Sorting and Export of Proteins at the Endoplasmic Reticulum

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Secretory proteins are transported from the endoplasmic reticulum (ER) to the Golgi complex in carriers that are formed by the concerted activities of cytoplasmic proteins in the coat protein complex II (COPII). COPII was first described in *Saccharomyces cerevisiae* and its basic functions are largely conserved throughout eukaryotes. The discovery of the TANGO1 (transport and Golgi organization 1) family of proteins is revealing insights into how cells can adapt COPII proteins to reorganize the ER exit site for the export of the most abundant and bulky molecules, collagens.

Eukaryotic cells are subdivided into functionally distinct membrane-bound organelles and the controlled sorting and trafficking of proteins between them is central to the regulation of cellular function. The endoplasmic reticulum (ER) is the largest organelle in the cell and is a major site of protein synthesis and transport, protein folding, and lipid synthesis.

In the ER, newly synthesized proteins undergo a series of modifications and encounter several molecular chaperones, which together assist proteins in their folding and release from the ER. Proteins receive post-translational modifications (PTMs) including *N*-linked glycosylation, disulfide bond formation, proline isomerization, and oligomerization. The ER is enriched in chaperones that help proteins fold and achieve their quaternary structure. Defects in folding and assembly are controlled in the ER and misfolded proteins are degraded by ER-associated degradation (ERAD) by extraction of clients into the cytoplasm or by degradation in lysosomes.

COMPARTMENTS OF THE SECRETORY PATHWAY AND VESICLES AS TRANSPORT INTERMEDIATES

George Palade's microscopy-based analyses of highly secretory, pancreatic acinar cells revealed the pathway followed by secretory proteins from the ER to the Golgi complex and on to the cell exterior. This schema of vesicle-mediated traffic of secretory cargoes has laid the foundation for a molecular understanding of inter-organelle protein traffic (Fig. 1).
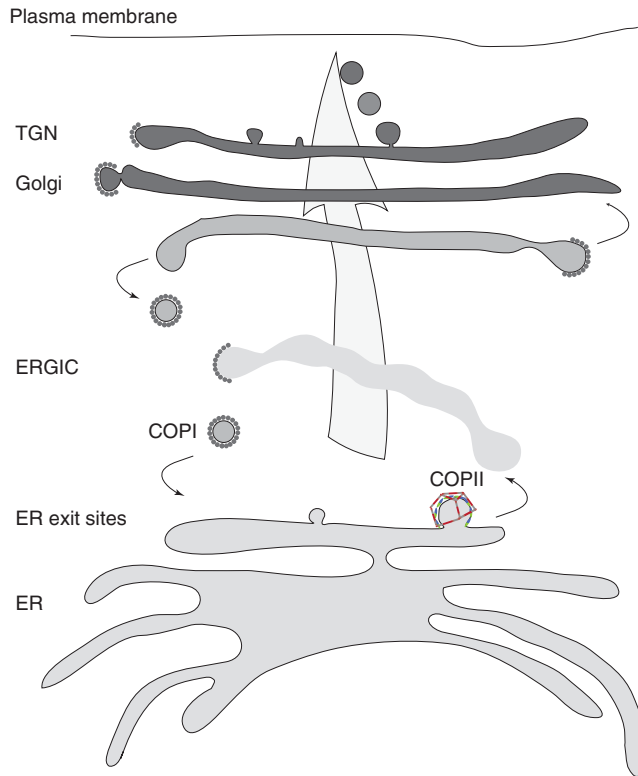
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Figure 1. The secretory pathway. A schema based on a foundation laid by George Palade's classical electron microscopic characterization of the cellular secretory pathway. Secretory proteins are synthesized and folded in the endoplasmic reticulum (ER). They then gather at specialized subdomains of the ER called ER exit sites, marked by coat protein complex II (COPII) proteins. In the conventional model, proteins are packaged into COPII-coated vesicles, which detach from the ER and fuse with the next compartment, the ERGIC (ER-Golgi intermediate compartment) and thence on through the Golgi apparatus to their final destination. Materials that need to be retrieved are packaged into a similar class of vesicles called COPI-coated vesicles for their retrograde transport to the ER.

Subsequent landmark genetic studies and in vitro reconstitutions have revealed that ER-to-Golgi bidirectional cargo transport is performed by concerted activities of coat protein complexes, coatomer proteins (COP), COPI, and COPII. These are cytoplasmic proteins, which are recruited to the site of cargo export, and assemble into lattices to sculpt membranes and produce vesicles of uniform size and shape. A framework for how cytoplasmic proteins called coatomers might assemble into a stereotypical lattice and mediate carrier formation was available from landmark studies on clathrin-dependent endocytosis (Pearse 1976; Goldstein et al. 1979) and COPI-mediated intra-Golgi transport (Orci et al. 1986; Malhotra et al. 1989; Serafini et al.

1991a,b; Waters et al. 1991). COPI coatomers function at the Golgi, controlling formation of COPI-coated vesicles for intra-Golgi transport, and for retrograde trafficking from the Golgi to the ER. Exiting the ER by COPII-coat-dependent carriers is the subject of this review.

The initial description of the COPII-coated vesicle as an ER-Golgi transport intermediate was based on studies in *Saccharomyces cerevisiae* and described the assembly of a 10-nm-thick electron dense coat on vesicles of ∼60 nm diameter. As secretory cargoes increase in size and complexity through evolution, COPII machinery has adapted concomitantly. Unlike *S. cerevisiae*, the activity of COPII is constrained at specialized subdomains of the ER called ER

exit sites (ERES) (Orci et al. 1991; Bannykh et al. 1996).

Mammalian cells have ∼300 ERES, which are distributed throughout the ER with 60% closely apposed to the Golgi apparatus (Hammond and Glick 2000). ERES, also called transitional ER (tER) is collection of tubulovesicular membranes and COPII-coated buds emanating from the ER in metazoans, but their definition and organization remains unclear in yeast. Studies in plant, *Pichia pastoris*, and mammalian cells suggest that an ERES should be viewed as part of an integrated unit together with the associated post-ER compartment such as the ER Golgi intermediate compartment (ERGIC) in metazoans (Ito et al. 2012, 2017; Glick 2014; Robinson et al. 2015).

