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The pathways of secretory cargo export at the endoplasmic reticulum

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Palade's original model proposed that secretory cargo is transported between stable compartments via vesicles. However, recent findings challenge this view, suggesting that secretory pathway compartments are dynamic, with cargo itself dictating whether transfer occurs via vesicles or through the continuity and maturation of compartmental structures. At the heart of this process is TANGO1, a key component of a molecular machine that works in concert with COPII proteins to construct export routes tailored to the size and quantity of secretory cargo.

George Palade's pioneering observations in rat pancreatic acinar cells revealed that newly synthesized proteins in the endoplasmic reticulum (ER) are transported to the Golgi apparatus, where they accumulate in large granules before being released to the extracellular space. He also noted the presence of small vesicles near the ER and Golgi cisternae. Drawing on these observations, Palade proposed that vesicular intermediates shuttle cargo between distinct compartments of the secretory pathway, specifically along a route from the ER to the Golgi apparatus and then to the plasma membrane[1]. Subsequent studies provided critical support for Palade's hypothesis on vesicle-mediated protein traffic. Roth and Porter demonstrated that yolk protein uptake in mosquito oocytes involved specialized membrane vesicles[2]. This was followed by the discovery by Brown, Goldstein, and Anderson that LDL-LDL receptor complexes are packaged into small, coated vesicles, which bud from the plasma membrane and undergo endocytosis[3]. These findings offered conceptual proof of vesicle-mediated trafficking of cargo between membrane-bound compartments. The later identification of Clathrin, COPI, and COPII vesicles further elucidated the mechanisms underlying vesicle-mediated transport within both endocytic and secretory pathways[4–7].

It is estimated that approximately one-third of the human genome encodes proteins that enter the ER, with the vast majority of these newly synthesized proteins exiting the ER on their journey to final destinations, either within the cell or for secretion into the extracellular space. Understanding the pathways and mechanisms by which cells export newly synthesized proteins—ensuring their delivery in the correct quantities and at the appropriate times—is of fundamental importance.

A nagging concern

The size of a COPII vesicle, with a 60 nm diameter, which transports secretory cargo from the ER to the Golgi complex, raises questions about how cells transport some of its most abundant and bulkiest cargo molecules, such as collagens, mucins, and lipoprotein particles. Humans, for instance, produce 28 different types of collagen, constituting 15–20% of the dry protein weight of the human body[8,9]. Additionally, humans secrete approximately a liter of mucin daily[10], and plasma cells can secrete thousands of antibody molecules per second[11,12]. Thus, how are cargoes that are too large to fit into COPII-coated vesicles, or those secreted in exceptionally large amounts, exported from the ER?

TANGO1

A genome-wide screen in *Drosophila* S2 cultured cells identified genes required for the secretion of an artificially engineered signal sequence-bearing horseradish peroxidase (ss-HRP)—a protein for which no specific receptor is expected for its exit from the ER through the secretory pathway. This screen identified the *SEC* genes previously known to be required for protein secretion[13], but of particular interest were genes that had not yet been assigned a function in the yeast secretory pathway and those that affected the organization of Golgi membranes[14]. Collectively, these genes were given the acronym *TANGO*, for Transport ANd Golgi Organization[14]. One of these *TANGO* genes was selected for further analysis and became known as *TANGO1*. Identification of new metazoan genes that affected the secretion and morphology of the Golgi complex was logical because, such cells face different challenges, particularly relating to the secretion of proteins that comprise the extracellular matrix. Secretory mechanisms may

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have, therefore, added novel components or changed modules. Also, in metazoans, the spatial organization of ER and Golgi membranes is linked to the balance of traffic between these compartments. For example, blocking transport from the ER with compounds such as Brefeldin A (BFA) causes a rapid relocation of Golgi membranes into the bulk of the ER[15]. Treatment with Ilimaquinone (IQ) causes complete vesiculation of the Golgi apparatus[16]. The effects of both BFA and IQ are readily reversible. The dynamic nature of these secretory compartments is further exemplified during mitosis in mammalian cells. The Golgi membranes undergo extensive fragmentation during mitosis, and the Golgi apparatus in the daughter cells is rebuilt from the Golgi membrane fragments, growing in size by acquiring additional material from the ER in post-mitotic cells[17,18]. An understanding of the activities that control the organization of the ER-Golgi interface and the organization of the respective compartments of the secretory pathway remains a challenge.

