J. Biochem. 2019;166(2):115–119 doi:10.1093/jb/mvz036

JB THE JOURNAL OF BIOCHEMISTRY

JB Review

Not just a cargo receptor for large cargoes; an emerging role of TANGO1 as an organizer of ER exit sites

Received March 30, 2019; accepted April 24, 2019; published online May 7, 2019

Kota Saito * and Miharu Maeda

Department of Biological Informatics and Experimental Therapeutics, Graduate School of Medicine, Akita University, 1-1-1 Hondo, Akita 010-8543, Japan

*Kota Saito, Department of Biological Informatics and Experimental Therapeutics, Graduate School of Medicine, Akita University, 1-1-1 Hondo, Akita 010-8543, Japan. Tel: +81-18-884-6065, Fax: +81-18-836-2603,
email: ksaito@med.akita-u.ac.jp

Proteins synthesized within the endoplasmic reticulum (ER) are exported from ER exit sites via coat protein complex II (COPII)-coated vesicles. Although the mechanisms of COPII-vesicle formation at the ER exit sites are highly conserved among species, vertebrate cells secrete a wide range of materials, including collagens and chylomicrons, which form bulky structures within the ER that are too large to fit into conventional carriers. Transport ANd Golgi Organization 1 (TANGO1) was initially identified as a cargo receptor for collagens but has been recently rediscovered as an organizer of ER exit sites. We would like to review recent advances in the mechanism of large cargo secretion and organization of ER exit sites through the function of TANGO1.

Keywords: collagen; COPII; ER; secretion; TANGO1.

Abbreviations: COPII, coat protein complex II; ER, endoplasmic reticulum; TANGO1, Transport ANd Golgi Organization 1.

Secretory proteins exit from special domains of the endoplasmic reticulum (ER) called ER exit sites via coat protein complex II (COPII)-coated vesicles. COPII-vesicle formation at the ER exit sites is initiated by the activation of the small GTPase Sar1 by the guanine-nucleotide exchange factor, Sec12. Activated Sar1 binds to the ER membrane, which recruits an inner coat complex Sec23/Sec24 and an outer coat complex Sec13/Sec31 to form COPII vesicles (*1*, *2*). Collagens and chylomicrons are too big to be accommodated into these conventional COPII vesicles; thus, how these bulky cargoes are exported from the ER had been an unanswered question for a long time (*3*). Transport ANd Golgi Organization 1 (TANGO1) had been initially discovered as a cargo receptor for collagens at the ER exit sites (*4*, *5*). Subsequently, it has been found that TANGO1 forms a macro molecular complex with cTAGE5 and Sec12, and the complex regulates Sar1 GTP binding and hydrolysis for efficient collagen secretion. In addition, TANGO1 recruits ER-Golgi Intermediate Compartment (ERGIC) membranes and forms a ring around the ER exit sites for proper collagen secretion. Surprisingly, recent progress suggests that TANGO1 functions as an organizer of the ER exit sites. In this review, we summarize recent discoveries regarding TANGO1 and related molecules and explain how these two apparently distinct functions can be accomplished by TANGO1.

Identification of TANGO1 in *Drosophila*

A genome-wide screening was performed in *Drosophila* S2 cells to identify the genes involved in secretion and organelle morphology (*6*). *Drosophila* TANGO1 was identified as a gene affecting constitutive secretion measured by a reporter (horseradish peroxidase fused to a signal sequence (ss HRP)), when depleted with RNA interference. Moreover, the Golgi enzyme mannosidase II was redistributed to the ER upon TANGO1 depletion in S2 cells, suggesting that TANGO1 is involved in general protein transport from the ER to Golgi in the *Drosophila* system.

