European Journal of Cell Biology 96 (2017) 198–205

Contents lists available at ScienceDirect

European Journal of Cell Biology

journal homepage: www.elsevier.com/locate/ejcb

Review

Traffic from the endosome towards *trans*-Golgi network

Uma Saimani, Kyoungtae Kim*

Department of Biology, Missouri State University, 901 S National, Springfield, MO 65807, United States

ARTICLE INFO

Article history:
Received 28 November 2016
Received in revised form 24 January 2017
Accepted 16 February 2017

Keywords:
Retrograde transport
Endosome
Trans-Golgi network
Tether
SNAREs
Sorting

ABSTRACT

Retrograde passage of a transport carrier entails cargo sorting at the endosome, generation of a cargo-laden carrier and its movement along cytoskeletal tracks towards *trans*-Golgi network (TGN), tethering at the TGN, and fusion with the Golgi membrane. Significant advances have been made in understanding this traffic system, revealing molecular requirements in each step and the functional connection between them as well as biomedical implication of the dysregulation of those important traffic factors. This review focuses on describing up-to-date action mechanisms for retrograde transport from the endosomal system to the TGN.

1. Introduction

Eukaryotic cells have many membrane-bound organelles. Constant communication and exchange of essential proteins and lipids occur between these compartments via intracellular trafficking, essential for cellular homeostasis, signal transduction, and cell viability (Tokarev et al., 2009; Watson et al., 2005). In the last few decades, much attention has been given to understanding intracellular trafficking. This has contributed to an explosive growth in unfolding discrete stages of traffic and identifying molecules that regulate each stage of transport, which has shed light on a mechanistic understanding of intracellular trafficking. For example, a novel lipid PI(3,4)P_2 (phosphatidylinositol-3,4-bisphosphate) was recently identified at the plasma membrane aiding scission and late stages of endocytosis (Posor et al., 2013). This disproves the notion that PI(4,5)P_2 (phosphatidylinositol-4,5-bisphosphate) is the only main phospholipid that regulates endocytosis at the plasma membrane. Emerging information about dynein, a microtubule minus-end directed motor, has been contradicting the traditional model which states that a single microtubule plus-end kinesin motor exerts around six times the force exerted by a dynein monomer necessitating multiple dynein monomers to come together for the cytoskeletal tug-of-war against a kinesin molecule. The new evidence shows that a single dynein forms a complex by interacting with two other non-motor proteins to win the tug-of-war (Belyy et al., 2016b). Results from another study revealed that a novel cytosolic protein, Cornichon-1, interacts with transmembrane ER (endoplasmic reticulum) cargo and allows the cargo to be packaged into Golgi-bound vesicles. The discovery has resulted in a deeper understanding of protein packaging at the ER (Zhang and Schekman, 2016). Such rapid and significant advancement has been possible because of accessibility to cutting edge technology, including multiphoton live cell imaging in conjunction with cell perfusion systems that has helped achieve remarkable progress in deciphering the spatiotemporal dynamics of proteins involved in intracellular trafficking (Atencia and Beebe, 2005; Huang et al., 2015; Tie et al., 2016). However, a limitation of multiphoton imaging is that its resolution is not sufficient for studying subcellular dynamics of proteins engaged in trafficking. This caveat can be overcome by using correlative light and electron microscopy, which provides high-resolution imaging of fluorescently-labeled proteins allowing capture of protein dynamics during trafficking (de Boer et al., 2015). Another high resolution microscopy technique is STED (Super-resolution optical stimulated emission depletion microscopy) that has very recently been used to decipher the morphology and identity of small endocytic organelles(Revelo et al., 2014) and the suborganellar compartmentalization of proteins within the peroxisome in human cells (Galiani et al., 2016). An alternative genetic technique, high-throughput small interfering RNA (siRNA) screen is becoming an increasingly popular tool to identify novel components and regulators involved in intracellular trafficking (Anitei et al., 2014).