The ERGIC is composed of tubules and vesicles, is defined by the presence of the transmembrane protein ERGIC-53 (Schweizer et al. 1988). ERGIC is likely to be a sorting station that controls trafficking between the ER and the Golgi. Interestingly, it has also been shown recently to provide membranes for the biogenesis of other cellular organelles such as autophagosomes (Ge et al. 2013).

COPII AND VESICLE FORMATION AT THE ER

A density-enrichment screen identified 23 complementation groups required for protein secretion in yeast (Novick and Schekman 1979; Novick et al. 1980). Molecular analyses of these *SEC* genes allowed the Schekman group to delineate distinct stages of biosynthetic protein secretion from the ER to extracellular space. Genetic analyses and cell-free reconstitution assays from these and further studies placed Sar1, Sec12, Sec16, Sec23/24, Sec13/31 in steps leading to COPII vesicle biogenesis and cargo export from the ER.

COPII-Coated Vesicle Formation

The small GTPase (Sar1) is recruited to a site at the ER membrane by the transmembrane guanine nucleotide exchange factor (GEF) Sec12 (Nakano et al. 1988; Barlowe and Schekman 1993). GTP-bound Sar1 exposes its amphipathic amino terminus, which is inserted into the ER membrane, thereby generating curvature (Bielli et al. 2005; Lee et al. 2005). Membrane-bound Sar1 recruits an inner layer of the COPII coat, composed of Sec23/24 heterodimers (Hicke et al. 1992). Sec23 is a GTPase activating protein (GAP) for Sar1 and provides an arginine into the GTP binding site of Sar1 to facilitate GTP hydrolysis (Yoshihisa et al. 1993). The inner coat then recruits an outer COPII layer composed of heterotetramers of Sec13/31 that assembles into an intrinsically curved, polyhedral lattice. Sec31 provides a tryptophan residue to the catalytic site of Sar1 that further stimulates the GAP activity of Sec23 (Antonny et al. 2001). GTP hydrolysis is directly linked to the fission of the vesicle from the ER membrane and its uncoating (Antonny et al. 2001). Collectively, the concerted activities of these COPII components selects cargo and sculpts membranes into vesicles (Fig. 2).

In addition to the COPII components described above, the gene SEC16 is essential for viability and encodes a protein that is necessary for cargo export from the ER. Sec16 interacts with various components at ERES to scaffold and organize exit site formation (Shaywitz et al. 1997; Connerly et al. 2005; Watson et al. 2006; Iinuma et al. 2007; Ivan et al. 2008; Hughes et al. 2009; Shindiapina and Barlowe 2010; Kung et al. 2012). Structural studies showed that Sec16 interactions with Sec13 provide a platform for the organized assembly of Sec23-24 and Sec13-31 at the ERES (Whittle and Schwartz 2010). Sec16 might also regulate the GTP cycle of the COPII coat and to stabilize the outer coat proteins after Sar1 GTP hydrolysis, thereby potentiating COPII vesicle biogenesis (Supek et al. 2002).

A Sec23-interacting protein (Sec23IP), also known as p125A, is present at ERESes in 1:1 stoichiometry with Sec13/31. Changing levels of p125A affects ERES morphology and cargo export (Tani et al. 1999; Shimoi et al. 2005; Klinkenberg et al. 2014).

TFG (Trk-fused gene) is a metazoan COPII-regulation factor with a proline-rich carboxy-terminal region that competes with Sec31 for binding to the inner coat. Binding of TFG to Sec23 is thought to promote release of Sec31 and uncoating to regulate the COPII cycle of assembly and disassembly (Hanna et al. 2017). Its
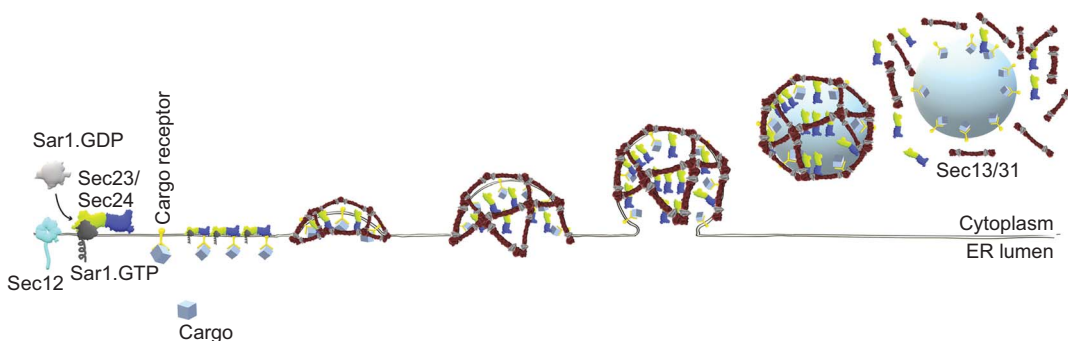
Figure 2. Coat protein complex II (COPII)-coated vesicle biogenesis. Cytosolic machinery assembles in a hierarchical manner at an endoplasmic reticulum (ER) exit site (ERES). The small GTPase Sar1 is recruited to the ER membrane. This in turn recruits an inner COPII coat of Sec23/Sec24. Secretory cargo in the ER binds to cargo receptors, which bind to Sec24. The Sar1-Sec23/24 "prebudding" complex recruits an outer COPII coat of Sec13/31 that sculpts the site into a vesicle. The vesicle buds off of the ER and forms a 60-nm coated vesicle. Vesicle uncoating exposes machinery required for vesicle targeting and fusion to a downstream compartment.

function has been reported to mediate clustering of COPII membranes between the ER and ERGIC (Johnson et al. 2015; McCaughey et al. 2016; Hanna et al. 2017, 2018; Peotter et al. 2019).