TANGO1-Family Proteins in Mammalian Cells

TANGO1 in vertebrates produces two major transcripts designated as TANGO1L (or TANGO1) and TANGO1S (*7*). TANGO1L shares the same domain organization as *Drosophila* TANGO1 and possesses an SH3 domain, a membrane-spanning region, two coiled-coil domains and a proline-rich stretch from the N-terminus (Fig. 1) (*8*, *9*). TANGO1S lacks an N-terminal SH3 domain but mostly shares sequences with TANGO1L (*10*). In vertebrates, TANGO1 possesses family proteins called cTAGE5 and TANGO1-like (TALI) (Fig. 1) (*11*). The relationship between cTAGE5 and TALI corresponds to that between TANGO1S and TANGO1L, as these proteins are products of alternative splicing. TALI shares the same domain organization as TANGO1L, as cTAGE5 does with TANGO1S. Of note, the expression of TALI is restricted to lungs, testis, small intestine, colon, pancreas, kidney, liver and prostate.

TANGO1L as a Collagen Cargo Receptor

TANGO1L was initially characterized as a Collagen VII cargo receptor at the ER exit sites (*8*). The SH3 domain of TANGO1L was shown to interact with Collagen VII by an *in vitro*-binding assay, and a proline-rich stretch of TANGO1L was shown to interact

Featured Article

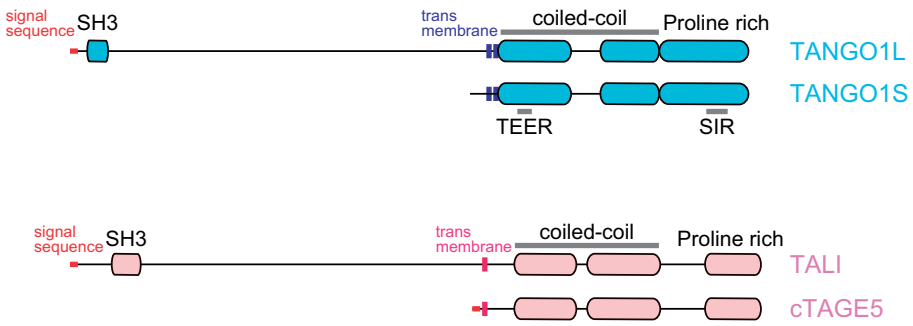

Fig. 1 Domain organization of TANGO1 family proteins.

with Sec23/Sec24 using a yeast two-hybrid assay. Knockdown of TANGO1L does not affect general protein secretion, but it specifically blocks secretion of Collagen VII, resulting in its accumulation within the ER. Based on these results, TANGO1L was identified as a novel cargo receptor required for exporting bulky Collagen VII from the ER (*8*). Soon after, knockout of TANGO1L was made in mice models and the mice showed severe defects in chondrogenesis (*7*). Further analysis revealed that the mice were defective in secretion of subsets of collagens including Collagens I, II, III, IV, VII and IX. These results indicated that TANGO1L might be involved in secretion of all collagen molecules. Indeed, recent biochemical analyses suggest that binding between TANGO1L and collagens are rather indirect and mediated by HSP47, a chaperone required for collagen folding (*12*). The chaperone-mediated collagen binding enables TANGO1L to bind to all sets of collagen molecules, and possibly it might recognize the folding status of collagens whether they are ready for secretion.

How Are Collagens Secreted by TANGO1 and Binding Molecules?

Initial characterization of TANGO1 suggested that TANGO1L acts as a cargo receptor without exporting from the ER. Accordingly, the proposed model indicated that the binding of TANGO1 with Sec23/Sec24 inhibits recruitment of the outer coat complex Sec13/Sec31, thereby stalling the completion of conventional COPII biogenesis and forming megacarriers that can accommodate collagens inside (Fig. 2A) (*8*). However, several other models for collagen export have been proposed based on the recent characterization of these proteins. We would like to introduce some of them in the following sections.