TANGO1 is required for secretion of collagens and other large molecules

Depletion of TANGO1 protein prevents the export of collagen VII from the ER[19]. Subsequent studies revealed that the deletion of the *TANGO1* gene in flies, zebrafish, and mice inhibits the secretion of several collagens[20–23]. Additionally, the loss of a TANGO1-like protein in worms results in the retention of vitellogenin in the ER[24]. A TANGO1 paralog called TALI, working in conjunction with TANGO1, is required for the export of ApoB-containing lipid particles from the ER[25,26]. In zebrafish, the loss of both TANGO1 and TALI is lethal, while the loss of either protein leads to the tissue-specific retention of certain bulky cargoes[22]. To date, two different types of mutations in human TANGO1 have been identified. One class produces a splice variant that, when expressed in cells already producing the endogenous full- length TANGO1, reduces collagen export. Patients with this mutation exhibit features associated with collagenopathies, as well as mental retardation[23]. The other class of mutation results in a complete loss of the protein, leading to fetal death at 14 weeks post-fertilization in humans[27]. Together, these findings confirm the essential role of TANGO1 and its isoforms in the export of collagens and ApoB-containing lipid particles from the ER.

The structure of TANGO1

TANGO1 is a transmembrane protein that resides in specialized domains within the otherwise contiguous ER called exit sites (ERES). At the ERES, TANGO1 assembles into a ring-like structure, but how TANGO1 localizes to these ER exit sites is not yet known. TANGO1 consists of three major parts, each playing a distinct role in its organization and function. The cytoplasmic-facing portion of TANGO1 comprises three distinguishable domains. At the C-terminus, a proline-rich domain binds to the COPII proteins Sec23 and Sec16. This is followed by a coiled-coil domain that interacts with a TANGO1 paralog called cTAGE5. Another coiled-coil domain, located proximal to the ER membrane, binds to TANGO1 itself, promoting oligomerization. This domain also contains a short stretch of 45 residues that binds to the NAG-RINT1-ZW10 (NRZ) tethering complex, thereby linking TANGO1 to the membranes of the ER- Golgi intermediate compartment (ERGIC)[28,29]. Within the membrane, TANGO1 has a full transmembrane domain (TM) followed by a short loop in the ER lumen, which is likely inserted into the inner ER membrane leaflet (IM). The primary function of the TM-IM is to provide a tight seal within the ER membrane, compartmentalizing the ER at the exit site[30]. The luminal part of TANGO1 is mostly unstructured, except for a few short coiled-coil domains and an SH3-like domain. The SH3-like domain binds collagens via a protein called Hsp47[31], although not all collagens bind to Hsp47, and Hsp47 is not expressed in flies and yet secrete collagen. TANGO1 has also been shown to bind directly to collagen IV[32]. Additionally, TANGO1 and TALI are required for the secretion of ApoB-containing lipid particles, and TANGO1 is essential for the secretion of mucins[25,26,33]. While the exact mechanism by which TANGO1/TALI recognizes these other cargoes remains unknown, it is likely that TANGO1, either directly or indirectly (through specific adapters), has the capacity to collect bulky secretory cargoes.

Coated vesicles and tunnels for cargo export from the ER

While small COPII-coated vesicles are clearly essential for the export of secretory cargo from the ER in yeast, at least one report suggests that early Golgi cisternae may directly contact the ER, potentially extracting cargo through a “hug and kiss” mechanism rather than relying solely on COPII-coated vesicles formation and release[34]. It has been a difficult challenge to visualize COPII-coated vesicles in animal cells. It is possible that these vesicles shed their coats soon after dissociating from the ER, which could explain the frequent observation of numerous uncoated vesicles near the ER.

Nevertheless, small COPII vesicles cannot export bulky, metazoan-specific cargoes. Recent work from several groups indicates that the trafficking of such large, vital secretory products likely occurs through long tubules or tunnels[35–38]. Tubules filled with cargo, including small molecules, like TNF-alpha, have been observed attached to the ER[36]. Another possibility is that ERGIC membranes fuse with the membrane ringed by TANGO1[39], creating a tunnel between the ER and the ERGIC. Modeling and simulations of TANGO1’s function estimate that such a tunnel could propel collagen between the ER and ERGIC at a rate of 1 nanometer/sec in the anterograde direction, consistent with observed physiological demand[40].

