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Review

From endosomes to the *trans*-Golgi network

Lei Lu[a,*], Wanjin Hong[b,c]

[a] School of Biological Sciences, Nanyang Technological University, 60 Nanyang Drive, Singapore 637551, Singapore
[b] Institute of Molecular and Cell Biology, 61 Biopolis Drive, Proteos, Singapore 138673, Singapore
[c] School of Pharmaceutical Sciences, Xiamen University, Xiamen, People's Republic of China

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ABSTRACT

The retrograde trafficking from endosomes to the *trans*-Golgi network (TGN) is one of the major endocytic pathways to divert proteins and lipids away from lysosomal degradation. Retrograde transported cargos enter the TGN via two itineraries from either the early endosome/recycling endosome or the late endosome and involve various machinery components such as retromer, sorting nexins, clathrin, small GTPases, tethering factors and SNAREs. Recently, the pathway has been recognized for its role in signal transduction, physiology and pathogenesis of human diseases.

Contents

Abbreviations: AD, Alzheimer disease; AP1, adaptor protein 1; APP, amyloid precursor protein; BAR, Bin/Amphiphysin/Rvs; CD-M6PR, cation-dependent mannose-6-phosphate receptor; CI-M6PR, cation-independent mannose-6-phosphate receptor; COG, conserved oligomeric Golgi complex; GRIP, Golgin97-RanBP-Imh1p-p230 *trans* Golgi protein; CTxB, Cholera toxin B fragment; EE, early endosome; EHD1, eps15 homology domain 1; EpsinR, Epsin related protein; ER, endoplasmic reticulum; FKBP, FK506 binding protein; FRB, FKBP rapamycin binding protein; GARP/VFT, Golgi associated retrograde protein complex/Vps fifty-three; GGA, Golgi localized, γ-ear containing; ARF, interacting protein; LDL, low-density lipoprotein; LE, late endosome; MTOC, microtubule organizing center; NSF, *N*-ethylmaleimide-sensitive factor; OCRL1, oculocerebrorenal syndrome of Lowe protein 1; PACS1, phosphofurin acidic cluster sorting protein 1; PE, Pseudomonas exotoxin; PI(3)P, phosphotidylinositol 3-phosphate; PI(3,5)P_2, phosphotidylinositol 3,5-bisphosphate; PI(4)P, phosphotidylinositol 4-phosphate; PI(4,5)P_2, phosphotidylinositol 4,5-bisphosphate; PM, plasma membrane; RE, recycling endosome; SNAP, soluble NSF attachment protein; SNARE, soluble NSF attachment protein receptor; SNX, sorting nexin; STxB, Shiga toxin B fragment; Syn, Syntaxin; TGN, *trans*-Golgi network; WASH, Wiskott–Aldrich syndrome protein and SCAR homolog.

* Corresponding author at: SBS-03n-18, School of Biological Sciences, Nanyang Technological University, 60 Nanyang Drive, Singapore 637551, Singapore.
Tel.: +65 6592 2591; fax: +65 6791 3856.
E-mail address: lulei@ntu.edu.sg (L. Lu).

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In recent years, the endosome-to-TGN trafficking has been recognized as one of the major retrograde pathways and received significant attention. This review focuses on our general understanding of this retrograde trafficking pathway in mammalian cells. Additional details and discussions can be found in several excellent reviews published recently [1–4].

1. Introduction of the endosome-to-TGN trafficking

1.1. The pathway to recycle the secretory machinery

In the secretory or biosynthetic pathway, cargos targeted to the endoplasmic reticulum (ER) sequentially pass through Golgi cisternae to the *trans*-Golgi network (TGN). The TGN is a hub of the membrane trafficking network of a mammalian cell. By default, secretory cargos are constitutively delivered to the plasma membrane (PM) for exocytosis. Alternatively, cargos with sorting signals could diverge from this default route to reach endosomes via the TGN-to-endosome pathway. The reverse pathway, the endosome-to-TGN trafficking, serves as an essential pathway to recycle the secretory machinery components, such as cargo adaptors or receptors. For example, lysosomal hydrolases are luminal soluble enzymes that are synthesized in the ER. Newly synthesized hydrolases acquire mannose-6-phosphate (M6P) modification once they are delivered to the Golgi apparatus. M6P acts as a unique sorting signal that is recognized by the M6P receptor (M6PR) at the TGN. When lysosomal hydrolases reach the TGN, the association between M6PR and M6P results in lysosomal hydrolases being packed into transport carriers destined for lysosomes via endosomes (the TGN-to-endosome pathway). Once delivered to endosomes, the acidic environment of endosomal lumen releases hydrolases from the M6PR. As endosomes mature to become lysosomes, hydrolases accumulate and become activated in lysosomes. Complimentary to this TGN-to-endosome pathway, the endosome-to-TGN trafficking retrieves M6PR back to the TGN for further rounds of loading of hydrolases [5] (Fig. 1). Failure in the retrieval of the M6PR results in the secretion of lysosomal hydrolases into the extracellular space instead of the lumen of lysosomes, leading to aberrant lysosomal functions.