Regulation of Sar1 GTPase Is Required for Collagen Secretion From the ER

Immunoprecipitation analysis revealed that there is a direct interaction between TANGO1L and cTAGE5 through coiled-coil regions of both proteins (*13*). Knockdown of cTAGE5 showed severe accumulation of collagen VII within the ER, indicating that cTAGE5 is also involved in collagen secretion from the ER. Accordingly, cTAGE5 has been thought to be a co-receptor of TANGO1L. Mass spectrometry analysis revealed that cTAGE5 interacts with Sec12 (*14*). Interestingly, TANGO1 does not bind to Sec12. The interaction domain of cTAGE5 for Sec12 was mapped to a few critical residues, which is the immediately at the C-terminus of the membrane-spanning region (*15*). A biochemical assay indicated that the interaction with cTAGE5 does not affect the guanine-nucleotide exchange activity of Sec12 toward Sar1; however, the localization of Sec12 is regulated by the interaction. When cells are depleted with cTAGE5, Sec12 no longer localizes to the ER exit sites and diffuses to the reticular ER. Moreover, cTAGE5 mutants that fail to interact with Sec12 cannot rescue defects in collagen secretion in cTAGE5-depleted cells. Interestingly, when wild type Sar1 is co-overexpressed with cTAGE5 mutants deficient in Sec12 binding, collagen can be exported from the ER, but this is not possible with Sar1 GTPase-deficient mutants. These results strongly suggest that Sec12 accumulation at the ER exit sites is required for collagen export by the activation of Sar1 in the proximity of ER exit sites (Fig. 2A).

It was previously reported that activated Sar1 has an ability to form elongated tubes *in vitro* and in semi intact cells. For details, please refer to our recent review article (*16*). Moreover, a recent study using biochemical and super resolution microscopic analyses has indicated that TANGO1, cTAGE5 and Sec12 are co-packaged with collagens to exit from the ER (Fig. 2B) (*17*). Consistent with previous data, Sec12 has an ability to enlarge COPII carriers when artificially targeted to collagens. Moreover, cTAGE5 enhances the GTPase-activating protein (GAP) activity of Sec23 towards Sar1, and this activity is necessary for collagen exit (*18*). These results indicate that Sar1 activation mediated by Sec12 is involved in the elongation of megacarriers. Conversely, cTAGE5-mediated Sar1 inactivation could be necessary for budding of the megacarriers. In summary, the Sar1 GTPase cycle plays important roles in collagen secretion from the ER (Fig. 2A).

TANGO1 and TALI Are Cargo Receptors for Chylomicrons and VLDL

TANGO1L and TALI have also been reported to interact with apolipoprotein B and serve as cargo receptors for pre-chylomicrons and pre-VLDLs from the