Intracellular trafficking is a broad term that describes a diverse spectrum of transport routes within a cell that include endocytosis

* Corresponding author.
E-mail address: kkim@missouristate.edu (K. Kim).

http://dx.doi.org/10.1016/j.ejcb.2017.02.005
0171-9335/

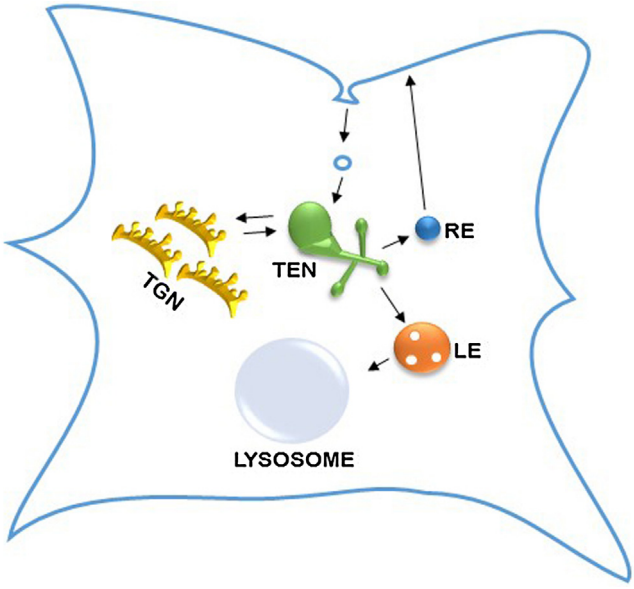

Fig. 1. Different transport routes from and to the early endosome. An endocytosed vesicle fuses with the early endosome (TEN). From the TEN, cargo can be recycled to the membrane through the recycling endosome (RE) or delivered to the lysosome for degradation through the late endosome (LE). The LE contains multiple intraluminal vesicles (ILVs) in its lumen. Some cargoes from the TEN recycle back to the plasma membrane first by passing the TGN, prior to a secretion process toward the plasma membrane. Another major branch of secretion pathway involves delivery of anterograde cargoes to the TEN and then to their final destinations. Overall, the endosome seems to play a pivotal role in connecting the different transport routes occuring within a eukaryotic cell.

by which extracellular materials and its own membrane receptors are internalized (Fig. 1). Endocytosed cargo is targeted to the early endosome from where it follows multiple routes depending on its sorting signals (Besterman and Low, 1983; Du Toit, 2015). Certain cargoes are rapidly recycled from the early endosome to the plasma membrane directly by the fast recycling pathway, or they follow the slow recycling route wherein cargo has to pass through the recycling endosome before reaching the plasma membrane (Fig. 1) (Hao and Maxfield, 2000). The early endosome matures into the late endosome, and cargo from the early or late endosome are targeted to the *trans*-Golgi network (TGN) via the retrograde route (Fig. 1) (Mallard et al., 1998; Rohn et al., 2000). The late endosome eventually fuses with the lysosome to deliver cargo for degradation (Fig. 1) (Bohley, 1995). Lastly, secretory proteins synthesized in the ER pass through the Golgi complex and are then secreted via the biosynthetic route (Rothman and Orci, 1992).

Dysregulation of the components involved in endosome-to-TGN transport is associated with various human diseases. For example, dysfunction of cargo sorting machinery at the endosome is associated with Parkinson's disease (Follett et al., 2016), as well as Alzheimer's disease (Kamagata et al., 2009; Kollmann et al., 2010; Muhammad et al., 2008; Willnow and Andersen, 2013). Therefore, a complete understanding of the molecular mechanism of the retrograde traffic is needed and is of significant biomedical importance. This review aims to provide up-to-date information pertaining to retrograde transport from the endosomal system to the TGN, and will be divided into the following four sections: 1) cargo sorting at the endosome; 2) fission and movement of transport carrier towards the TGN; 3) tethering at the TGN; and 4) fusion at the TGN.