Two distinct classes of ER exit sites

Recent studies have shown that optically trapping TANGO1 and Sec23 at ER exit sites arrests all cargo exports from the ER. Interestingly, bulky collagens, such as collagen VII and collagen I, are arrested at only 40% of ER exit sites (ERES), while small molecules like signal sequence -Green Fluorescent protein (ss-GFP) and pancreatic adenocarcinoma upregulated factor (PAUF) are retained at nearly 80% of these sites. This finding suggests that although small molecules can exit through most portals, the export of collagens is more restricted and limited to less than half of the total exit sites[41].

Such observations imply the existence of at least two distinct exit routes: one supports the export of small secretory cargo via COPII-coated vesicles, and another is dedicated to the export of bulky cargo through tunnels. The use of these exit routes likely depends on the cell type and the cargo load. For example, dermal fibroblasts that secrete large amounts of collagen might predominantly use tunnels. Conversely, a B-cell, which typically secretes few if any larger cargoes, could utilize small COPII-coated exit sites, but might switch to tunnels when primed to secrete copious amounts of antibodies, using sites specifically dedicated to the export of large or abundant cargoes (Fig. 1). It remains to be demonstrated that the two categories of exit sites are in fact molecularly distinct.

The fate of long tubules or tunnels once packed with large cargoes

It is reasonable to assume that once a long tubule is packed with large cargoes, it is severed from the ER exit site (ERES) by a mechanism similar to that used for cutting small COPII-coated vesicles. Recycling cargoes are then extracted from this tubule, which is a composite of the ERES and ER-Golgi intermediate compartment (ERGIC), and returned to the ERGIC or ER via COPI-coated vesicles. This scenario likely explains the presence of COPI coats on long tubules observed emanating from the ER as visualized using light microscopy[36]. The remaining tubule subsequently fuses with the *cis*-Golgi cisterna. In this model, COPII-coated vesicles budding from one class of exit sites

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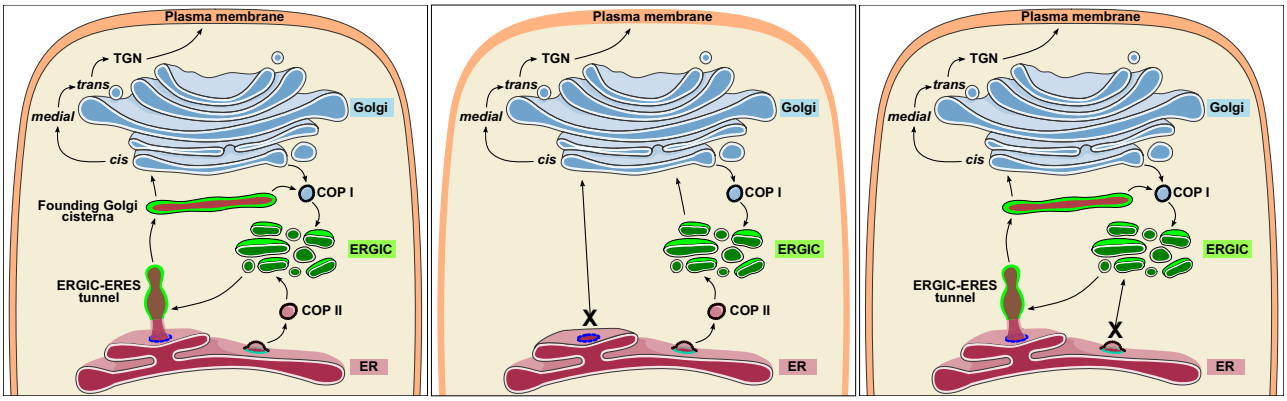

Fig. 1 | Cargo dictates the composition of the secretory pathway. In metazoans, the secretion of large cargoes in substantial quantities cannot be managed by standard COPII vesicles alone. Data suggest that export sites at the ER are segregated, with ~40% of the sites dedicated to the export of bulky molecules like collagens. The transport in bulk of large cargoes, such as collagens, mucins, lipoprotein particles, and antibodies, is mediated by tunnels. Once a tunnel is filled with cargo, its connection to the ER exit site (ERES) is severed. It remains unclear whether this cargo-filled saccule fuses with the *cis*-Golgi cisterna or matures until it consists solely of cargo destined for secretion. In most cell types, both types of exit sites are utilized: small cargoes are exported via COPII vesicles, while large cargoes like collagens are transported via tunnels (**left panel**). However, depending on the cell type, there may be a preference for one type of exit site over the other (**middle and right panels**).

deliver their content to the ERGIC. A pool of ERGIC then fuses with the ERES, and the ERES-ERGIC composite is cleaned up by COPI-mediated recycling.

