and TGN41 (mouse orthologue of TGN38) were identified by screening of human or mouse cDNA library using serum against rat TGN38 (Banting and Ponnambalam, 1997). When TGN38/46 was overexpressed in cultured cells, TGN38/46 was not only localised to the TGN but also to cytoplasmic structures and the cell surface, suggesting that TGN38 may have the ability to traffic between different intracellular compartments (Banting et al., 1998; Ghosh et al., 1998). The recycling of TGN38/46

was confirmed by the use of specific antibody uptake assays to track transport of cell surface TGN38/46 back to the Golgi in cultured cells (Banting et al., 1998; Ghosh et al., 1998). Using CHO cells stably expressing a TGN38 chimera reporter construct, Ghosh et al. (1998) showed that TGN38 was internalised into transferrin-positive endosomes en route to the TGN. Our recent studies tracking the itinerary of TGN38 have indicated that this cargo is transported to the Golgi directly from early endosomes (Lieu and Gleeson, 2010).

SNAREs that undergo endosome to TGN recycling

Certain SNAREs, in particular v-SNAREs, can also cycle between endosomes and TGN. Recycling of SNAREs is essential so that the v-SNAREs involved in the TGN to endosome transport step can cycle back to the endosomes for reuse. Both VAMP4 and syntaxin 6 have been demonstrated to have the ability to recycle between intracellular compartments using specific antibody uptake assay (Kasai and Akagawa, 2001; Tran et al., 2007) However, the detailed trafficking itineraries of both VAMP4 and syntaxin 6 have yet to mapped.

Transmembrane enzymes

A number of transmembrane enzymes, which are proprotein convertases that catalyse the proteolytic maturation of precursor proteins, undergo cycling between the TGN and the cell surface. The most extensively examined is furin, a serine endoprotease that cleaves many substrates including transforming growth factor ß (Thomas, 2002), which has been shown to be internalised into endosomes and trafficked to the TGN (Mallet and Maxfield, 1999). The ß-secretase, BACE, an endopeptidase responsible for the cleavage of amyloid precursor protein, is also considered to undergo recycling based on the analysis of its steady state distribution (He et al., 2005; Wahle et al., 2005).

Sorting machinery of early endosome-to-TGN transport

As for other vesicular transport pathways, retrograde transport between the endocytic compartments and the TGN is presumed to require the formation of membrane-bound carriers. Hence, molecular components required for formation of transport carriers must be recruited from the cytosol to specific domains of the endosomal membrane for retrograde transport. A large number of components have been implicated in retrograde trafficking of cargo from endosomes (Table 2) and the precise role of these machinery components in the sorting of cargo and formation of transport carriers is currently receiving considerable attention. Here we will focus on the components required for cargo sorting and

Table 2. Trafficking components required for sorting of cargos in endosomes.

