*Acta Physiologica Sinica*, February 25, 2014, 66(1): 1–6
DOI: 10.13294/j.aps.2014.0001 http://www.actaps.com.cn



**Invited Review**

# A perspective from transport protein particle: Vesicle tether and human diseases

Chunman Li[1,*], Sidney Yu[1, 2]

[1] *School of Biomedical Sciences and* [2] *Epithelial Cell Biology Research Centre, The Chinese University of Hong Kong, Hong Kong, China*

**Abstract:** Vesicle-mediated transport of proteins is a highly regulated, multi-step process. When the vesicle is approaching its target membrane compartment, many factors are required to provide specificity and tethering between the incoming vesicle and the target membrane, before vesicle fusion can occur. Tethering factors, which include multisubunit complexes, coiled-coil proteins, with the help of small GTPases, provide the initial interaction between the vesicle and its target membrane. Of the multisubunit tethering factors, the transport protein particle (TRAPP) complexes function in a number of trafficking steps, including endoplasmic reticulum (ER)-to-Golgi transport, intra- and post-Golgi traffic and autophagosome formation. In this review, we summarize the updated progress in structure and function of TRAPP complexes as well as human diseases caused by genetic mutations in TRAPP.

**Key words:** transport protein particle; vesicles; coat protein complex II; mental retardation; limb girdle muscular dystrophy

# 转运蛋白颗粒复合体在囊泡拴系中的作用与相关疾病

李春满[1,*]，余小彬[1, 2]

香港中文大学[1]生物医学学院；[2]上皮细胞研究中心，香港

**摘 要**：在真核细胞中，囊泡介导的蛋白质转运是一个高度可控的多步骤过程。在囊泡与靶细胞器膜成分融合之前，许多因子参与了它们之间的特异性识别和拴系。其中大部分由多亚基复合体或卷曲螺旋蛋白构成的拴系因子，在小G蛋白的协助下，介导了囊泡与靶细胞器膜成分之间最初的结合。转运蛋白颗粒(transport protein particle, TRAPP)复合体就是一种广泛参与囊泡在细胞内转运的多亚基拴系因子。本文将就TRAPP复合体结构与功能的最新研究进展及与TRAPP复合体基因突变相关疾病做一简单综述和总结。

**关键词**：转运蛋白颗粒复合体；囊泡；COPII衣被蛋白；精神发育迟滞；肢带型肌营养不良症
**中图分类号**：Q71；R34

## 1 Introduction

Eukaryotic intracellular vesicle trafficking is a highly regulated process mediated by many different factors, including soluble N-ethylmaleimide-sensitive factor attachment protein receptors (SNAREs), tethering factors, coat proteins and small GTPases[1–5]. The transport protein particle (TRAPP) complex, initially identified as the tethering factor for endoplasmic reticulum (ER)-derived coat protein complex II (COPII) vesicles, is a multi-subunit protein complex involving at various steps in vesicle transport capable of binding coat proteins, promoting the organization of SNARE proteins and functioning as guanine nucleotide exchange factors (GEF) for Rab/Ypt GTPases [6].

Three forms of TRAPP complex, TRAPPI, II and III, have been identified in yeast, but only the crystal structure of TRAPPI was solved [7–10]. In the mammalian context, the composition and the structure of TRAPP complexes are still far beyond elucidation. In this

*Corresponding author. Tel: +852-39435752; Fax: +852-26035022; E-mail: b113318@cuhk.edu.hk

review, we summarize the updated progress in structure and function of TRAPP as well as human diseases caused by genetic mutations in TRAPP subunits.