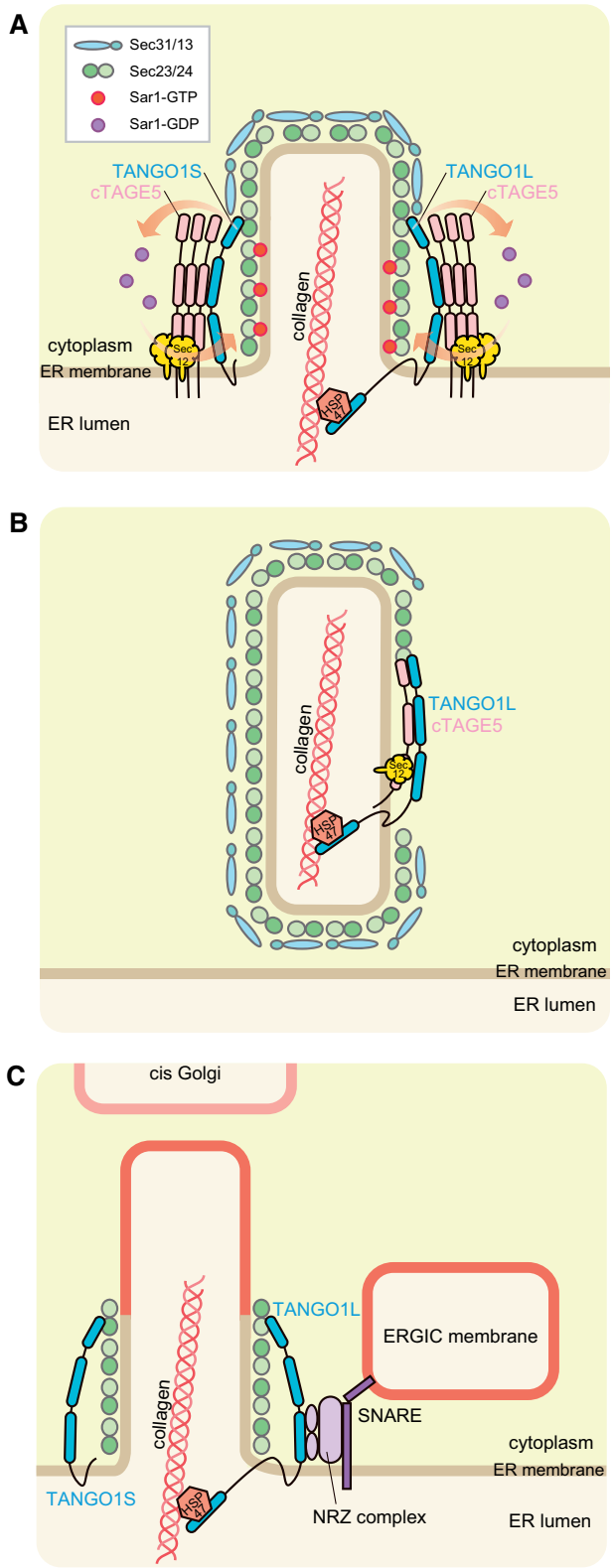

Fig. 2 Models for large cargo secretion by TANGO1 family proteins. (**A**) TANGO1L/cTAGE5/Sec12, TANGO1S/cTAGE5/Sec12 complexes are localized to the ER exit sites. The complexes regulate the Sar1 GTPase cycle to produce megacarriers for collagen secretion. (**B**) TANGO1L/cTAGE5/Sec12 are copackaged with collagens into megacarriers. (**C**) TANGO1 recruits ERGIC membranes by forming a ring-like structure around the ER exit sites. TANGO1 might create tunnels for the ER to Golgi cargo transport.

ER (*11*). TANGO1L and TALI interact with each other in a manner similar to how TANGO1L interacts with cTAGE5, a short splicing variant of TALI (*13*). These results suggest that long isoforms of TANGO1-family proteins might be evolved to serve as cargo receptors, specifically for large cargoes.

TANGO1 Tethers ERGIC Membranes for a Large Cargo Transport

Sly1, an SM family protein which is thought to regulate SNARE-mediated vesicle fusion process, was crosslinked to TANGO1. Further analysis indicated that sly1 is required for collagen export from the ER (*19*). These results prompted to identify SNARE proteins required for collagen export. Syntaxin18 and BNIP1 were identified as t-SNAREs localized to the ER and ykt6 was identified as v-SNARE localized to ERGIC, and all were required for collagen exit from the ER (*19*, *20*). Moreover, recent immunoprecipitation analysis suggests that TANGO1's cytoplasmic 40-amino acid region termed the Tether for ERGIC at the ER (TEER) domain interacts with the NRZ complex composed of NAG (NBAS), RINT1 and ZW10, and the NRZ complex is required for collagen secretion (*21*). The NRZ complex has been known to act as a tether for retrograde transport from ERGIC to ER in coordination with ER SNARE proteins such as Syntaxin18 and BNIP. Thus, these results indicate that an ERGIC to ER transport is required for collagen export from the ER. Indeed, the TEER domain is required for ERGIC membrane recruitment. Taken together, it has been proposed that TANGO1 recruits ERGIC membranes to form megacarriers which can accommodate collagens inside (Fig. 2C).