Mammalian proteins	Functional information	Reference
Vps26-Vps35-Vps29	Sub complex of the mammalian retromer involved in retrograde transport of CI-M6P-R , Shiga toxin and TGN38	Haft et al., 2000; Arighi et al., 2004; Seaman, 2004; Popoff et al., 2007
Vps34	Phosphatidylinositol 3-kinase involved with the retrograde transport of ricin	Skanland et al., 2007
SNX1	Component associated with the retromer and is required for retrograde transport of CI-M6P-R and Shiga toxin	Carlton et al., 2004; Bujny et al., 2007; Utskarpen et al., 2007; Lieu and Gleeson, 2010
SNX2	Component associated with the retromer and is required for retrograde transport of ricin and TGN38	Skanland et al., 2007; Lieu and Gleeson, 2010
SNX4	Member of the sorting nexin family involved in retrograde transport of ricin	Skanland et al., 2007
SNX5	Member of the sorting nexin family involved in retrograde transport of CI-M6P-R	Wassmer et al., 2007
SNX6	Member of the sorting nexin family involved in retrograde transport of CI-M6P-R and BACE	Wassmer et al., 2007; Hong et al., 2009
Clathrin	Structural protein that is the main component of the clathrin coated vesicles	Saint-Pol et al., 2004; Popoff et al., 2007; Esk et al., 2010
EpsinR	Monomeric clathrin based adaptor that is thought to sort retrograde cargo into clathrin coated vesicles	Saint-Pol et al., 2004
GGA	Clathrin based monomeric adaptor involved in endosome to TGN transport of BACE and M6P-R	Wahle et al., 2005; Scott et al., 2006; Canuel et al., 2008; Canuel et al., 2009
Rab9	Small GTPase involved in trafficking of M6PR from the late endosome	Riederer et al., 1994
Rab11	Small GTPase involved in sorting and trafficking of Shiga toxin from the recycling endosome	Wilcke et al., 2000; Miserey-Lenkei et al., 2007
TIP47	Rab 9 effector, involved in retrograde transport of M6P-R from the late endosome	Diaz et al., 1997; Carroll et al., 2001
AP-1	Heterotetrameric clathrin based adaptor that is involved in retrograde transport of TGN38 and M6PR	Saint-Pol et al., 2004
PACS-1	Phosphofurin-acidic-cluster- sorting protein 1 involved in retrograde transport of M6P-R from the early endosome	Hinners et al., 2003; Scott et al., 2006
Dynamin	Large GTPase involved in vesicle formation	Lauvrak et al., 2004
OCRL	Lowe-syndrome protein with phosphatidylinositiol-4,5 bisphosphate activity that regulate clathrin coat formation	Choudhury et al., 2005

retrograde transport from early endosomes as the advances associated with the events within the early endosome have been particularly revealing.

Retromer

The retromer complex has been shown to mediate the retrograde transport of a number of cargos from the early endosome (Bujny et al., 2007; Bonifacino and Hurley, 2008; Franch-Marro et al., 2008; Port et al., 2008). Retromer was first identified as important for the retrograde transport of cation-independent M6P-R (CI-M6P-R) (Arighi et al., 2004; Seaman, 2004), and more recently also shown to regulate retrograde transport of other cargos such as Wntless, Shiga toxin, and polymeric immunoglobulin receptors (Verges et al., 2004; Popoff et al., 2007; Belenkaya et al., 2008; Franch-Marro et al., 2008; Port et al., 2008; Yang et al., 2008). Retromer comprises two sub-complexes: a cargo recognition trimer of Vps26-Vps35-Vps29 and a sorting nexin (SNX) dimer that contains PX and Bar domains that bind lipid and curve membranes (Seaman, 2005; Rojas et al., 2007). Retromer plays a critical role not only in the sorting of cargos but also the generation of transport intermediates (Popoff et al., 2007; Rojas et al., 2007; Bonifacino and Hurley, 2008; Cullen, 2008; Wassmer et al., 2009). SNX1, SNX2 , SNX5 and SNX6 have been shown to be important components of retromer (Carlton et al., 2004; Rojas et al., 2007; Cullen, 2008), and recent studies have identified multiple forms of retromer which contain specific combinations of the four sorting nexins (Wassmer et al., 2009).

Vps26-Vps35-Vps29 forms a trimer complex considered to participate in cargo recognition while the SNX dimer is likely to be involved in generation of transport intermediates from the early endosome (Carlton et al., 2004, 2005; Seaman, 2004; Rojas et al., 2007). Bonifacino and colleagues (Arighi et al., 2004) demonstrated that Vps35 interacts with the cytoplasmic tail of the CI-M6P-R. By immunoprecipitation and sequence alignment, the conserved amino acid motif WLM on the cytoplasmic tail of CI-M6P-R was shown to bind to Vps35 and Vps26 to regulate retrograde transport of the receptor (Seaman, 2007). A functional role for the Vps26-Vps35-Vps29 trimer in regulating endosome to TGN transport of CI-M6P-R was demonstrated by the RNAi silencing of Vps35 and Vps26 in HeLa cells (Arighi et al., 2004; Seaman, 2004). In HeLa cells lacking Vps35 or Vps26, both endogenous CI-M6P-R and a chimeric reporter construct (CD8-M6P-R) containing the cytoplasmic tail of CI-M6P-R fused to the transmembrane domain of CD8 were redistributed from the TGN to the early endosome (Arighi et al., 2004; Seaman, 2004, 2007). As a consequence of CI-M6P-R missorting in retromer-depleted cells, there was also increased degradation of endogenous CI-M6P-R, leading to hypersecretion of lysosomal enzymes (Arighi et al., 2004; Seaman, 2004, 2007).