Cargo Capture into COPII Vesicles by Receptors

For export from the ER, secretory cargo is captured and packaged into COPII-coated vesicles at ERES. These processes require export motifs in fully folded and export-competent client proteins. Export motifs are often short (2–15 residue) sequences nested within the cargo polypeptide chain. Export motifs are recognized by transmembrane sorting receptors that couple secretory cargo to COPII through interactions with both cargo and coat proteins. Cargo receptors are packaged into the COPII-vesicle and then transported to the next compartment of the secretory pathway. Receptors release bound cargo in pre-Golgi or Golgi compartments, and then they are recycled back to the ER for further cargo export. Different receptors recognize different signals in the cargo including carbohydrate and/or polypeptide signals (Appenzeller et al. 1999; Belden and Barlowe 2001; Barlowe and Helenius 2016). Receptor recycling is brought about by COPI-dependent vesicles via the ERGIC to the ER.

On model membranes such as liposomes, Sar1 and COPII coat proteins are sufficient to select transmembrane cargos, deform membranes into buds, and finally generate vesicles (Matsuoka et al. 1998). COPII components show a high degree of functional and structural conservation throughout evolution and yeast and human proteins can substitute for each other's functions.

A role for Sec23/Sec24 in cargo recruitment into nascent vesicles was proposed when a complex of Sar1, Sec23/24, was shown to interact with transmembrane cargoes and receptors for secretory proteins (Aridor et al. 1998; Kuehn et al. 1998). Genetic, biochemical, and structural data have provided a molecular basis for how Sec24 subunits recognize and bind specific ER exit motifs in cargoes for their selective uptake into vesicles (Miller et al. 2003; Mossessova et al. 2003; Mancias and Goldberg 2007). Sec24 has several cargo-binding sites, which allows for the recognition of several different cargoes by the COPII coat. Multiple isoforms of Sec24 provide additional diversity in interactions with cargo. Yeast expresses three Sec24 homologs (Sec24, Iss1/Sfb2, and Lst1/Sfb3), whereas mammals express four (Sec24A-D). Based on sequence identity, the four isoforms are separated into two subfamilies, Sec24A/B and Sec24C/D (Pagano et al. 1999; Tang et al. 1999).

The ERGIC53 and ER vesicle (Erv) families of proteins are the best characterized cargo recep-

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tors that function in capturing cargo into COPII vesicles for ER export (Dancourt and Barlowe 2010). ERGIC-53, so named because it is a 53 kDa protein that localizes to the ERGIC, is an oligomeric single-pass transmembrane protein with a bulky amino-terminal ER-lumenal domain and a short, cytoplasmic carboxy terminal. The cytoplasmic stretch has a diphenylalanine (FF) motif, which interacts with COPII proteins for incorporation into COPII vesicles (Kappeler et al. 1997). There is also a dilysine (KKXX) signal, which promotes capture into COPI-dependent retrograde carriers to the ER (Kappeler et al. 1997). The ERGIC53 lumenal domain is homologous to L-type lectins that show Ca^{2+}-dependent binding to high-mannose oligosaccharides. The cargo, cathepsin Z-related protein, was shown to bind ERGIC-53 in the ER and dissociate in a post-ER compartment (Appenzeller et al. 1999).

Yeast Erv proteins show similar general properties as ERGIC53 cargo receptors. Deletion of individual *ERV* genes cause specific secretory proteins to be retained in the ER. Erv proteins cycle between the ER and Golgi using similar signals in their cytoplasmic sequences for recognition by COPII and COPI machinery (Belden and Barlowe 2001; Malkus et al. 2002).

There must be sufficient diversity in cargo capture to permit specific selection of a large number of cargoes (Barlowe 2003). ER export motifs have been identified as hydrophobic and aromatic carboxy-terminal amino acids, such as the two phenylalanine residues (FF) present at the carboxyl terminus of cargo receptors like ERGIC53 and the p24 family, or a single valine residue, as present on the carboxyl terminus of CD8 (Iodice et al. 2001; Nufer et al. 2002). Another export motif comprises di-acidic Glu-X-Asp (ExD) or DxE sequences (Nishimura and Balch 1997; Ma et al. 2001). There is some diversity in the how these motifs (either the FF or DXE) interact with COPII machinery that might both provide greater stringency in cargo selection and drive cargo packaging out of the ER. Both kinds of motifs bind Sec23/24. Other binding sites have been identified in Sec24 for the YNNSNPF signal of the yeast SNARE Sed5, and for LxxLE and DxE class signals present on certain SNARE and cargo proteins.

Several cargo-receptor interactions and motifs are yet to be characterized, which will reveal the diversity and cargo specificity of protein trafficking out of the ER. Export motifs facilitate the export of membrane proteins from the ER, but they are not always sufficient to promote export, suggesting that combinatorial interactions between coat proteins, the lipid membrane, accessory proteins, and other motifs on the cargo protein may build avidity for cargo selection. For some cargoes, the transport signal is a conformational epitope formed only when the cargo is in an export-competent conformation (Mancias and Goldberg 2007). More recent evidence has identified that some lysosomal proteins need to assemble into complexes in the ER before they are exported together as a single functional unit (Bajaj et al. 2020; Devireddy and Ferguson 2022). Export motif recognition by ERES machinery can therefore provide a regulation point that may control ER export.

ER exit is highly selective, while secretory cargo is being packaged for export, resident chaperones, and partially folded proteins must be retained (Barlowe and Helenius 2016; Gomez-Navarro and Miller 2016). COPII recognition of the export motif can mediate a five- to 20-fold concentration of secretory cargo into COPII-dependent vesicles. ERES machinery, receptors, and cargo exclude resident and misfolded proteins, both by active concentration of p24 receptors that drive out nonsecretory cargoes or by crowding out of other proteins (Ma et al. 2017; Gomez-Navarro et al. 2020).

Additional components of the budded COPII-dependent container include proteins such as the small GTPase Rab1 (Segev et al. 1988) and v-SNAREs that allow for fusion to the target membrane.