1.1. Cargo sorting at the endosome

Recent studies have revealed that the early endosome is, in fact, a network comprised of two main microdomains including the Tubular Endosomal Network (TEN) and Vacuolar domain (Bonifacino and Rojas, 2006). The latter is a hub for endosome maturation and formation of Intraluminal vesicles (ILVs), which are small vesicles found in the lumen of the late endosome (Fig. 1). The matured, late endosome eventually fuses with the lysosome. The cellular processes of endosome maturation and endolysosomal degradation pathway are discussed in great depth in an article by Curtiss et al. (2007). TEN is comprised of highly tubulated subdomains harboring multiple cargo exit sites. The extension of endosomal membrane with high surface area to lumenal volume ratio makes TEN ideal for exporting cargo (Bonifacino and Rojas, 2006; Burd, 2011). Results from a recent study have shown that the ER has cargo exit sites that don't coincide with its cargo arrival sites (Ackema et al., 2013). The possibility of TEN also having such exclusive sites for cargo import and cargo export opens up an interesting avenue for future research.

A select group of cargo travel from the endosome to the TGN, including mannose 6-phosphate receptors (MPR), Soluble *N*-ethylmaleimide-sensitive factor activating protein receptors (SNAREs), toxins, and other proteins that require continuous retrieval to the TGN for their function. Proper sorting of these cargo at the endosome is essential for the successful endosome-to-Golgi traffic, demanding coat proteins, adaptors, and sorting nexins (Kornfeld, 1992; Pfeffer, 2011). A well-studied coat protein-adaptor pair is clathrin and AP-1. Expression of a mutated version of clathrin or AP-1 resulted in impaired retrieval of the B subunit of Cholera toxin (*CtxB*) from the early endosomes to the TGN (Matsudaira et al., 2015). AP-1 and clathrin also assist sorting of another well-known cargo, MPR, from the late endosome to the TGN (Meyer et al., 2000). There are two variants of MPR: cation-dependent MPR (CD-MPR) and cation-independent MPR (CI-MPR), of which CD-MPR utilizes clathrin and AP-1 for its transport (Schweizer et al., 2000). AP-1 recognizes a di-leucine (D/ExxxLL/I, D-Aspartate, E-Glutamate, x-any amino acid, L-leucine, and I-Isoleucine) and a tyrosine (YxxØ, Y-tyrosine and Ø-any hydrophobic amino acid) sorting motifs on the cytosolic face of the cargo CD-MPR, and then recruits the coat protein clathrin. CD-MPR has an additional Tyr-Phe motif in its cytoplasmic tail that is critical for its endosomal sorting and recognition by AP-1. Clathrin polymerizes to form a protein coat around the extending endosomal tubule, that can then be pinched off by dynamin, whose physiological role will be discussed in the section titled 'Fission and transport to the TGN' (Moore et al., 1987; Progida and Bakke, 2016). AP-1 is primarily known to work at the Golgi, but recent evidence indicates that it also works at the endosome and the plasma membrane (Huang et al., 2001; Owen et al., 2004). While the plasma membrane has an abundant amount of PI(4, 5)P, the endosomal and Golgi membranes comprise PI3P (phosphatidyl inositol-3-phosphate) and PI4P (phosphatidyl inositol-4-phosphate), respectively (Balla, 2016; van Meer and de Kroon, 2011; van Meer et al., 2008). Importantly, AP-1 has an intrinsic ability to bind to these phospholipids, allowing it to be recruited to and function at the corresponding membranes (Heldwein et al., 2004). Regardless of its subcellular location, AP-1, a heterotetrameric adaptor composed of γ, β1, μ1, and σ1 subunits, universally recognizes the dileucine or tyrosine motifs via a selective interaction of its subunit with its cargo

(Lee et al., 2008). For example, the μ1A subunit of AP-1 recognizes the tyrosine motif in the cytosolic face of cargo at the Golgi membrane (Bonifacino and Dell'Angelica, 1999), while its γ/σ1 hemicomplex binds the dileucine motif (Janvier et al., 2003; Traub, 2005). However, the question of whether these subunits of AP-1 recognize, in a similar manner mentioned above, the aforementioned cargo loaded at the endosome remains elusive.

Another well-known coat protein working at the endosome is the retromer complex. The retromer complex was first identified in yeast, and it is functionally dissected into two major subcom-