In contrast to the Vps26-Vps35-Vps29 trimer, the role of mammalian SNX dimers in regulating retrograde transport of CI-M6P-R remains controversial. As indicated above, four members of the mammalian SNX family have been proposed to associate with retromer to regulate retrograde transport of CI-M6P-R (Carlton et al., 2004, 2005a; Rojas et al., 2007; Wassmer et al., 2007). Early work from the Cullen laboratory showed that SNX1 positive tubules arising from endocytic-like structures co-localised with similar tubular structures labelled for the CD8-M6P-R fusion protein, indicating that SNX1 positive tubules are involved in CI-M6P-R transport from the early endosome (Carlton et al., 2004). The silencing of SNX1 by siRNA disrupted recycling of endogenous CI-M6PR and the CD8-M6P-R reporter construct (Carlton et al., 2004; Seaman, 2004). In SNX1 depleted cells, CI-M6P-R was not TGN localised but rather distributed into punctate structures that co-localised with markers of the early endosome, suggesting that SNX1 is essential for early endosome to TGN transport of CI-M6P-R (Carlton et al., 2004; Seaman, 2004).

SNX1 and SNX2 can form either homodimers or heterodimers with each other or with SNX5 and SNX6 (Haft et al., 1998, 2000; Gullapalli et al., 2004; Kerr et al., 2006; Rojas et al., 2007; Wassmer et al., 2007). Given that SNX2 has been reported to dimerise with SNX1, the silencing of SNX2 may have been expected to lead to the missorting of CI-M6P-R. However, this was not the case. RNAi silencing of SNX2 did not significantly block recycling of CI-M6P-R and the receptor was concentrated at the TGN at steady state (Carlton et al., 2005b). There is an emerging view that SNX1 and SNX2 can function independently in membrane transport (Gullapalli et al., 2004, 2006; Bujny et al., 2007; Skanland et al., 2007; Mari et al., 2008; Lieu and Gleeson, 2010). SNX1 has also been proposed to interact with two other SNX molecules, namely, SNX5 and SNX6 in mammalian cells (Kerr et al., 2006; Wassmer et al., 2007). Furthermore, the different combination of SNX dimers SNX1/SNX2 and SNX5/SNX6 may regulate transport of different cargos by the generation of distinct domains and tubules at the early endosome. The recent finding that different sorting nexins are involved in specific transport of TGN38 and Shiga toxin (Lieu and Gleeson, 2010) is consistent with this view. Given the two pathways arising from the early endosome, this would most likely require both SNX1 and SNX2 to be localised to distinct domains of the early endosome. Recent studies have shown that early endosomes can give rise to an extensive tubular endosomal network (TEN) or tubular sorting endosome (TSE) in which proteins destined for recycling to distinct cellular destinations are sorted to multiple exit sites (Bonifacino and Rojas, 2006; Cullen, 2008; Pavelka et al., 2008). Moreover, members of the SNX family have been reported to localise to different exit sites of the TEN/TSE (Carlton et al., 2004; Traer et al., 2007).

Further investigation is clearly required to define the precise distribution of different cargo and sorting nexins to the exit sites of TEN/TSE.