TANGO1 Forms Macromolecular Complexes at the ER Exit Sites

Blue Native PAGE analysis was conducted to identify a complex entity of TANGO1 and its binding proteins (*10*). Blue Native PAGE is a method of electrophoresis that relatively preserves complex entities, so that the contents of molecular complexes can be identified. TANGO1L migrates with cTAGE5 and Sec12 as a 900 kDa complex, whereas TANGO1S forms a 700 kDa complex with cTAGE5 and Sec12. Silver staining indicated that the complex formed does not include other reported interactors, indicating that the other interactions are weak and/or transient. Further investigation revealed that cTAGE5 has a capacity to form a homo-multimer. Thus, mammalian cells possess two membrane-spanning macro-molecular complexes at the ER exit sites (Fig. 2A). Notably, cTAGE5 knockout mice possess embryonic lethal phenotype which is more severe than that of the TANGO1L knockout mice (*22*). These results indicate that cTAGE5 has broader functions than TANGO1L alone. Thus, it would be interesting to compare the phenotypes of the cTAGE5 knockout and TANGO1L/TANGO1S double knockout mice.

TANGO1 Forms Rings Around the ER Exit Sites

STED microscopic analysis of collagen-secreting cells revealed that TANGO1 forms a ring-like structure around the ER exit sites (*23*). Interestingly, the NRZ complex as well as the TEER domains of TANGO1 are necessary for TANGO1 ring formation (*21*). TANGO1 rings encircle COPII proteins and shrink when collagens are secreted. In addition, TANGO1 self-associates via the TEER domain, possibly mediated by the NRZ complex. Interaction with cTAGE5 is also required for proper TANGO1 ring formation. These results indicated that the TANGO1L/cTAGE5/Sec12 complex and the TANGO1S/cTAGE5/Sec12 complex serve as core units, and a rather loose association of TANGO1 itself mediates the ring-like organization. Based on these results, a theoretical model has recently been proposed that TANGO1 forms a linear filament that encircles around COPII coats, which stabilize the neck of the nascent carrier (*24*). In addition, a recent hypothesis suggests that TANGO1-mediated ER to ERGIC fusion might create a tunnel between ER and Golgi, if ERGIC fuses with the Golgi membrane before the fission of ER-derived vesicles completed (Fig. 2C) (*25*).

TANGO1 Organizes the ER Exit Sites by Recruiting Sec16

TANGO1S lacks collagen recognition motifs but is still required for collagen export from the ER (*10*). These results led us to investigate the role of TANGO1S in secretion. Cells depleted of both TANGO1L and TANGO1S showed not only blocked collagen secretion but also a delay in general cargo secretion. Under these conditions, the co-localization efficiency of Sec16 and Sec31 is significantly reduced, indicating that COPII proteins dissociate from each other. Further characterization revealed that TANGO1 directly interacts with Sec16. Domain mapping revealed that the C-terminal 60 amino acid region of TANGO1, termed the SIR domain, is required for Sec16 binding. Conversely, the ER exit site localization domain of Sec16 is necessary for TANGO1 interaction. TANGO1 mutants failed to interact with Sec16 do not rescue the reduced co-localization between Sec16 and Sec31. These results suggest that the interaction between TANGO1 and Sec16 is required for proper organization of the ER exit sites. Sec16 has been known to interact with most of the COPII proteins and thought to be an organizer or regulator of the ER exit sites (*26*). However, Sec16 is a peripheral membrane protein and, therefore, has to be localized to the ER exit sites for executing its function. We have discovered that localization of Sec16 to the ER exit sites is mediated by its interaction with TANGO1. In addition, localization of cTAGE5, and hence, Sec12, to the ER exit sites is also dependent on the interaction of cTAGE5 with TANGO1. These results suggest that TANGO1 serves as an organizer of the ER exit sites in cooperation with Sec16 (Fig. 3) (*27*). Interestingly, *Drosophila* TANGO1, the only TANGO1 family protein in this species, has also been shown to organize ER exit sites (*28*, *29*). It has also been reported that