Some proteins that escape the ER and need to be retrieved from the ERGIC and Golgi apparatus to the ER. This retrograde cargo recruitment into COPI-dependent vesicles is mediated by the KDEL receptor for soluble cargoes that contain a carboxy-terminal sequence of amino acids K/RDEL (Semenza et al. 1990; Tang et al. 1993). Cargo receptors, KDEL receptors, and other transmembrane proteins contain the motif

KKXX for capture into COPI-coated vesicle for retrograde transport to the ER.

Is All Biosynthetic Transport Mediated by COPII-Coated Vesicles?

Unlike yeast, metazoans secrete collagens and other similarly bulky proteins that compose the extracellular matrix (ECM) or chylomicrons and mucins. Although the export of these molecules is COPII-dependent, they are too big to be encased in a standard COPII-coated vesicle of the kind described above. This is not a small problem because collagens compose 25% of our dry protein weight and they are in fact the most abundant metazoan proteins. This led to a search for a cellular mechanism to increase the size of COPII-coated vesicles to form megacarriers.

ADAPTING COPII FOR BULKY CARGOES

A conceptually straightforward solution to the problem of big cargo export would be if cells assemble a bigger COPII coat lattice to extract a larger volume of ER, creating a COPII megacarrier. Changing the dimensions and geometry of COPII lattice assembly could be brought about by using specific COPII protein isoforms or different adaptors. One isoform of Sec24 called Lst1 in yeast was identified that allowed for COPII-coated carriers to increase from 75 nm up to 87 nm in diameter (Shimoni et al. 2000). But the resulting increase in size of a COPII vesicle is still too small for metazoan collagens.

Using correlative light and electron microscopy (CLEM) and superresolution imaging, it was shown subsequently that monoubiquitination of Sec31A, mediated by the klhl12 adaptor subunit of the Cullin 3 (CRL3) E3 ligase complex, might increase the dimension of the outer COPII coat. Overexpression of klhl12 formed enlarged COPII structures and enhanced the rate of collagen secretion (Jin et al. 2012). KLHL12- and COPII-containing structures were visualized, isolated, and were shown to contain collagen-1 (Gorur et al. 2017; Yuan et al. 2018). CUL3 knockdown has a more profound effect than klhl12 knockdown, suggesting redundancy in CUL3 adaptors for this process. Collagen-containing COPII vesicles contain hsp47, a chaperone that stabilizes the triple helical form of procollagen, which is either recycled back to the ER (Nakai et al. 1992; van Dijk et al. 2020) or as also shown, does not exit the ER (Omari et al. 2020). Furthermore, these vesicles were observed in cells and in a cell-free reaction. A similar cell-free COPII budding reaction revealed megacarriers containing another bulky cargo, ApoB-containing very light density lipoprotein (VLDL) (Gusarova et al. 2003; Melville et al. 2019).

More recently, it has been shown that CRL3^{KLHL12} influences collagen synthesis in human skin fibroblasts and that transport of collagen-1 is independent of CRL3^{KLHL12} (Kim et al. 2018). Subsequent reports have described structures with ERES markers that contain overexpressed tagged collagen, which are targeted for lysosomal degradation (Omari et al. 2018; Gorrell et al. 2021). A model procollagen-2 with characterized mutations that result in misfolded triple helices were further enriched in these degradative structures (Omari et al. 2018). These collagen-1-containing degradative structures were shown to contain klhl12, Cul3, and LC3 and the investigators suggested that KLHL12 and Cul3-mediated ubiquitination is involved in collagen degradation (Omari et al. 2018). Luini and colleagues have argued that collagen export is performed by uncoated, pleomorphic carriers (Mironov et al. 2003). On the other hand, live confocal video microscopy from Stephens and colleagues showed collagen transport from ER to the Golgi without the involvement of long-range trafficking of large vesicular structures (McCaughey et al. 2018).

Other reported ways to control COPII-mediated collagen export from the ER include the activity of Sedlin, which binds and regulates efficient cycling of Sar1 to allow nascent carriers to grow (Venditti et al. 2012). Additionally, TFG has been reported to cluster ERES-ERGIC machinery to affect the dynamics and size of COPII-dependent carriers, although the details are unresolved (Johnson et al. 2015; McCaughey et al. 2016).

It is clear that collagen export is COPII-dependent, but export can be for either secretion, or degradation, from an ERES. The morphology of

the proposed containers for these two distinct routes, their composition, the conditions for their formation, and the presence or absence coatomers (partial or total coating) needs to be clarified. A handle to understand the mechanism of collagen export and how luminal collagen and cytoplasmic COPII coats are linked, stems from the discovery of the TANGO1 (transport and Golgi organization 1) family of proteins.

TANGO1 IS REQUIRED FOR BULKY AND HIGH-VOLUME CARGOES

In a genome-wide RNAi screen for genes whose depletion led to reduced secretion of an engineered horseradish peroxidase (Bard et al. 2006), the protein TANGO1 was identified. In invertebrates, there is only one TANGO1 gene producing a single protein. In vertebrates, the whole gene and some individual portions have duplicated to give rise to the MIA (melanoma inhibitory activity) family of proteins. In mammals, the family consists of four genes, OTOR (otoraplin), MIA, MIA2, and MIA3 (TANGO1) (Fig. 3). At least two translated isoforms each of the paralogs MIA2 and MIA3 have been characterized thus far; the gene for MIA3 produces TANGO1 and TANGO1-Short and the paralog MIA2 produces TALI and cTAGE5 (cutaneous T-cell lymphoma-associated antigen 5).