## 2 The structures and functions of TRAPP

The TRAPPI complex consists of seven subunits named Trs20, Trs23, Trs33, Trs31, Bet5 and two copies of Bet3 in yeast. Their mammalian orthologs are TRAPPC2, TRAPPC4, TRAPPC6, TRAPPC5, TRAPPC1 and TRAPPC3 respectively. In the TRAPPI complex, the subunits were organized through lateral juxtaposition into a flat and elongated particle with two lobes: the Trs20-Trs31-Bet3 heterotrimer constitutes one lobe, while the Bet3-Trs33-Bet5 heterotrimer constitutes the other lobe, linked together by the subunit Trs23[11]. TRAPPI plays an essential role in ER-to-Golgi transport. The major functions of TRAPPI include: (1) COPII vesicle tether; (2) Ypt1/Rab1 GEF activity; and (3) Regulation of the v- and t-SNARE pairing [11]. Thus far, there are two models proposed to explain how TRAPPI mediates vesicle tethering. In one model (Fig. 1*A*), TRAPPI assembles onto COPII vesicle through the interaction between Bet3/TRAPPC3 and Sec23. Then COPII vesicle-docked TRAPPI activates Ypt1/Rab1 via the GEF activity. The activated Ypt1/Rab1 recruits tethering factor Uso1/p115 onto the COPII vesicles through an interaction with COPII vesicle-associated SNARE. Finally, Uso1/p115 brings the vesicle close to target membrane to prepare fusion and the TRAPPI complex is released from the COPII vesicle [12]. This model is consistent with the observation that the TRAPP subunit Bet3/TRAPPC3 can directly interact with the COPII coat subunit sec23 [13], and Bet3 acts after COPII budding but before Rab1 and α-SNAP during ER-Golgi transport [14]. In addition, this model may also explain how TRAPPI appears to act in homotypic fusion of COPII vesicles in mammalian cells since a copy of TRAPPC3 in each of the two lobes of the complex interacts with sec23 from two different COPII vesicles and bring them together [6]. In the second model, the TRAPPI complex was proposed lying flat on Golgi membrane and interacts with the incoming vesicle. In this model, TRAPPI complex is anchored through the Bet3 subunit to the Golgi, where it catalyzes nucleotide exchange on membrane bound Ypt1/Rab1-GDP, then the Ypt1/Rab1-GTP recruits Uso1/p115 to tether with COPII vesicles. Uso1/p115 brings the COPII vesicle closer to the Golgi membrane and promotes TRAPPI vesicle tethering mediated by interaction between Bet3 and Sec23. The Trs20/TRAPPC2 subunit may also interact with SNARE proteins to regulate v- and t-SNARE pairing[7, 15]. The localization of Bet3 to the cis-Golgi complex[16], as well as biochemical studies showing that Bet3 functions on this compartment support this model (Fig. 1*B*). It is noteworthy that in yeast, TRAPPI complex stably binds to the Golgi even under conditions disrupting membrane traffic and causing the Golgi apparatus to disperse. It was also indicated that the Golgi-bound TRAPPI complex did not recycle between the Golgi and the ER compartments. However, in the mammalian context, significant amount of TRAPPC3 (about 85%), the most conserved TRAPPI subunit, was found in the cytosol comparing the relatively small fraction (about 15%) associated with membrane[14]. The cytosolic TRAPPC3 also exists in two distinct pools, a high molecular weight pool representing the TRAPP complex bound pool and a low molecular weight pool reflecting the free form of TRAPPC3. Based on this finding, we suppose that in mammalian cells, the assembled TRAPPI complexes exist in both the cytoplasm and the Golgi apparatus but with different functions. The cytosolic TRAPPI binds to COPII vesicle at ER exit sites through direct interactions between TRAPPC2 and Sar1-GTP as well as TRAPPC3 and Sec23, whereas the membrane-localized TRAPPI complex activates Uso1/Rab1-GDP. The GTP-bound Ypt1/Rab1 binds to Uso1/p115, which brings the COPII vesicle close to the target membrane to enable fusion (Fig. 1*C*). TRAPPC2 binds Sar1-GTP prior to TRAPPC3-sec23 interaction to control the active state of Sar1, thus accelerating dissociation of Sar1 from membranes. The TRAPPC3-sec23 interaction may stabilize the COPII vesicles by preventing the sec23 phosphorylated by other kinases until they were close enough to Golgi membrane in which the TRAPPC3 was replaced by Hrr25p, a sec23 kinase [17].

In yeast, TRAPPII consists of all TRAPPI subunits and three additional large proteins, Trs65, Trs120 (TRAPPC9) and Trs130 (TRAPPC10). It was proposed that the mammalian ortholog of Trs65 is C5orf44 but such notion has yet to be extensively tested. Much less is known about the structure of TRAPPII complex. Cryo-electron microscopy (EM) revealed that yeast TRAPPII forms dimer in which the TRAPPII-specific subunits are sandwiched between two TRAPPI complexes. With the outer layer on both sides containing the TRAPPI cores, Trs120 and Trs130 cap opposite