Clathrin/AP-1/phosphofurin acidic-cluster-sorting protein 1

Clathrin adaptors such as AP-1, phosphofurin acidic-cluster-sorting protein 1 (PACS-1) and EpsinR have been proposed to recruit clathrin from the cytosol and coordinate the sorting of M6P-R into clathrin coated vesicles at the early endosome membrane for transport to the TGN (Ghosh and Kornfeld, 2003; Saint-Pol et al., 2004). Depletion of AP-1 or PACS-1 by interference RNA (RNAi) in cultured cells resulted in relocalisation of M6P-R from TGN to early endosome, suggesting a role for AP-1 and PACS-1 in early endosome to TGN transport (Meyer et al., 2000; Scott et al., 2006). Both AP-1 and PACS-1 co-operate to regulate retrograde transport of M6P-R at the early endosome (Ghosh and Kornfeld, 2003). PACS-1 is an adaptor protein that can enhance binding of M6P-R to AP-1 in a phosphorylation dependent manner (Hinners and Tooze, 2003). Furthermore, a physiological function for AP-1 in recycling of M6P-R was demonstrated in mouse embryonic fibroblasts lacking μ1A-adaptin, where M6P-R was not concentrated at the TGN as in wild type cells, but rather was localised to the early endosome (Meyer et al., 2000). Recycling of M6P-R was also analysed in μ1A-adaptin deficient cells using a biochemical assay that measured sialylation of M6P-R at the TGN (Meyer et al., 2000). In μ1A-adaptin deficient cells, there was inefficient sialylation of the M6P-R compared to wild type cells, indicating a decrease in recycling of CD-M6P-R to the TGN (Meyer et al., 2000). AP-1 and PACS-1 both interact with sequences within the cytoplasmic tail of M6P-R to mediate retrograde transport of M6P-R from early endosomes to the TGN (Crump et al., 2001; Ghosh and Kornfeld, 2003).

An important question is whether clathrin/AP-1/PACS-1 complex and retromer function in the same pathway or mediate distinct retrograde transport pathways. Preliminary analysis have indicated that AP-1/PACS-1 and the mammalian retromer seem to define two parallel pathways in which CI-M6P-R can be recycled back to the TGN from the early endosome (Seaman, 2007). Components of the AP-1 complex such as γ-adaptin and components of retromer such as Vps26 and Vps35 do not co-localise extensively on the membranes of the early endosomes (Seaman, 2007). Furthermore, only very weak interactions between AP-1 and retromer components, Vps35 and Vps26 have been detected by yeast two hybrid and immunoprecipitation experiments, suggesting that these two complexes do not appear to interact with each other (Seaman, 2007). Regardless, both the AP-1/PACS-1- and retromer-dependent pathways define retrograde transport routes that are distinct from the Rab9-dependent late endosome route.

Tethering and fusion of retrograde carriers at the TGN

Incoming transport intermediates from the endocytic compartments need to dock and fuse with the TGN membrane to release their cargo. The process of docking and membrane fusion of transport carriers at the TGN is highly specific and is regulated by specialised molecules such as small GTPase, tethers and t-SNAREs (Sannerud et al., 2003; Bonifacino and Rojas, 2006; Sztul and Lupashin, 2006). Several small GTPase, tethering molecules, and t-SNAREs localised to the TGN have been identified by biochemical and genetic analysis to be essential for fusion of endosome derived transport intermediates (Table 3).

SNARE complexes involved in fusion of endosome-derived transport carriers at the TGN

At least three SNARE complexes have been described which are involved in regulating retrograde transport to the TGN. The use of different t-SNAREs for retrograde transport is likely to reflect the requirements of different SNARE complexes for docking and fusion of transport carriers from the different retrograde transport pathways. These SNARE complexes include firstly the t-SNAREs, syntaxin 6, syntaxin 16 and Vti1a, which can pair with the v-SNAREs VAMP3 or VAMP4 (Mallard et al., 2002), secondly, the t-SNAREs, syntaxin 5, GS15 and GS28 which can pair with the v-SNARE, Ykt6 (Xu et al., 2002; Tai et al., 2004) and a more recently described, third SNARE complex consisting of t-SNAREs, syntaxin 10, syntaxin 16 and Vti1a which can pair with v-SNARE, VAMP3 (Ganley et al., 2008). Some of these SNARE components, in particular syntaxin 6, syntaxin 5, syntaxin 16, Vti1a and VAMP3, can function in more than one SNARE complex (Mallard et al., 2002; Xu et al., 2002; Tai et al., 2004; Murray et al., 2005; Wang et al., 2005; Ganley et al., 2008).

