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Review

trans-Golgi network-bound cargo traffic

Pelin Makaraci, Kyoungtae Kim*

Department of Biology, Missouri State University, 901 S National Ave., Springfield, MO 65807, USA

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ABSTRACT

Cargo following the retrograde trafficking are sorted at endosomes to be targeted the *trans*-Golgi network (TGN), a central receiving organelle. Though molecular requirements and their interaction networks have been somewhat established, the complete understanding of the intricate nature of their action mechanisms in every step of the retrograde traffic pathway remains unachieved. This review focuses on elucidating known functions of key regulators, including scission factors at the endosome and tethering/fusion mediators at the receiving dock, TGN, as well as a diverse range of cargo.

1. Introduction

1.1. Recent advances in membrane trafficking

The communication between membrane-bound organelles is crucial for cell homeostasis (Spang, 2016). Membrane components, such as lipids and proteins that are essential for cell vitality, are transported between membrane-bound compartments via intracellular trafficking (Spang, 2016). Though the morphology of membrane-bound organelles is well studied, the molecular mechanisms behind the trafficking between these compartments are not entirely understood. Advanced microscopic analyses have allowed researchers to characterize the novel function of proteins implicated in trafficking pathways (Miller et al., 2015). For example, the fluorescence resonance energy transfer (FRET) technology was adopted to examine the conformational change of dynamin polymers caused by a structural change occurring in the dynamin pH (Pleckstrin Homology) domain upon binding at the surface of the membrane (Mehrotra et al., 2014). Furthermore, the authors proposed that the structural change in the pH domain contribute negatively to the dynamin-mediated membrane scission process. Another advanced fluorescence microscopy technique is called the stimulated emission depletion (STED) technology, which was developed to overcome the fluorescence microscopy resolution limitation (~200 nm) (van Weering et al., 2010). STED uses two different laser beams, one of which is used to excite the fluorophore and the other laser beam for bleaching the vast majority of fluorophores on the plane of focus, leaving a minimal number of fluorescence probes to be detected, thereby drastically improving the resolution (Hanne et al., 2015). Recently, this STED technology was exploited to resolve the approaching transport vesicle to the close proximity of the TGN tubular structure by visualizing the subcellular localization of TGN46, a marker for the TGN (Wegel et al., 2016). Interestingly, the correlative light-electron microscopy (CLEM) technique uses the labeling power of the fluorescence microscopy and the resolution power of transmission electron microscopy to characterize and visualize the dynamics of subcellular compartments (de Boer et al., 2015). For instance, the ultrastructure of the transport intermediates or carriers derived from the TGN was investigated with the CLEM technique, shedding some insights into the transport mechanism of cargo destined for the plasma membrane (Polishchuk et al., 2000). Recently, a group of researchers has utilized the same technology to reveal the delivery mechanism of transport carriers of uroplakins, originated from the Golgi, toward the plasma membrane (Kreft et al., 2010). Interestingly, they found that Golgi apparatus fragments formed via a nacodazole treatment are present near the vicinity of the plasma membrane to facilitate the uniform delivery of uroplakins to the apical side of uroepithelial cells. The CLEM technology also was employed to investigate the loading of collagen IV into a post-Golgi carrier (Banushi et al., 2016). The authors demonstrated that the sorting of collagen IV is dependent on the presence of VIPAR, a Vps33 B binding partner that is implicated in cargo trafficking toward the plasma membrane.

1.2. Significance of the intracellular trafficking

Dysfunction of the intracellular trafficking can lead to diseases such as Alzheimer's disease that is characterized by the accumulation of amyloid-β (Aβ) in neurons, due to hyperactivation or overproduction of β-site APP-cleaving enzyme 1 (BACE1), which cleaves the amyloid

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

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Table 1
Cargoes traveling from endosomes to the Golgi.

Types of cargoes	Intracellular trafficking	Required cargo type	References
Shiga toxin	Early endosome-to-TGN	Clathrin	Selyunin et al. (2017)
Cholera toxin	Early endosome-to-TGN	Clathrin	Matsudaira et al. (2015)
Ricin toxin	Early endosome-to-TGN	Clathrin	Taubenschmid et al. (2017)
Wntless	Early endosome-to-TGN	The retromer complex	Seaman (2012)
M6PRs	Late endosome-to-TGN	The retromer complex	McKenzie et al. (2012)
Vps10	Late endosome-to-TGN	The retromer complex	Purushothaman et al. (2017)
Sortilin	Early endosome-to-TGN	The retromer complex	Coutinho et al. (2012)
TGN38/46	Early endosome-to-TGN	The retromer complex	Chia et al. (2011)
BACE1	Early endosome-to-TGN	The retromer complex	Zhang and Song (2013)
Furin	Late endosome-to-TGN	Clathrin	Mahajan et al. (2013)

precursor protein for the production of Aβ (Wang et al., 2014). Alternatively, it has been shown that defects in retrograde traffic, involving membrane trafficking from the endosome to the Golgi (Table 1), are associated with Alzheimer's disease (Buggia-Prévot and Thinakaran, 2015). Under this condition, endocytosed BACE1 resides persistently at the late endosome and furthermore, its enzyme activity is triggered by the acidic pH of the environment, resulting in elevated production of Aβ in the lumen of the late endosome (Ye and Cai, 2014). The accumulated Aβ are secreted from the cells via a recycling pathway to promote the Alzheimer's pathological condition (Ye et al., 2017). Therefore, understanding not only the regulation of the BACE1 activity during retrograde trafficking in detail but also other molecular requirements involved in the endosome-to-Golgi retrograde trafficking could be essential to intervene in Aβ production relevant to Alzheimer's disease pathologies (Zhang and Song, 2013).