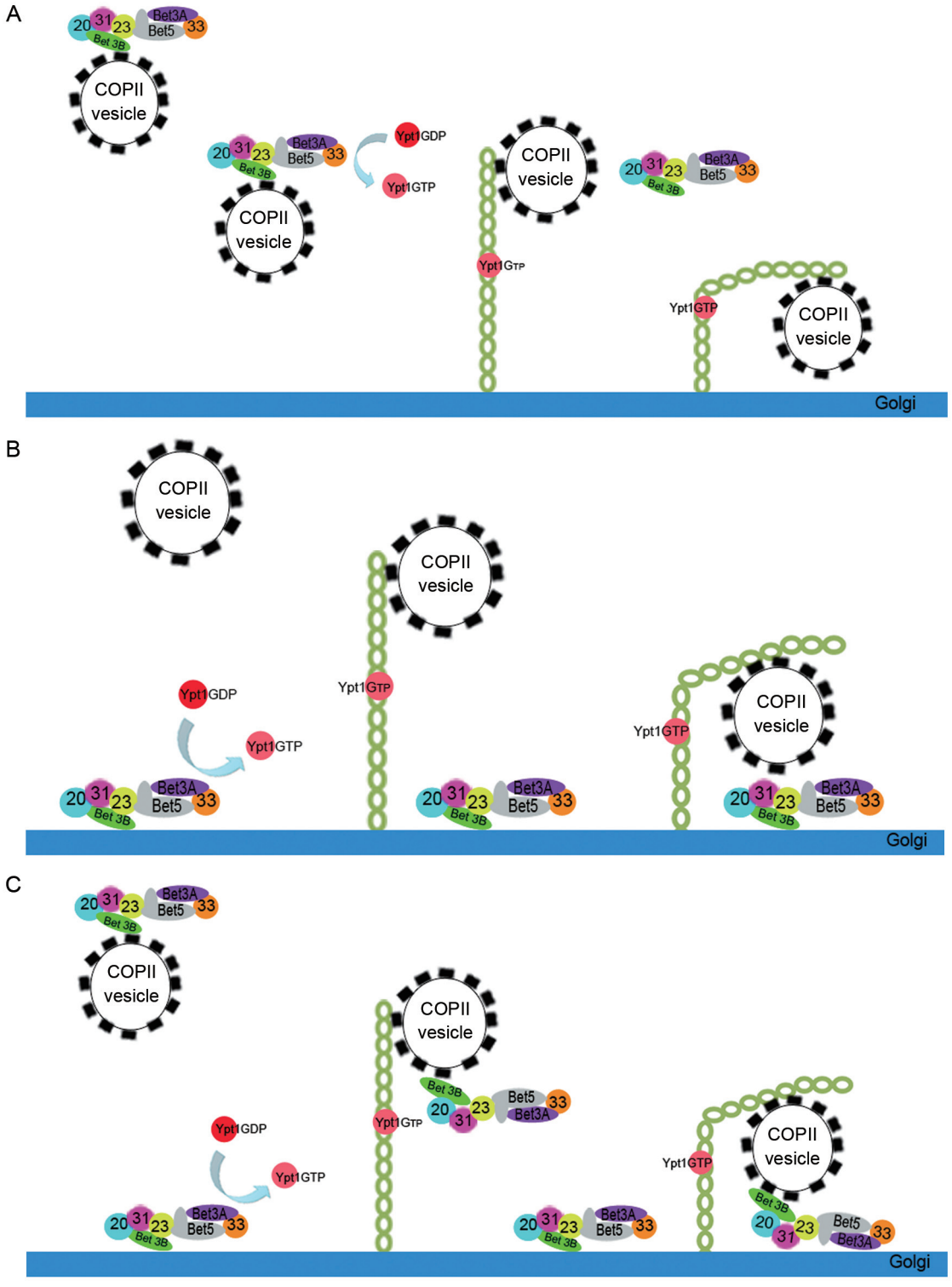


Fig. 1. Models of TRAPPI tethering COPII vesicles. *A*: TRAPPI binds to COPII vesicle via Bet3 and sec23 interaction. Then TRAPPI catalyzes nucleotide exchange of Rab1/Ypt1-GDP. Rab1/Ypt1-GTP binds to the long coiled-coil tethering protein (p115/Uso1), which brings the vesicle close to the Golgi membrane. *B*: Membrane bound TRAPPI catalyzes nucleotide exchange of Rab1/Ypt1-GDP. The Ypt1/Rab1-GTP recruits Uso1/p115 to tether with COPII vesicles. p115/Uso1 brings the vesicle close to the target membrane to interact with TRAPPI. *C*: Cytosolic TRAPPI binds to COPII vesicle via Bet3 and sec23 interaction first. Then membrane-bound TRAPPI catalyzes nucleotide exchange of Rab1/Ypt1-GDP. Rab1/Ypt1-GTP binds to the long coiled-coil tethering protein (p115/Uso1), which brings the vesicle close to the Golgi membrane.