Two SNARE complexes have been implicated in endosome to TGN transport of Shiga toxin. Overexpression of dominant negative mutants of syntaxin 6 and 16 (cytosolic, non-membrane bound form), and more recently the silencing of syntaxin 16 by siRNA blocked retrograde transport of Shiga toxin (Mallard et al., 2002; Amessou et al., 2007; Lieu and Gleeson, 2010). In addition, the silencing of syntaxin 5 and GS15 by siRNA also dramatically reduced the efficiency of endosome to TGN transport of Shiga toxin (Tai et al., 2004; Amessou et al., 2007). It is unclear why two SNARE complexes are involved in retrograde transport of the same cargo. One possibility is that Shiga toxin may utilise multiple endosome-to-TGN transport pathways for its intracellular trafficking, thus different SNARE complexes are required for fusion of transport

intermediates from different retrograde pathways.

Tethering factors

Tethers mediate the initial docking events of transport carriers with their target organelle. Almost all the tethering factors that have been implicated in endosomal-to-TGN transport steps function either as heter-oligomeric complex (GARP, COG and TRAPP-II) or as dimers (golgin 97, p230, GCC185 and GCC88) (Luke et al., 2005; Lupashin and Sztul, 2005; Short et al., 2005; Sztul and Lupashin, 2006). The GARP complex consists of four subunits, Vps51, Vps52, Vps53 and Vps54 and was originally identified in yeast as having a function in the retrograde transport of carboxypeptidase from the endosome to the late Golgi (yeast equivalent of TGN) (Liewen et al., 2005). In mammalian cells, the GARP complex has been shown to be recruited to the TGN by Rab6 (Liewen et al., 2005) and is involved in general tethering of retrograde carriers at the TGN (Perez-Victoria et al., 2008). Silencing of Vps52 using siRNA, or the overexpression of a Vps54 L967Q mutant in HeLa cells resulted in a general block in endosomal to TGN transport of M6P-R, TGN46 and Shiga toxin (Perez-Victoria et al., 2008). The COG complex is another multi subunit tethering complex that consists of eight subunits, subunit COG1-8 (Ungar et al., 2006). In mammalian cells, siRNA depletion of COG3 can also block in retrograde transport of Shiga toxin (Ungar et al., 2006). No role for the TRAPP-II complex has yet been described for endosomal to TGN transport in mammalian cells.

Another potentially important group of tethering factors involved in fusion of endosome-derived transport carriers are the TGN golgins. There are four TGN golgins namely, p230/golgin245 (p230), golgin 97, GCC88 and GCC185 (Golgi Coil-Coiled) in mammalian cells (Erlich et al., 1996; Griffith et al., 1997; Kjer-Nielsen et al., 1999; Luke et al., 2003). Unlike the multi-subunit tethering factors described above, TGN golgins form exclusive homodimers and are localised to distinct regions of the TGN (Derby et al., 2004; Gleeson et al., 2004; Luke et al., 2005).

TGN golgins

TGN golgins have been reported to regulate retrograde transport pathways, possibly acting to tether endosome-derived transport carriers (Lu et al., 2004; Reddy et al., 2006; Derby et al., 2007; Lieu et al., 2007; Jing et al., 2010) or by acting as scaffold molecules to co-ordinator the organisation of membrane domains (Goud and Gleeson, 2010). For example, analysis of the retrograde transport pathways in TGN golgin-depleted cells has revealed that specific transport of the TGN38 and Shiga toxin was regulated by GCC88 and GCC185,

Table 3. Trafficking components involved in docking and fusion of transport intermediates at the trans-Golgi network.