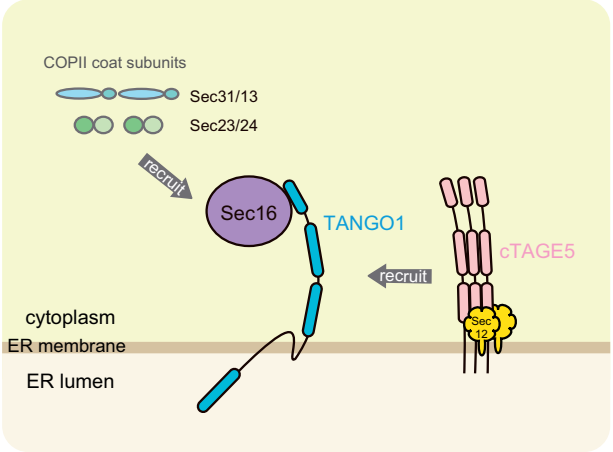

Fig. 3 TANGO1 organizes the ER exit sites with Sec16. TANGO1 recruits Sec16 and cTAGE5/Sec12 to the ER exit sites. Sec16 then recruits Sar1 and inner coat proteins to form carriers for secretion.

Drosophila TANGO1 is required for secretion of bulky cargo, including collagen IV and Dumpy (*29*, *30*). These results suggest that *Drosophila* TANGO1 not only organizes the ER exit sites but is also required for a large cargo secretion. Conversely, in mammals, TANGO1 family proteins divide up the roles; long isoforms TANGO1L and TALI, are specifically involved in large cargo secretion, the short isoform TANGO1S, in association with TANGO1L, is required for the ER exit site organization by interacting with Sec16, and the short isoform cTAGE5 and probably TALI are required for concentrating Sec12 around the ER exit sites for efficient Sar1 activation.

Concluding Remarks

It has been 10 years since TANGO1 was initially identified as a cargo receptor for collagen VII (*8*). A considerable amount of knowledge has been accumulated regarding the functions of TANGO1 and its family proteins. Besides, their clinical significance has been recently reported (*31–33*). However, how these proteins act in a time-dependent manner for initially assembling the ER exit sites and secreting large cargo remains to be investigated.

Funding

This work was supported by Grant-in-Aid for Scientific Research (17H03651 to K.S. and 18H06063 to M.M.) from the Ministry of Education, Culture, Sports, Science and Technology of Japan, by Takeda Science Foundation to K.S., by The Uehara Memorial Foundation to K.S., by The Naito Foundation to K.S. and by Suzuken Memorial Foundation to M.M.

Conflict of interest

None declared.

References

1. Miller, E.A. and Schekman, R. (2013) COPII - a flexible vesicle formation system. *Curr. Opin. Cell Biol* **25**, 420–427.
2. Aridor, M. (2018) COPII gets in shape: lessons derived from morphological aspects of early secretion. *Traffic* **19**, 823–839