ends of TRAPPI forming the middle layer, where two Trs65 molecules dimerize into a twofold symmetry[18]. In this model, Trs120 is attached to the Trs33-end of TRAPPI. However, recent studies show that Trs20 binds to Trs120 both in yeast and in mammalian cells[9, 19]. Therefore, two other models were given based on this finding[20]. In one model, Trs120 binds to Trs20 in one TRAPPI monomer and Trs33 in the other anti-parallel TRAPPI monomer to bridge the two TRAPPI complexes, and Trs130 and Trs65 stabilize the dimer. In the second model, Trs120 interacts with Trs20 and Trs33 in one TRAPPI complex, and then the TRAPPII complex is formed via Trs130 and Trs65. The mammalian TRAPPII does not appear to form dimer since it has a molecular weight of 600 kDa in a gel filtration column, identical to the size of yeast TRAPPII isolated from Trs65-deleted strain. TRAPPII also has the GEF activity towards Ypt1/Rab1, suggesting that it preserves the same catalytic site as TRAPPI, and this activity has been found both in yeast and in mammalian cells[6, 21]. However, TRAPPI and TRAPPII serve as GEFs for Ypt1 and Ypt31/32 (orthologs of human rab1 and rab11) respectively[10]. The Ypt31/32 GEF activity may be related to the TRAPPII-specific subunits because: first, mutations in Trs120 and Trs130 abolished this activity while increased the Ypt1 GEF activity; second, Trs130 interacts with the nucleotide-free form of Ypt31 in a yeast two-hybrid assay[10]; third, the Ypt31/32 intracellular distribution has been altered in Trs130 mutant cells[10]. As a tethering factor, TRAPPII complex has been reported to interact with COPI coat complex and to be involved in multiple transport pathways. In yeast, Trs120 mutation blocked the transport from early endosome to Golgi, while Trs130 mutation displays general defects beyond ER-to-Golgi step[22]. Similar results were obtained from mammalian cells[21].

Accumulating evidence indicates that TRAPP is also involved in many other cellular processes. The TRAPPII complex is required for the centrosomal trafficking of Rabin8 and ciliogenesis. TRAPPC9 can directly bind to $p150^{Glued}$ to inhibit the interaction between $p150^{Glued}$ and Sec23/Sec24 both *in vitro* and *in vivo* [23]. On the other hand, novel components of mammalian TRAPP are continually identified. For instance, the mammalian TRAPPC11 and TRAPPC12, which have no homologues in yeast, have been identified to regulate ER-to-Golgi trafficking at a very early stage [24].

It has been proposed that TRAPPIII complex contains TRAPPI core subunits plus Trs85/TRAPPC8 [8, 25], but the Trs85-containing complex in yeast was detected in the range of 1.3 MDa, far bigger than the sum of TRAPPI and Trs85. Trs130, a TRAPPII-specific subunit, is also co-fractionated with Trs85-containing complex, suggesting the exact subunit composition of TRAPPIII needs further characterization. This complex is specifically localized to the preautophagosomal structure (PAS) through a direct interaction of Trs85 and Atg17 as well as Atg9. TRAPPIII participates in autophagy formation by activating Ypt1 to recruit the Atg1 kinase [8, 26].