TANGO1 and cTAGE5 localize exclusively to ERES, doing so via interactions of their proline-rich domains (PRDs) to Sec23A and Sec16. Once at an ERES, TANGO1, cTAGE5, Sec12, and Sec23 mutually recruit and restrict each other along with their interactors. Data from *Drosophila*, zebrafish, medaka fish, and mammals suggest that the TANGO1 family is required for the secretion of several different collagens including I, II, III, IV, VII, and IX from chondrocytes, fibroblasts, endothelial cells, and mural cells (Saito et al. 2009; Wilson et al. 2011; Lerner et al. 2013; Tiwari et al. 2015; Ishikawa et al. 2017; Lekszas et al. 2020; Christen et al. 2021; Clark and Link 2021; Guillemyn et al. 2021). TANGO1 is also required for cargoes that are secreted in huge volumes including mucin (Zhang et al. 2014). TANGO1, TALI, and cTAGE5 show a similar effect on the ER export of another bulky cargo, apolipoproteins (Pitman et al. 2011; Santos et al. 2016). Collagen-1 hypersecretion in pathological fibrogenesis is mediated by TANGO1 in mice and its genetic depletion is protective against liver fibrosis (Maiers et al. 2017).

Altogether, these data suggest that TANGO1 has arisen in metazoa as an adaptation for the ER export of bulky cargoes like collagens. Although TANGO1 is an ERES-resident, protein-linking, export-competent cargo to COPII machinery, it is not a conventional cargo receptor. Unusually, it does not leave the ER along with the departing cargo. A collagen-1-containing intermediate that also contained klhl12, Sec31, TANGO1, cTAGE5, and Sec12 has been reported as the megacarrier for collagen export from the ER (Yuan et al. 2018). It is also important to note that unlike cargo receptors, TANGO1 binds Sec23A, not Sec24 (Saito et al. 2009; Ma and Goldberg 2016).

Mechanism of TANGO1 Function

Current data indicate that TANGO1 has at least two distinct functions: (1) to capture and export collagen, and (2) to organize the ERES.

In the ER lumen, an SH3-like domain is required for TANGO1 to interact with collagen (Saito et al. 2009). In vertebrates, the SH3-like domain binds to the collagen-specific chaperone HSP47 (SerpinH1) (Ishikawa et al. 2016). HSP47 binds to triple-helical procollagen and therefore it could serve as a link between TANGO1 and most procollagens. Perhaps not all collagens interact via Hsp47; they might bind directly to TANGO1 or use other linking mechanisms. It remains unclear how the SH3-like domain functions in invertebrates, which lack HSP47, but one possibility is that it may interact directly with procollagen (Ishikawa et al. 2016; Arnolds and Stoll 2022).

On the cytoplasmic face of the ER, TANGO1 has two extended stretches predicted to adopt a coiled-coil fold. The membrane-proximal coiled coil (CC1) is required for self-association of TANGO1 in both human and *Drosophila* TANGO1 (Raote et al. 2018; Reynolds et al. 2019). Interestingly, the same 40 amino acids required for the self-association
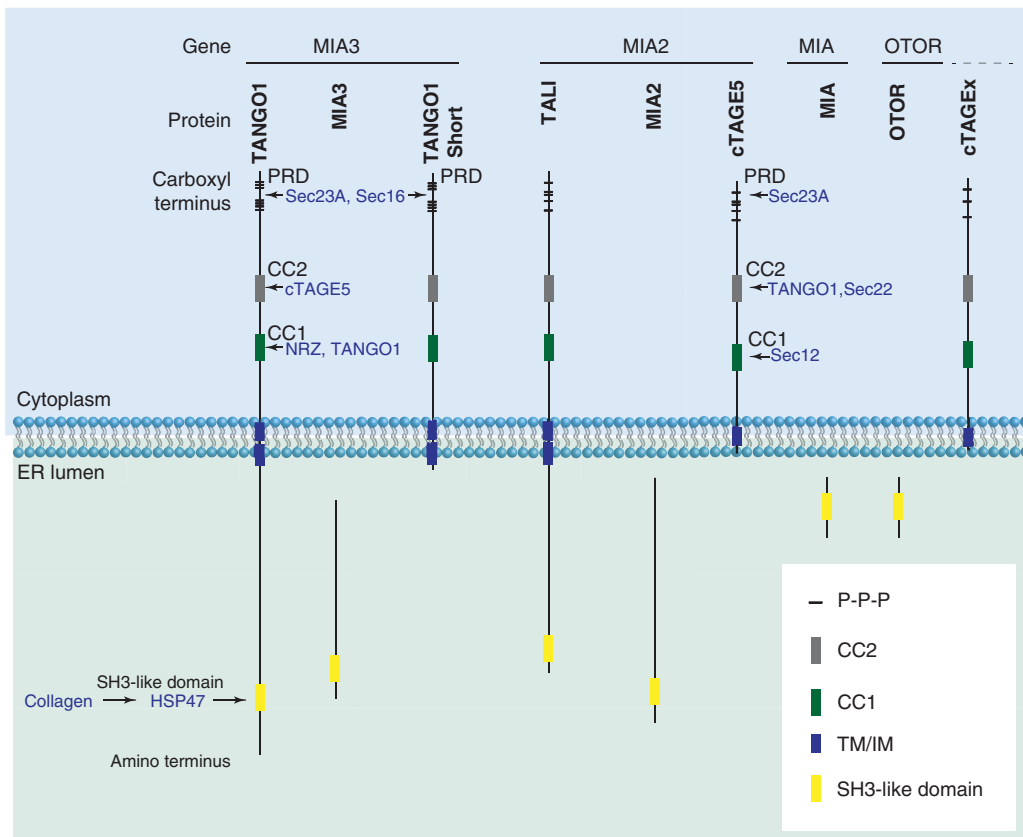
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Figure 3. The transport and Golgi organization 1 (TANGO1) family of proteins. Mammalian TANGO1 family of proteins. Full-length TANGO1 or TANGO1-like (TALI) consists of an endoplasmic reticulum (ER)-lumenal part, with extensive regions that are predicted to be intrinsically disordered and an SH3-like domain. The cytoplasmic face of the ER membrane contains coiled coils (CC1 and CC2) and a carboxy-terminal proline-rich domain (PRD). Secreted isoforms MIA and otoraplin are almost exclusively an SH3-like domain. Other paralogs and their isoforms include TANGO1-Short, cTAGE5, and several predicted cTAGEx proteins (where x is 2, 4, 6, 8, 9, and 15). Each domain interacts with a specific set of proteins as indicated.

are also the site of interaction with a retrograde multisubunit tether complex called the NRZ tether (Raote et al. 2018). *Drosophila* TANGO1 interacts with the golgin GM130, which is also associated with membrane tethering (Liu et al. 2017). Tethers are extended proteins or multisubunit complexes present on target membranes, sampling the environment for incoming membrane-bound carriers. These carriers dock to the tethers and finally fuse to the target membrane in a SNARE-dependent process.