3. Fromme, J.C. and Schekman, R. (2005) COPII-coated vesicles: flexible enough for large cargo? *Curr. Opin. Cell Biol.* **17**, 345–352
4. Saito, K. and Katada, T. (2015) Mechanisms for exporting large-sized cargoes from the endoplasmic reticulum. *Cell. Mol. Life Sci.* **72**, 3709–3720
5. Malhotra, V., Erlmann, P., and Nogueira, C. (2015) Procollagen export from the endoplasmic reticulum. *Biochm. Soc. Trans.* **43**, 104–107
6. Bard, F., Casano, L., Mallabiabarrena, A., Wallace, E., Saito, K., Kitayama, H., Guizzunti, G., Hu, Y., Wendler, F., Dasgupta, R., Perrimon, N., and Malhotra, V. (2006) Functional genomics reveals genes involved in protein secretion and Golgi organization. *Nature* **439**, 604–607
7. Wilson, D.G., Phamluong, K., Li, L., Sun, M., Cao, T.C., Liu, P.S., Modrusan, Z., Sandoval, W.N., Rangell, L., Carano, R.A., Peterson, A.S., and Solloway, M.J. (2011) Global defects in collagen secretion in a Mia3/TANGO1 knockout mouse. *J. Cell Biol.* **193**, 935–951
8. Saito, K., Chen, M., Bard, F., Chen, S., Zhou, H., Woodley, D., Polischuk, R., Schekman, R., and Malhotra, V. (2009) TANGO1 facilitates cargo loading at endoplasmic reticulum exit sites. *Cell* **136**, 891–902
9. Ma, W. and Goldberg, J. (2016) TANGO1/cTAGE5 receptor as a polyvalent template for assembly of large COPII coats. *Proc. Natl. Acad. Sci. U S A* **113**, 10061–10066
10. Maeda, M., Saito, K., and Katada, T. (2016) Distinct isoform-specific complexes of TANGO1 cooperatively facilitate collagen secretion from the endoplasmic reticulum. *Mol. Biol. Cell* **27**, 2688–2696
11. Santos, A.J., Nogueira, C., Ortega-Bellido, M., and Malhotra, V. (2016) TANGO1 and Mia2/cTAGE5 (TALI) cooperate to export bulky pre-chylomicrons/VLDLs from the endoplasmic reticulum. *J. Cell Biol.* **213**, 343–354
12. Ishikawa, Y., Ito, S., Nagata, K., Sakai, L.Y., and Bachinger, H.P. (2016) Intracellular mechanisms of molecular recognition and sorting for transport of large extracellular matrix molecules. *Proc. Natl. Acad. Sci. U S A* **113**, E6036–E6044
13. Saito, K., Yamashiro, K., Ichikawa, Y., Erlmann, P., Kontani, K., Malhotra, V., and Katada, T. (2011) cTAGE5 mediates collagen secretion through interaction with TANGO1 at endoplasmic reticulum exit sites. *Mol. Biol. Cell* **22**, 2301–2308
14. Saito, K., Yamashiro, K., Shimazu, N., Tanabe, T., Kontani, K., and Katada, T. (2014) Concentration of Sec12 at ER exit sites via interaction with cTAGE5 is required for collagen export. *J. Cell Biol.* **206**, 751–762
15. Tanabe, T., Maeda, M., Saito, K., and Katada, T. (2016) Dual function of cTAGE5 in collagen export from the endoplasmic reticulum. *Mol. Biol. Cell.* **27**, 2008–2013
16. Saito, K., Maeda, M., and Katada, T. (2017) Regulation of the Sar1 GTPase cycle is necessary for large cargo secretion from the endoplasmic reticulum. *Front. Cell Dev. Biol.* **5**, 75
17. Yuan, L., Kenny, S.J., Hemmati, J., Xu, K., and Schekman, R. (2018) TANGO1 and SEC12 are copackaged with procollagen I to facilitate the generation of large COPII carriers. *Proc. Natl. Acad. Sci. U S A* **115**, E12255–E12264
18. Sasaki, N., Shiraiwa, M., Maeda, M., Yorimitsu, T., Sato, K., Katada, T., and Saito, K. (2018) cTAGE5 acts as a Sar1 GTPase regulator for collagen export. *bioRxiv* 452904