## 3 TRAPP and diseases

### 3.1 TRAPPC2 and spondyloepiphyseal dysplasia tarda (SEDT)

At least three TRAPP subunits have been shown to be associated with human diseases. Mutations in TRAPPC2 cause an X-linked recessive osteochondrodysplasia named SEDT (MIM 313440), occurring almost exclusively in males. Therefore, TRAPPC2 is also named Sedlin. Individuals with this disorder have a short trunk and neck, with short stature caused by impaired growth of the spinal bones. According to The Human Gene Mutation Database (HGMD, http://www.hgmd.org/), more than 40 mutations in TRAPPC2 gene related to SEDT have been reported, including splice site mutations, nonsense mutations, deletions and missense mutations. Most of these mutations, except the mutation D47Y, result in truncation of the protein or cause protein misfolding and therefore induce the loss of normal physiological functions. Since TRAPPC2 works as an adaptor for the formation of TRAPPII and TRAPPIII by direct interaction with TRAPPC9 or TRAPPC8 respectively, it was speculated that the loss of functional TRAPPC2 will significantly affect intracellular membrane trafficking mediated by TRAPPII and TRAPPIII, resulting in serious consequences in skeletal development. Of note, the D47Y mutation in TRAPPC2 also impairs the interaction between TRAPPC2 and TRAPPC9 or TRAPPC8 although the mutant protein is normally folded. However, there is no evidence that the patients of SEDT have any other membrane traffic related defects. It seems only the collagen trafficking in chondrocytes affected[27]. There are several possibilities to explain this phenomenon: First, there are homologs of TRAPPC2 at three chromosomal loci. Among them, the homolog on chromosome 19 can be expressed[28, 29]. Second, another gene, TCA17, which

has homology to TRAPPC2, may substitute the function of the missing TRAPPC2. Last, in the TRAPPII complex, TRAPPC9 binds to TRAPPC2 and TRAPPC6 simultaneously, therefore, TRAPPII complex may not completely disintegrated when the function of TRAPPC2 is defective. Recently, Venditti *et al*. compared the impact of TRAPPC2 knockdown on trafficking of procollagen type II (PCII) and type I (PCI) with other cargoes including the temperature-sensitive variant of vesicular stomatitis virus G (ts045-VSV-G), CD8a, albumin and a1-antitrypsin. They found that PCI and PCII were the only cargoes whose ER exit was affected by TRAPPC2 depletion. They further explored the molecular mechanisms of TPAPPC2-regulated ER exit of PC and suggested that TANGO1, a receptor required for packing PC into COPII vesicles, recruited TRAPPC2 to ER exit through physical interaction. At ER exit, TRAPPC2 binds to Sar1-GTP to control the active state of Sar1. Therefore, TRAPPC2 dysfunction in SEDT patients may induce an increase in Sar1-GTP which in turn leads to the formation of abnormal carriers that are not suitable to form megacarriers[30].

### 3.2 TRAPPC9 and intellectual disability (ID)

The genetic lesions in TRAPPC9 displayed a distinct phenotype characterized by moderate to severe ID and brain anomalies[31]. All the TRAPPC9 pathogenic variants reported so far are loss-of-function mutations with a premature stop codon, resulting in nonfunctional, truncated proteins. These truncated TRAPPC9 lose the TRAPPC2 and TRAPPC10 binding domain, suggesting that the assembly and function of TRAPPII complex must have been impaired. Since the exact intracellular transport pathway(s) that TRAPPII involved in has remained unclear, it is hard to elucidate the pathological mechanism at the molecular and cellular levels.

### 3.3 TRAPPC11 and limb girdle muscular dystrophy (LGMD)

Two mutations in TRAPPC11 have been reported recently. Three individuals with homozygous c.2938G > A(p.Gly980Arg) missense mutation in the gryzun domain present with LGMD while five individuals with the homozygous c.1287+5G>A splice-site mutation resulting in a 58 amino acid in-frame deletion (p.Ala372_Ser429del) in the foie gras domain present with myopathy, infantile hyperkinetic movements, ataxia, and intellectual disability[32]. At the cellular level, immunostaining of Golgi marker proteins showed punctate Golgi dispersal in cells from affected individuals similar to the Golgi pattern in TRAPPC11 knockdown Hela cells [24]. In cells from individuals with in-frame deletion of TRAPPC11, normal ER to Golgi traffic along with delayed Golgi to cell surface traffic was seen when using vesicular stomatitis virus G (VSVG) as a transport marker. Moreover, the late endosomal/lysosomal component LAMP1 showed a reduced, centriolar distribution in cells from affected individuals while in control cells LAMP1 was seen in puncta throughout the cells. This phenomenon suggests that TRAPPC11 is involved in the formation of or the trafficking in late endosomes/lysosomes. It will be of interest in the future to examine the role of TRAPPC11-containing TRAPP complex on membrane transport from early endosome to late endosome/lysosome and from trans-Golgi to late endosome/lysosome.