Mammalian proteins	Functional information	Reference
NSF, α-SNAP	Fusion factor that are involved in SNARE complex disassembly	Jahn and Scheller, 2006; Jahn and Scheller, 2006
GS15, syntaxin 5, GS28, Ykt6	SNAREs that form a complex that is involved in retrograde transport of Shiga toxin	Tai et al., 2004; Amessou et al., 2007
Syntaxin 6, syntaxin 16, Vti1a, VAMP3/VAMP4	SNAREs that form a complex that is involved in retrograde transport of Shiga toxin, TGN38 and M6P-R from the early/recycling endosome	Mallard et al., 2002; Amessou et al., 2007
Syntaxin 10, syntaxin 16, VAMP3, Vti1a	SNAREs that form a complex that is involved in retrograde transport of M6P-R from Rab 9 positive late endosome	Wang et al., 2005; Ganley et al., 2008
Rab6A`	Rab GTPase that can recruit the GARP complex to TGN membrane	Mallard et al., 2002; Del Nery et al., 2006; Smith et al., 2009
R6IP1 (Rab6 interacting protein 1)	An interacting protein that associate with both Rab6 and Rab11	Miserey-Lenkei et al., 2007
ARFRP1	Small Arf-like GTPase that is required for recruitment of Arl1 to TGN membrane	Behnia et al., 2004; Shin et al., 2005; Zahn et al., 2006; Nishimoto-Morita et al., 2009
Arl1	Small Arf-like GTPase involved in recruitment of golgin 97 and p230/golgin 245 to the TGN membrane	Lu et al., 2004; Shin et al., 2005; Nishimoto-Morita et al., 2009
golgin 97, p230/golgin 245	TGN golgins that are involved in retrograde transport of Shiga toxin and Cholera toxin	Lu et al., 2004; Yoshino et al., 2005
GCC185	TGN golgin that is involved in retrograde transport of both Shiga toxin and M6P-R	Reddy et al., 2006; Derby et al., 2007
GCC88	TGN golgin that is involved in retrograde transport of both TGN38 and M6P-R	Lieu et al., 2007; Lieu and Gleeson, 2010
COG complex	Component of the COG complex that is involved in retrograde transport of Shiga toxin	Ungar et al., 2006; Smith et al., 2009
GARP complex	Multi-subunit tethering complex that is involved in fusion of TGN46, Shiga toxin and M6P-R at the TGN	Perez-Victoria et al., 2008; Perez-Victoria and Bonifacino, 2009

respectively. In cells lacking GCC185, a specific block in retrograde transport of Shiga toxin and M6P-R but not TGN38 was observed (Reddy et al., 2006; Derby et al., 2007). In GCC185 depleted cells, Shiga toxin did not accumulate in early endosomes but was concentrated in Rab11-positive recycling endosomes, indicating that GCC185 is important for transport between the recycling endosome and the TGN (Derby et al., 2007). A block in retrograde transport in GCC185 depleted cells may also result in a block in recycling of essential trafficking components required for other transport pathways, as indicated by the detection of a late stage block in ER to Golgi transport (Derby et al., 2007).

In contrast to GCC185 depleted cells, different effects in retrograde transport were observed in GCC88-depleted cells. The silencing of GCC88 dramatically reduced the efficiency of endosome to TGN transport of TGN38 and M6P-R. Both TGN38 and M6P-R accumulated in the early endosome in GCC88 depleted cells, suggesting that GCC88 was required for efficient retrograde transport from the early endosomes (Lieu et al., 2007). Unlike GCC185 depleted cells, retrograde transport of Shiga toxin was not affected in GCC88 depleted cells. The kinetics of Shiga toxin transport as well as level of Golgi localised Shiga toxin in GCC88 depleted cells was not significantly reduced compared to control cells, strongly arguing that depletion of GCC88 had no apparent affect on retrograde transport of Shiga toxin from the recycling endosome. The finding that different TGN golgins are involved in specific transport of TGN38 and Shiga toxin is consistent with the proposal that these cargos utilise independent endosome to TGN transport pathways (Lieu et al., 2007; Lieu and Gleeson, 2010).