1.2. The pathway to diverge from lysosomal degradation

In the endocytic pathway, cargos on the PM are internalized to the early endosome (EE) or the sorting endosome, which, by default, gradually matures to become the late endosome (LE). The LE eventually becomes a lysosome by fusing to existing lysosomes, resulting in the degradation of cargos in the lysosome lumen. Cargos can be selectively salvaged from the degradation fate by two major recycling pathways: (1) the endosome-to-PM pathway, including the one via the recycling endosome (RE), and (2) the endosome-to-TGN pathway, including those from the EE, the RE and the LE (Fig. 1). Because of the central position of the TGN, cargos recycled via the endosome-to-TGN pathway could further access a variety of organelles of secretory and endocytic pathways. The endosome-to-TGN pathway can be hijacked by exogenous pathogens for targeting to their destined organelles. For example, Shiga toxin, Cholera toxin and Ricin evade lysosomal degradation after endocytosis by the endosome-to-TGN pathway before reaching the ER for its cytotoxic effects (see Section 3.2) [6]. Inhibition of retrograde trafficking pathways provides an effective therapeutic strategy to combat the infection of these toxins. For example, the treatment with the inhibitor of the retrograde trafficking, manganese [7], which is specific to Shiga toxin, or the small molecular compound Retro-1 or 2 [8], protects cultured cells or animals from toxic effects of these toxins.

2. Two endocytic pathways leading to the TGN

The EE/RE-to-TGN and the LE-to-TGN pathways have been proposed as two major endocytic itineraries leading to the TGN. They were originally defined and represented by Tac-TGN38 and Tac-furin [9,10] (Fig. 1), which are the fusion of two type I transmembrane proteins, the extracellular domain of interleukin 2 receptor α subunit (Tac) and the cytosolic domain of rat TGN38 or furin. Shortly after endocytosis, both Tac-TGN38 and Tac–furin first reach the EE. However, their subsequent itineraries differ. A significant amount of Tac-TGN38 enters the RE or the endocytic recycling compartment. The RE comprises of a cluster of membrane tubules localized around the microtubule organizing center (MTOC) and the Golgi complex. In contrast, the EE is mainly peripherally distributed. From the RE, a fraction of Tac-TGN38 recycles back to the PM while the rest enters the TGN. Although the significance of the RE in the endosome-to-TGN trafficking of TGN38 is challenged by recent findings [11], it is agreed upon that TGN38 reaches the TGN without passing through the LE. Beside TGN38 (or TGN46 in human), the cation-independent (CI)-M6PR [12,13] and Shiga toxin B fragment (STxB) [11,13,14] have also been well documented to utilize similar trafficking itineraries and often serve as markers for the EE/RE-TGN pathway. The endocytic itinerary of Tac-furin is different from Tac-TGN38. Tac-furin remains in the same compartment when the EE matures to become the LE, from which it enters the TGN via the LE-to-TGN pathway, bypassing the RE [10,15].

Endocytic trafficking involves dynamic and continuous maturation of endosomal compartments. The EE, the RE and the LE represent endosomal compartments of different maturation stages and thus clearly defined boundaries among them do not exist. Hence, it is possible that the retrograde trafficking of a cargo to the TGN takes place continuously during the EE to LE maturation, with some cargos predominantly sorted at the EE while others at the LE. Supporting this view, it has been documented that a certain amount of furin and CI-M6PR could also be sorted to the TGN from the EE and the LE, respectively [15–17] (also see Section 5.1.4).

3. Cargos utilizing the endosome-to-TGN trafficking

Although the TGN-to-PM trafficking is rapid and generally considered to be by default, most PM membrane cargos do not take retrograde routes back to the TGN as revealed by monitoring the re-sialylation (a TGN specific enzymatic reaction) of de-sialylated surface membrane proteins [18]. This finding indicates that the endosome-to-TGN pathways could be restricted to privileged cargos. On the other hand, almost all yeast membrane proteins residing on the late Golgi (equivalent to the TGN in mammalian cells) cycle between endosomes and the TGN [19–21], suggesting there could be a vast range of cargos utilizing the endosome-to-TGN trafficking pathway in mammals. The repertoire of mammalian cargos transiting this pathway is expanding rapidly. A list of cargos discussed in this review, which is by no means exhaustive, is included in Table 1. Both proteins,

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