## 4 Future perspective

In the last five years, we have witnessed increasing reports of genetic diseases with mutations identified in different TRAPP subunits. For SEDT, the first genetic disease associated with TRAPP identified almost fifteen years ago, we are beginning to understand that the cause of skeletal developmental defects in these individuals is impairment of ER export of PCII. TRAPPC2 can regulate the GTP-binding status of Sar1. These findings bring new concepts and excitement to the TRAPP research field. For mutations in TRAPPC9 and TRAPPC11, the molecular etiology remains elusive. However, as with the story of SEDT, new concepts and excitement will be expected as we move forward to unravel the disease mechanism.

## REFERENCES

1 Whyte JR, Munro S. Vesicle tethering complexes in membrane traffic. J Cell Sci 2002; 115(13): 2627–2637.
2 Gerst JE. SNAREs and SNARE regulators in membrane fusion and exocytosis. Cell Mol Life Sci 1999; 55(5): 707–734.
3 Lee MC, Miller EA. Molecular mechanisms of COPII vesicle formation. Semin Cell Dev Biol 2007; 18(4): 424–434.
4 Schekman R, Orci L. Coat proteins and vesicle budding. Science 1996; 271(5255): 1526–1533.
5 Pfeffer SR. Transport vesicle docking: SNAREs and associates. Annu Rev Cell Dev Biol 1996; 12: 441–461.
6 Cai Y, Chin HF, Lazarova D, Menon S, Fu C, Cai H, Sclafani A, Rodgers DW, De La Cruz EM, Ferro-Novick S, Reinisch KM. The structural basis for activation of the Rab Ypt1p by the TRAPP membrane-tethering complexes. Cell