19. Nogueira, C., Erlmann, P., Villeneuve, J., Santos, A.J., Martinez-Alonso, E., Martinez-Menarguez, J.A., and Malhotra, V. (2014) SLY1 and Syntaxin 18 specify a distinct pathway for Procollagen VII export from the endoplasmic reticulum. *Elife* **3**, e02784
20. Santos, A.J., Raote, I., Scarpa, M., Brouwers, N., and Malhotra, V. (2015) TANGO1 recruits ERGIC membranes to the endoplasmic reticulum for procollagen export. *Elife* **4**, e10982
21. Raote, I., Ortega-Bellido, M., Santos, A.J., Foresti, O., Zhang, C., Garcia-Parajo, M.F., Campelo, F., and Malhotra, V. (2018) TANGO1 builds a machine for collagen export by recruiting and spatially organizing COPII, tethers and membranes. *Elife* **7**, e32723
22. Wang, Y., Liu, L., Zhang, H., Fan, J., Zhang, F., Yu, M., Shi, L., Yang, L., Lam, S.M., Wang, H., Chen, X., Wang, Y., Gao, F., Shui, G., and Xu, Z. (2016) Mea6 controls VLDL transport through the coordinated regulation of COPII assembly. *Cell Res.* **26**, 787–804
23. Raote, I., Ortega Bellido, M., Pirozzi, M., Zhang, C., Melville, D., Parashuraman, S., Zimmermann, T., and Malhotra, V. (2017) TANGO1 assembles into rings around COPII coats at ER exit sites. *J. Cell Biol.* **216**, 901–909
24. Raote, I., Garcia-Parajo, M.F., Malhotra, V., and Campelo, F. (2019) TANGO1 regulates membrane tension to mediate procollagen export. *bioRxiv*, 576637
25. Raote, I. and Malhotra, V. (2019) Protein transport by vesicles and tunnels. *J. Cell Biol.* **218**, 737–739
26. Sprangers, J. and Rabouille, C. (2015) SEC16 in COPII coat dynamics at ER exit sites. *Biochem. Soc. Trans.* **43**, 97–103
27. Maeda, M., Katada, T., and Saito, K. (2017) TANGO1 recruits Sec16 to coordinately organize ER exit sites for efficient secretion. *J. Cell Biol.* **216**, 1731–1743
28. Liu, M., Feng, Z., Ke, H., Liu, Y., Sun, T., Dai, J., Cui, W., and Pastor-Pareja, J.C. (2017) Tango1 spatially organizes ER exit sites to control ER export. *J. Cell Biol.* **216**, 1035–1049
29. Rios-Barrera, L.D., Sigurbjornsdottir, S., Baer, M., and Leptin, M. (2017) Dual function for Tango1 in secretion of bulky cargo and in ER-Golgi morphology. *Proc. Natl. Acad. Sci. U S A* **114**, E10389–E10398
30. Lerner, D.W., McCoy, D., Isabella, A.J., Mahowald, A.P., Gerlach, G.F., Chaudhry, T.A., and Horne-Badovinac, S. (2013) A Rab10-dependent mechanism for polarized basement membrane secretion during organ morphogenesis. *Dev. Cell* **24**, 159–168
31. Ishikawa, T., Toyama, T., Nakamura, Y., Tamada, K., Shimizu, H., Ninagawa, S., Okada, T., Kamei, Y., Ishikawa-Fujiwara, T., Todo, T., Aoyama, E., Takigawa, M., Harada, A., and Mori, K. (2017) UPR transducer BBF2H7 allows export of type II collagen in a cargo- and developmental stage-specific manner. *J. Cell Biol.* **216**, 1761–1774
32. Maiers, J.L., Kostallari, E., Mushref, M., deAssuncao, T.M., Li, H., Jalan-Sakrikar, N., Huebert, R.C., Cao, S., Malhi, H., and Shah, V.H. (2017) The unfolded protein response mediates fibrogenesis and collagen I secretion through regulating TANGO1 in mice. *Hepatology* **65**, 983–998
33. Venditti, R., Scanu, T., Santoro, M., Di Tullio, G., Spaar, A., Gaibisso, R., Beznoussenko, G.V., Mironov, A.A., Mironov, A. Jr., Zelante, L., Piemontese, M.R., Notarangelo, A., Malhotra, V., Vertel, B.M., Wilson, C., and De Matteis, M.A. (2012) Sedlin controls the ER export of procollagen by regulating the Sar1 cycle. *Science* **337**, 1668–1672