GCC88 and GCC185 may play a role in the transport of essential trafficking machinery to the endosome, where they are required for retrograde transport of cargos from the endocytic compartments. Alternatively, GCC88 and GCC185 may be effector molecules to mediate the recruitment of specific SNARE molecules required for the docking and fusion of endosome derived transport intermediates. This latter proposal is supported by findings that specific t-SNAREs were mislocalised in either GCC88 or GCC185 depleted cells. In GCC88 depleted cells, syntaxin 6 was redistributed from the TGN into cytoplasmic structures (Lieu et al., 2007) while the depletion of GCC185 resulted in a disruption in the localisation of syntaxin 5 and syntaxin 16 (Lieu and Gleeson, unpublished observations). An interaction between GCC185 and syntaxin 16 was recently reported by immuno-precipitation (Ganley et al., 2008). A lack of SNARE pairing in either GCC88 or GCC185 depleted cells may block fusion of endosome-derived transport intermediates at the TGN, thus blocking retrograde transport of Shiga toxin and TGN38. Overall, these findings indicate that TGN golgins may interact directly or indirectly with specific t-SNAREs to regulate retrograde transport from the early/recycling endosome. Notably, both GCC185 and GCC88 are the first examples in which tethering molecules can influence the localisation of t-SNAREs at the TGN. Interactions of TGN golgins with t-SNAREs would provide a mechanism for the organisation of domains of the TGN to establish hot spots for fusion of incoming retrograde transport carriers.

Conclusion

In summary, retrograde pathways include pathways from the late endosome to the TGN as well as from the early endosomes and recycling endosomes to the TGN. Three distinct pathways have been defined in mammalian cells. It is now clear that multicellular organisms have a greater complexity in their retrograde transport pathways, both in components and number of pathways, than single cell yeast. The evolution of these pathways is likely to reflect specialised functions associated the physiological pathways of multicellular organisms. Further functions for retrograde transport pathways are likely to be discovered by the identification of additional endogenous cargos that use these pathways, particularly in specialised cells.

Understanding retrograde transport pathways is essential for dissection of molecular mechanisms relevant to infection and disease. Retrograde transport pathways are essential for the entry of pathogenic products such as bacterial toxins. Disruption of retromer mediated endosome-to-TGN transport results in perturbation in development (Pan et al., 2008; Port et al., 2008; Yang et al., 2008) and enhancement of production of amyloid plaques associated with Alzheimer's disease (Muhammad et al., 2008). The relevance of retrograde transport in the recycling of amyloid precursor protein and the processing ß-secretases, BACE, needs to be further investigated.

Many machinery components have now been identified which play a role in endosomal sorting and in the regulation of TGN fusion events. However, the co-ordination of the interactions of machinery components to regulate these transport pathways is not well understood. In addition, the sorting signals of cargo required for selective endosome-to-TGN transport are poorly defined. The current information indicates a high degree of specificity in the choice of retrograde transport pathway for individual cargo, implying the existence of transport-specific sorting signals. The mechanisms for sorting in the early endosomes and the generation of transport intermediates for retrograde transport also need to be better characterised. High-resolution imaging will continue to play an important role in the identification of populations of cargo-loaded transport carriers emerging from the early and late endosomes. For example, transport intermediates from the early endosome to the TGN have been reported to arise from the tubular structures of the TSE/TEN (Mari et al., 2008). By 3D electron tomography, these transport intermediates are usually non-branched, short tubules and vesicles without

a clathrin coat, found in close proximity to the early endosome (Mari et al., 2008).

The molecular dissection of retrograde transport pathways will open new opportunities for intervention in health and disease. The recent high throughput screen to identify small molecule inhibitors of retrograde transport that protected mice from a lethal ricin challenge (Stechmann et al., 2010a,b) highlights the potential of these pathways to be selectively targeted for therapeutic intervention.

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