2008; 133(7): 1202–1213.
7 Sacher M, Barrowman J, Wang W, Horecka J, Zhang Y, Pypaert M, Ferro-Novick S. TRAPP I Implicated in the specificity of tethering in ER-to-Golgi transport. Mol Cell 2001; 7(2): 433–442.
8 Lynch-Day MA, Bhandari D, Menon S, Huang J, Cai H, Bartholomew CR, Brumell JH, Ferro-Novick S, Klionsky DJ. Trs85 directs a Ypt1 GEF, TRAPPIII, to the phagophore to promote autophagy. Proc Natl Acad Sci U S A 2010; 107(17): 7811–7816.
9 Tokarev AA, Taussig D, Sundaram G, Lipatova Z, Liang Y, Mulholland JW, Segev N. TRAPP II complex assembly requires Trs33 or Trs65. Traffic 2009; 10(12): 1831–1844.
10 Morozova N, Liang Y, Tokarev AA, Chen SH, Cox R, Andrejic J, Lipatova Z, Sciorra VA, Emr SD, Segev N. TRAPPII subunits are required for the specificity switch of a Ypt-Rab GEF. Nat Cell Biol 2006; 8(11): 1263–1269.
11 Kim YG, Raunser S, Munger C, Wagner J, Song YL, Cygler M, Walz T, Oh BH, Sacher M. The architecture of the multisubunit TRAPP I complex suggests a model for vesicle tethering. Cell 2006; 127(4): 817–830.
12 Yu S, Liang Y. A trapper keeper for TRAPP, its structures and functions. Cell Mol Life Sci 2012; 69: 3933–3944.
13 Cai H, Yu S, Menon S, Cai Y, Lazarova D, Fu C, Reinisch K, Hay JC, Ferro-Novick S. TRAPPI tethers COPII vesicles by binding the coat subunit Sec23. Nature 2007; 445(7130): 941–944.
14 Loh E, Peter F, Subramaniam VN, Hong W. Mammalian Bet3 functions as a cytosolic factor participating in transport from the ER to the Golgi apparatus. J Cell Sci 2005; 118(6): 1209–1222.
15 Lorente-Rodriguez A, Barlowe C. Entry and exit mechanisms at the cis-face of the Golgi complex. Cold Spring Harb Perspect Biol 2011; 3(7): a005207.
16 Barrowman J, Sacher M, Ferro-Novick S. TRAPP stably associates with the Golgi and is required for vesicle docking. EMBO J 2000; 19(5): 862–869.
17 Lord C, Bhandari D, Menon S, Ghassemian M, Nycz D, Hay J, Ghosh P, Ferro-Novick S. Sequential interactions with Sec23 control the direction of vesicle traffic. Nature 2011; 473(7346): 181–186.
18 Yip CK, Berscheminski J, Walz T. Molecular architecture of the TRAPPII complex and implications for vesicle tethering. Nat Struct Mol Biol 2010; 17(11): 1298–1304.
19 Zong M, Wu XG, Chan CW, Choi MY, Chan HC, Tanner JA, Yu S. The adaptor function of TRAPPC2 in mammalian TRAPPs explains TRAPPC2-associated SEDT and TRAPPC9-associated congenital intellectual disability. PLoS One 2011; 6(8): e23350.
20 Taussig D, Lipatova Z, Kim JJ, Zhang X, Segev N. Trs20 is required for TRAPP II assembly. Traffic 2013; 14(6): 678–690.
21 Yamasaki A, Menon S, Yu S, Barrowman J, Meerloo T, Oorschot V, Klumperman J, Satoh A, Ferro-Novick S. mTrs130 is a component of a mammalian TRAPPII complex, a Rab1 GEF that binds to COPI coated vesicles. Mol Biol Cell 2009; 20: 4205–4215.
22 Cai H, Zhang Y, Pypaert M, Walker L, Ferro-Novick S. Mutants in trs120 disrupt traffic from the early endosome to the late Golgi. J Cell Biol 2005; 171(5): 823–833.
23 Zong M, Satoh A, Yu MK, Siu KY, Ng WY, Chan HC, Tanner JA, Yu S. TRAPPC9 mediates the interaction between p150Glued and COPII vesicles at the target membrane. PLoS One 2012; 7: e29995.
24 Scrivens PJ, Noueihed B, Shahrzad N, Hul S, Brunet S, Sacher M. C4orf41 and TTC-15 are mammalian TRAPP components with a role at an early stage in ER-to-Golgi trafficking. Mol Biol Cell 2011; 22(12): 2083–2093.
25 Wang J, Menon S, Yamasaki A, Chou HT, Walz T, Jiang Y, Ferro-Novick S. Ypt1 recruits the Atg1 kinase to the preautophagosomal structure. Proc Natl Acad Sci U S A 2013; 110(24): 9800–9805.
26 Kakuta S, Yamamoto H, Negishi L, Kondo-Kakuta C, Hayashi N, Ohsumi Y. Atg9 vesicles recruit vesicle-tethering proteins Trs85 and Ypt1 to the autophagosome formation site. J Biol Chem 2012; 287(53): 44261–44269.
27 Gedeon AK, Colley A, Jamieson R, Thompson EM, Rogers J, Sillence D, Tiller GE, Mulley JC, Gecz J. Identification of the gene (SEDL) causing X-linked spondyloepiphyseal dysplasia tarda. Nat Genet 1999; 22(4): 400–404.
28 Scrivens PJ, Shahrzad N, Moores A, Morin A, Brunet S, Sacher M. TRAPPC2L is a novel, highly conserved TRAPP-interacting protein. Traffic 2009; 10(6): 724–736.
29 Gecz J, Hillman MA, Gedeon AK, Cox TC, Baker E, Mulley JC. Gene structure and expression study of the SEDL gene for spondyloepiphyseal dysplasia tarda. Genomics 2000; 69(2): 242–251.
30 Venditti R, Scanu T, Santoro M, Di Tullio G, Spaar A, Gaibisso R, Beznoussenko GV, Mironov AA, Mironov A, Jr., Zelante L, Piemontese MR, Notarangelo A, Malhotra V, Vertel BM, Wilson C, De Matteis MA. Sedlin controls the ER export of procollagen by regulating the Sar1 cycle. Science 2012; 337(6102): 1668–1672.
31 Marangi G, Leuzzi V, Manti F, Lattante S, Orteschi D, Pecile V, Neri G, Zollino M. TRAPPC9-related autosomal recessive intellectual disability: report of a new mutation and clinical phenotype. Eur J Hum Genet 2013; 21(2): 229–232.
32 Bogershausen N, Shahrzad N, Chong JX, von Kleist-Retzow JC, Stanga D, Li Y, Bernier FP, Loucks CM, Wirth R, Puffenberger EG, Hegele RA, Schreml J, Lapointe G, Keupp K, Brett CL, Anderson R, Hahn A, Innes AM, Suchowersky O, Mets MB, Nurnberg G, McLeod DR, Thiele H, Waggoner D, Altmuller J, Boycott KM, Schoser B, Nurnberg P, Ober C, Heller R, Parboosingh JS, Wollnik B, Sacher M, Lamont RE. Recessive TRAPPC11 mutations cause a disease spectrum of limb girdle muscular dystrophy and myopathy with movement disorder and intellectual disability. Am J Hum Genet 2013; 93(1): 181–190.