The TANGO1 paralog cTAGE5 recruits Sec12 to ERES via a membrane proximal coiled coil. Carboxy-terminal, proline-rich domains of

TANGO1 family members bind Sec23 and Sec16 (Saito et al. 2009; Ma and Goldberg 2016; Maeda et al. 2017).

TANGO1 depletion in *Drosophila* tissues reduces ERES size and number and increases the spatial segregation of ERES from the Golgi apparatus, suggesting that TANGO1 contributes to COPII clustering, ERES architecture, and ER-Golgi tethering. Superresolution microscopy in human cell lines, in *Drosophila* fat bodies, and larval salivary glands showed linear, filamentous arrays of TANGO1 surrounding exit sites (Liu et al. 2017; Raote et al. 2017; Reynolds et al. 2019), suggesting that TANGO1 assembles

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into a ring-like filament in the plane of the ER membrane, encircling and corralling COPII components (Raote et al. 2020).

Structural data suggest that the proline tripeptide (PPP) motifs in the proline-rich domains of TANGO1 and cTAGE5 engage in multivalent interactions with multiple copies of the pre-budding complex of Sar1A-Sec23-Sec24. This binding allows for flexibility in COPII lattices, which can now adopt a different shape to stabilize an alternate membrane curvature. The proposed model was that TANGO1 and cTAGE5 act as master scaffolds to switch COPII inner coat lattice between a cylindrical form and its usual spherical structure (Ma and Goldberg 2016; Hutchings et al. 2018).

TANGO1-Dependent ER Exit

Combining all these aspects of COPII function and how the TANGO1 family of proteins can remodel ERES machinery, we can arrive at a possible model of TANGO1-dependent export from the ER. TANGO1 and cTAGE5 along with the scaffolding protein Sec16 define the location and size of an ERES. At the neck of this export route, cTAGE5 recruits Sec12, which would ensure a stable supply of Sar1A at the site (Sato and Nakano 2005; Saito et al. 2014; Sasaki et al. 2018). COPII proteins including coatomers and Sar1, and Sec16 remain as a collar (Kurokawa et al. 2016; Iwasaki et al. 2017; Shomron et al. 2021) forming a treadmilling sheet of COPII that polymerizes at the neck in which cTAGE5 and TANGO1 activate Sar1, and depolymerizes further away from the ER (Fig. 4).

TANGO1 recruits tethering proteins, the NRZ complex in mammals or GM130 in *Drosophila*. Via the tether, TANGO1 recruits post-ER membranes to the ERES. Once tethered at the site, these retrograde ERGIC membranes need to fuse back to the ER for anterograde movement of collagen (Santos et al. 2015).

Vesicles, Tubules, or Tunnels for Cargo Export from the ER

Free COPII vesicles have been reported in yeast, in thin sections of cultured mammalian cells (Zeuschner et al. 2006), and in cell-free reac-
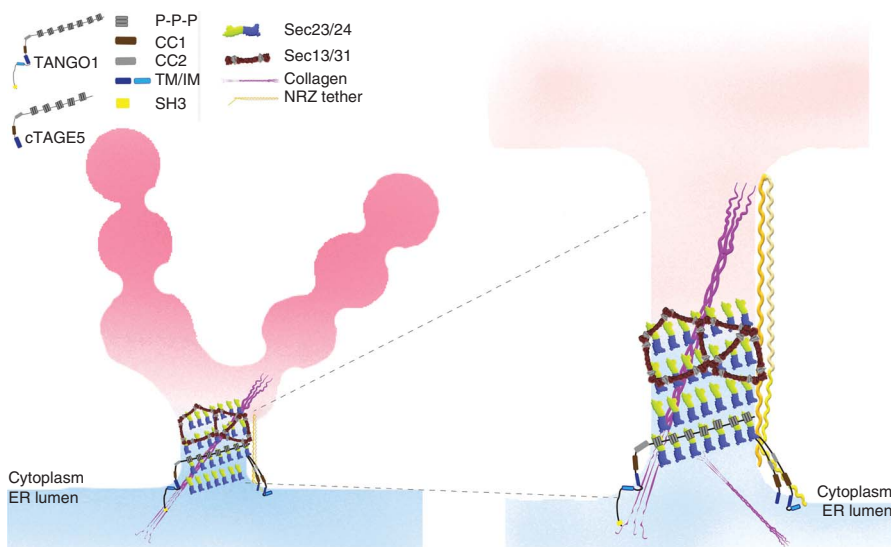

Figure 4. TANGO1 (transport and Golgi organization 1) stabilizes a transient tunnel between the endoplasmic reticulum (ER) and the ER-Golgi intermediate compartment (ERGIC). TANGO1 at the base of nascent bud, binds to multiple Sec23/24 and promotes a cylindrical coat protein complex II (COPII) assembly. Via the NRZ tether, TANGO1 holds the ERGIC (pink membranes) in place at the ER exit sites (ERES). This could result in a transient continuity generated between the ER (blue) and the ERGIC (pink).

tions. One could argue that the prevalence of free COPII vesicles in the cell-free reactions is caused by the relaxed organization and decreased proximity of the ERGIC and the ERES compared with intact cells. Nonetheless, isolated COPII vesicles, at least those isolated from yeast cell-free reactions, are functional in cargo delivery to the Golgi.