The following sections are dedicated to the discussion of the main events and key molecules required for retrograde trafficking pathways. The retrograde transport of proteins involves two major intracellular tubular network systems, the *trans*-Golgi network (TGN) and endosomes. Therefore, in the next section the structure and function of the TGN will be discussed, followed by in-depth discussion of the mechanism underlying the endosome-to-Golgi traffic pathway.

1.3. *trans-Golgi network is the center of biological cargo delivery*

The Golgi apparatus, consisting of multiple layers of the saucer-like membrane called cisternae, functions as a key protein sorting and shipping station of cells (Osterrieder, 2012). In higher eukaryotic cells, the Golgi apparatus consists of a stack of 3–20 cisternae (Suda and Nakano, 2012). However, the budding yeast *Saccharomyces cerevisiae* displays a morphology of separately distributed Golgi cisternae throughout the cell (Suda and Nakano, 2012). In eukaryotic cells, rough ER is the synthesis site of ER resident and secretory proteins. Secretory proteins are packed in an ER-derived transport vesicle and delivered from the rough ER to the Golgi complex. The Golgi complex can be separated into five regions: *cis*-Golgi network (CGN), *cis*-, *medial*-, *trans*-Golgi, and *trans*-Golgi network (TGN) (Martínez-Menárguez, 2013). The CGN, situated closest to the ER, is responsible for both receiving ER-derived transport vesicles and shipping ER resident proteins back to the ER (Ishii et al., 2016). The TGN is located on the opposite side of the CGN, towards the *trans*-Golgi, and is involved in the final stage of sorting, packing, and delivering of most of, if not all, secretory proteins to their destinations (Crevenna et al., 2016).

In an exocytic event, cargo-carrying transport vesicles derived from the TGN travel to the plasma membrane. Upon fusion of the vesicle with the plasma membrane, soluble cargoes are secreted out to the extracellular matrix, but for transmembrane proteins, the plasma membrane is their final destination. Many externally located proteins, including collagens and cytokines, are secreted out of the cell via a constitutively active secretion pathway (Malhotra and Erlmann, 2015). However, some specialized cells store soluble proteins or small molecules in secretory vesicles to release on demand, responding to the external signals, and this process is referred to as regulated secretion. For instance, pre-synaptic nerve cells harbor secretory vesicles with neurotransmitters. In the case of binding of a chemical messenger to its receptor at the nerve cell plasma membrane, these vesicles travel toward and fuse with the plasma membrane to release neurotransmitters to the extracellular matrix (Valenzuela and Perez, 2015).

The lysosome is another last stop for the cargo-carrying vesicle emerging from the TGN. Upon delivery, the majority of the cargo are activated to function as hydrolases at the lysosome. For example, α-glucosidase, a lysosomal hydrolase, contains a mannose-6-phosphate (M6P) that serves as a molecular tag for proper sorting at the TGN upon interaction with a cation-independent M6P receptor (CI-M6PR) (Schuller et al., 2013). Upon arrival at the late endosome, α-glucosidase dissociates from the receptor due to an acidic environment established in the lumen of the late endosome (Coutinho et al., 2012). CI-M6PR is then retrieved back to the TGN for the next round of cargo delivery (Table 1) (Schuller et al., 2013). In the budding yeast *Saccharomyces cerevisiae* function to coordinate, two parallel traffic pathways function to coordinate the delivery of cargo destined for the vacuole. Vacuolar enzymes of carboxypeptidase Y (CPY) and carboxypeptidase S (CPS) are first delivered to the endosome and then to the vacuole. In contrast, alkaline phosphatase (ALP) is directly transported to the vacuole from the TGN (Table 1) (Feyder et al., 2015). In particular, a soluble protease CPY is sorted in the lumen of the TGN with the help of its receptor Vps10 and transported to the endosome where CPY is dissociated from the receptor (Feyder et al., 2015). Vps10 recycles back to the TGN via a retrograde trafficking pathway (Table 1), whereas CPY-carrying endosomes fuse with the vacuole to release the cargo.

1.4. *Diverse range of cargo for the endosome-to-Golgi retrograde pathway*

Internalization of extracellular materials along with the plasma membrane receptors on the cell occurs via a process called endocytosis (Irannejad et al., 2014). Post-endocytosed vesicles undergo a homotypic fusion with one another to form the early or sorting endosome, which matures into the late endosome by recruiting more Rab7 GTPase (Hegedus et al., 2016; Rink et al., 2005). Endosomes act as a central hub for protein traffic coming from endocytic and biosynthetic pathways, and for outgoing traffic to the plasma membrane. The latter includes at least three different routes, a fast recycling that rapidly occurs between the early endosome and the plasma membrane, a slow recycling that involves recycling vesicles, and lastly the retrograde trafficking that requires Golgi involvement (Schindler et al., 2015). Different Rab GTPases are implicated in these recycling events, but detailed mechanisms of cargo selection and loading are poorly understood. Furthermore, the molecular requirements necessary for the release or pinching-off of the cargo-carrying vesicle remain elusive. The outgoing traffic from the endosome to the Golgi, the retrograde pathway, will be discussed comprehensively in this section.

The endosome-to-Golgi retrograde pathway is a crucial step for