ERGIC: the cellular bank of membranes

ERGIC is characterized by the presence of specific recycling receptors, such as ERGIC-53. ERGIC receives membranes from the Golgi cisterna via COPI-coated vesicles, and the ER via COPII vesicles. ERGIC is typically visible as a collection of tubules and vesicles, likely representing uncoated COPI and COPII vesicles that are in transit and destined to fuse, forming larger tubules. These ERGIC tubules and vesicles then fuse with the ERES to generate saccules for the trafficking of bulky cargoes[38]. ERGIC membranes are also reported to function in providing membranes for the production of autophagosomes[42]. A new emerging theme is the involvement of ERGIC membranes in the trafficking of proteins that are secreted without entering the conventional ER-Golgi pathway. For example, interleukin 1ß is reported to translocate into ERGIC membranes as the entry point for its pathway of secretion from cells[42,43]. Interestingly, recent research has shown that even in a unicellular eukaryote like yeast, there is an equivalent of the ERGIC, which likely shares the same origin and function as its metazoan counterpart[44]. Thus, ERGIC emerges as a cellular bank that builds credit, in terms of membranes, by receiving COPI and COPII vesicles. This pool of ERGIC membranes is then supplied to cellular processes for producing secretory and degradative intermediates.

Targeting TANGO1 for skin scarring and fibrosis pathologies

Collagen hypersecretion is a significant issue in wound response, leading to scarring and tissue fibrosis. Membrane-permeant peptides that target the TANGO1-cTAGE5 interface have been shown to reduce collagen secretion in primary human dermal fibroblasts, and in collagen-hypersecreting, fibrotic cells from patients with scleroderma. Moreover, in a zebrafish model of wound healing, these peptides reduce collagen deposition and slow the migration of granulocytes. Interestingly, the peptides predominantly inhibit the secretion of collagens and extracellular matrix (ECM) components such as fibronectin and laminin, while membrane metalloproteinase 1 is hypersecreted. These findings strongly suggest that TANGO1 and its binding partner cTAGE5 can be targeted to alleviate collagen-related human pathologies, such as scarring and fibrosis[45]. Additionally, the data support the recent proposal that small and large cargoes prefer different routes for their export from the ER[41], although it is equally possible that the small secreted molecules simply don't require TANGO and cTAGE5 machinery.

What's next?

While significant progress has been made, many key questions remain unanswered. Nonetheless, recent advances indicate that our current understanding of the secretory pathway differs from Palade's original model of stable compartments communicating solely through vesicle trafficking between those depots. In reference to the ER-Golgi body segment of the secretory pathway, the following critical questions remain unresolved:

1. How is the ER compartmentalized into exit sites?
2. How are exit sites selected by cargo, or what distinguishes ERES or their choice of cargo for export?
3. Is TANGO1 specifically involved in the export of bulky proteins, and is the defect in the secretion of certain small proteins due to TANGO1's role in organizing the ER exit site?
4. How does TANGO1 pack cargo into exiting tunnels, and how are these tunnels sensed as fully packed with cargo?
5. How are tunnels loaded with cargo detached from the ERES and moved forward while leaving TANGO1 at the exit site?
6. What is the fate of the ER-ERGIC composite saccule containing the large cargo? Does it fuse with the first cisterna of the Golgi apparatus, or does it continue to mature and ultimately fuse with the plasma membrane?
7. The loss of TANGO1 results in the abnormal export of TMED receptors to the cell surface—locations where they are typically not present[46]. This suggests that TANGO1 plays a critical role in maintaining the proper localization and function of these proteins by regulating their intracellular transport. How different regions of TANGO1 work together as a coordinated system to organize and execute these functions remains to be further explored.
8. To what extent do conventional, COPII vesicles contribute to protein export from the ER?
9. The regulation of ERES-specific proteins by kinases and mechanical forces is an emerging area of interest. However, the precise timing, location, and mechanisms by which these processes are employed in response to physiological conditions remain to be clarified[47–54].

In summary, TANGO1 acts as a molecular machine that orchestrates several crucial processes: it constructs ER exit sites, facilitates

the export of large cargo from the ER, and helps retain specific proteins within the ER by regulating their trafficking pathways. Notably, no TANGO1-like molecules are found beyond the ER exit sites, underscoring the importance of this step in sorting, packaging, and exporting cargo along the secretory pathway in accordance with cellular physiology.

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The author declares no competing interests.

Additional information

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