Extended tubular structures emanating from an ERES have also been reported in electron micrographs over the past four decades, along with more recent video microscopy, suggesting that there could be continuities between the ER and the ERGIC or even the Golgi (Claude 1970; Morré et al. 1971; Lindsey and Ellisman 1985; Sesso et al. 1994; Stinchcombe et al. 1995; Bannykh et al. 1996). Whether these are physiologically relevant is questioned from observations of similar tubules under conditions of defective transport—Fromme et al. observed these tubules in cranio-lenticulo-sutural dysplasia (CLSD) skin cells that had a heterozygous missense mutation in SEC23A. Bacia et al. observed constricted tubules projecting from GUVs in incubations conducted with nonhydrolyzable GTP (Fromme et al. 2007; Bacia et al. 2011).

Schekman and colleagues speculated that the coat may depolymerize from the tip of a bud, thus leaving a collar of COPII that persists until vesicle constriction and fission. Recent studies have indeed shown that instead of forming only a spherical vesicle, COPII can be visualized as a collar at the ER–ERES boundary, with an anastomosis of membranes at the ERES in mammalian cells as well as in *Drosophila* (Shomron et al. 2021; Weigel et al. 2021; Yang et al. 2021).

An uncoated tip of a nascent carrier will have exposed fusion machinery that could allow it to fuse with a target membrane, even before the carrier has been cut off from the ER. Such a fusion would result in a short-lived tunnel between the ER and the next compartment (Raote and Malhotra 2019). Transient continuities between the ER and the *cis*-Golgi have been suggested to transfer cargo (termed hug-and-kiss) in *S. cerevisiae* (Kurokawa et al. 2014). A similar association of ERES and *cis*-Golgi membranes is seen in *P. pastoris*, which is driven by the Dsl1 multisubunit retrograde tether complex, ortholog of the

metazoan NRZ tether (Roy Chowdhury et al. 2020). It is not clear how these associations between ERES and retrograde tethers are maintained in non-metazoan eukaryotes because these species do not express TANGO1, but it is possible that they are formed and stabilized by stochastic processes resulting from transient higher local concentrations of machinery for anterograde and retrograde machinery. Metazoan activities like TANGO1 may have evolved to reinforce this functionally integrated unit of the ERES-Golgi interface, by controlling the timing and shape COPII assembly and physically recruiting tethers to the ERES.

Under these circumstances, COPII components remain at the ERES although anterograde cargo departs in anterograde transport intermediates marked by components of the downstream compartment that were tethered at the ERES.

Altogether, TANGO1 organizes the early secretory pathway, functionally linking cargo, coatomers, Sar1 activity, and a downstream compartment (Raote and Malhotra 2021). Other secretory modules have also been incorporated into the metazoan repertoire to control some of these aspects of ER export and the ER-Golgi interface, with a common feature being that they link activities at the ERES to a downstream compartment. Collagen folding in the ER lumen is brought together with cytoplasmic ER-ERGIC tethering activities by TMEM131 (Zhang et al. 2020). COPII-coated transport carriers may be tethered at the ER-ERGIC interface and their coat assembly and disassembly may be regulated in time and space by TFG (Hanna et al. 2017, 2018). The coat component p125A (Sec23ip) is a major Sec31A-interacting protein and, like TANGO1, controls the interactions between the Sec31A and Sec23A via tri-proline repeats (Shimoi et al. 2005; Ong et al. 2010). In addition, p125A also recognizes and binds to phospholipid (PI4P) enriched at the ERGIC, again serving to couple COPII budding with the presence of ERGIC membranes (Klinkenberg et al. 2014). The combination of all these proteins and activities ensure that COPII budding domains at the ER are always closely juxtaposed to ERGIC membranes.

Table 1. Post-translational modifications (PTMs) of COPII proteins

Protein	PTM	Regulator	Effect	References
Sar1A	Ubiquitination	Unknown	Unknown	Hornbeck et al. 2015
Sar1B	Phosphorylation	PKCz	Unknown	Siddiqi and Mansbach 2012;
	Ubiquitination	Unknown	COPII response to large cargoes	Hornbeck et al. 2015
Sec12	*N*-glycosylation	Unknown	Unknown	Nakano et al. 1988; d'Enfert et al. 1991; Sato et al. 1996
	O-mannosylation	Unknown	Unknown	
	Phosphorylation	Hrr25/CK1δ LTKE	Negative regulation of vesicle budding	Murakami et al. 1999
			Positive regulator of ERES abundance and export	Centonze et al. 2019
Sec16	MARylation	dPARP16	Sec body biogenesis	Aguilera-Gomez et al. 2016
	Phosphorylation	ERK2	ERES biogenesis	Farhan et al. 2010; Tillmann et al. 2014; Zacharogianni et al. 2011
	Phosphorylation	ERK7/MAPK15	Localization to ERES	
	Phosphorylation	ULK1/2	Control ER export rates	Joo et al. 2016
	Phosphorylation		Sec23 interaction	Yorimitsu and Sato 2020
Sec23	Phosphorylation	Hrr25/CK1δ	Vesicle uncoating and membrane fusion	Lord et al. 2011
	Ubiquitination	Uba1, Ubc4, Rsp5, Ubp3, Bre5, Cdc48	Sec23 turnover	Cohen et al. 2003
Sec23A	*O*-GlcNAcylation	OGT	Collagen export from the ER	Cox et al. 2018
	Phosphorylation	ULK1	Controls ER export	Gan et al. 2017
	Ubiquitination	Unknown	Protein localization and turnover	Amodio et al. 2009
Sec23B	Phosphorylation	ULK1	Autophagosome biogenesis	Jeong et al. 2018
Sec24	Phosphorylation	Hrr25/CK1δ	Unknown	Lord et al. 2011
Sec24C	Phosphorylation	Akt	Control Sec23A affinity	Sharpe et al. 2011
	Phosphorylation	Unknown	Unknown	Dudognon et al. 2004; Kettenbach et al. 2011
	O-GlcNAcylation	OGT	Mitotic shutdown of ERES export	Dudognon et al. 2004; Cox et al. 2018
Sec24D	Phosphorylation	Akt	Control Sec23A binding	Sharpe et al. 2011
Sec13	Phosphorylation	Unknown	Unknown	Hornbeck et al. 2015
Sec31	Phosphorylation	Unknown	Unknown	Shugrue et al. 1999
	Phosphorylation	Unknown	Unknown	
	Phosphorylation	Unknown	Unknown	
	Phosphorylation	Unknown	Localization to ERES	Koreishi et al. 2013
	O-GlcNAcylation	OGT	Localization to ERES	Cho and Mook-Jung 2018
	O-GlcNAcylation	OGT		Cox et al. 2016
	Ubiquitination	ARIH1		Scott et al. 2016
	Ubiquitination	KLHL12	Formation of enlarged COPII-containing structures	Yamasaki et al. 2006; Shibata et al. 2007; Jin et al. 2012
TANGO1	Phosphorylation	CK1	Mitotic ERES breakdown	Maeda et al. 2020
	O-GlcNAcylation	PGANT4	Secretory granule apical secretion	Zhang et al. 2014
		Unknown	Insulin secretion	

Table 2. Pathological conditions associated with ERES machinery

Protein	Disease/phenotype	References
Sar1A	Chylomicron retention	Jones et al. 2003
Sar1B	Chylomicron retention	Jones et al. 2003; Charcosset et al. 2008
	Abetalipoproteinemia	Magnolo et al. 2013
	Hypocholesterolemia	Levic et al. 2015
Sec12	Diabetes mellitus (non-insulin-dependent)	Park et al. 2018
	Prolactinoma	Zhang et al. 2010
Sec16	Obesity	Hotta et al. 2009
Sec23A	Craniolenticulosutural dysplasia	Boyadjiev et al. 2006
Sec23B	Congenital dyserythropoietic anemia	Bianchi et al. 2009; Schwarz et al. 2009
Sec24D	Osteogenesis imperfecta (Cole Carpenter syndrome)	Garbes et al. 2015; Takeyari et al. 2018
Sec24B	Neural tube defects	Yang et al. 2013
Sec13	Von Hippel–Lindau syndrome	Swaroop et al. 1994
Sec31	Neurodevelopmental disorder with spastic quadriplegia, optic atrophy, seizures, and structural brain anomalies	Halperin et al. 2019
p125A (Sec23ip)	Cranial, skeletal, and neurodevelopmental effects	Arimitsu et al. 2011; Reuter et al. 2017
TANGO1 (MIA3)	Coronary artery disease	Samani et al. 2007
	Clinodactyly, brachydactyly, diabetes, scoliosis, pruritic skin lesions	Lekszas et al. 2020; Guillemyn et al. 2021
MIA2	Lymphoma, T cell, cutaneous	Koch et al. 2003
	Fahr's syndrome	Lemos et al. 2011

REGULATING ER EXPORT

A challenge that awaits the field is to develop an integrated understanding of how ERES machinery is regulated to allow for rapid, dynamic changes in secretory requirements. Traffic out of the ER generates large fluxes of proteins and lipids, which must be compensated for dynamically by new synthesis or by retrograde transport. The ERES-ERGIC-Golgi interface also provides proteins and membranes for several processes, including the biogenesis of autophagosomes and lipid droplets (Ishihara et al. 2001; Ge et al. 2013, 2017; Graef et al. 2013; Wang et al. 2014). Failure of these homoeostatic mechanisms can lead to a disruption of cellular functioning.

One form of regulation comes from post-translational modifications of COPII subunits and primer proteins that might modulate their activity (Table 1, derived from Bisnett et al. 2021); however, the mechanistic bases of these controls remain unclear. ER-resident leukocyte tyrosine kinase (LTK)-mediated Sec12 phosphorylation modulates the number of ERESs and amount of ER-Golgi traffic (Centonze et al. 2019). When large amounts of cargo arrive at ERESs, AREX (autoregulation of secretory flux) is activated by a cargo–Sec24 complex, which triggers kinases to enhance cargo export from the ER (Subramanian et al. 2019).

ER-to-Golgi transport can be modulated by ALG-2 binding to ERES and altering the recruitment of coat proteins to the ERES. PEF1 and ALG2 acts as a co-adaptor to link cytosolic Ca^{2+} to $Cul3^{KLHL12}$ recognition and sustained ubiquitination of the substrate Sec31 (McGourty et al. 2016). Short bursts of agonist-driven Ca^{2+} signaling increases ALG-2-dependent outer coat targeting to ERES to stimulate transport, whereas extended Ca^{2+} has the opposite effect (Sargeant et al. 2021). TFG also functions in a Ca^{2+}-dependent manner through the association with the ALG-2 (Kanadome et al. 2017). Altogether, there are multiple indications for a regulatory role for Ca^{2+} levels in COPII budding.

Pathophysiological Conditions

Most mammalian COPII subunits have one or more paralogs with some divergence and partial redundancy in function, as loss-of-function of individual copies often results in genetic pathophysiologies. COPII genes are associated with several diseases (Table 2), several of which have no clear links to cargo packaging. Notably, congenital dyserythropoietic anemia type II (CDAII) is caused by mutations in Sec23B (Bianchi et al. 2009; Schwarz et al. 2009) but there is no known cargo packaging defect. Analysis of the mechanistic link between the gene and the phenotype will reveal new aspects of how these proteins work and are regulated under physiological conditions.

Multiple bacteria and viruses remodel secretory organelle membranes to generate specialized sites for their RNA replication or assembly and often use host COPII machinery in the remodeling (den Boon and Ahlquist 2010; Hsu et al. 2010; Inoue and Tsai 2013). ERES machinery repurposing by intracellular pathogens is also revealing novel aspects of how the machinery can work and which specific steps and interactions are useful for therapeutic interventions.

CONCLUSIONS AND OPEN QUESTIONS

Decades of studies have cemented our understanding of how COPII proteins mold and pinch a portion of ER into a small-coated vesicle for cargo export. The discovery of the TANGO1 family of proteins is helping in addressing long-standing questions of how bulky cargoes are exported by a COPII-dependent pathway. The challenge now is to address how metazoan proteins like TANGO1 influence COPII proteins to restrict their assembly as a collar at the neck of a carrier emanating from the ER, how bulky cargo is packed into the ensuing container, and what the biochemical properties are of the cargo-filled container.

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