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REVIEW

A trapper keeper for TRAPP, its structures and functions

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Abstract During biosynthesis many membrane and secreted proteins are transported from the endoplasmic reticulum, through the Golgi and on to the plasma membrane in small transport vesicles. These transport vesicles have to undergo budding, movement, tethering, docking, and fusion at each organelle of the biosynthetic pathway. The transport protein particle (TRAPP) complex was initially identified as the tethering factor for endoplasmic reticulum (ER)—derived COPII vesicles, but the functions of TRAPP may extend to other areas of biology. Three forms of TRAPP complexes have been discovered to date, and recent advances in research have provided new insights on the structures and functions of TRAPP. Here we provide a comprehensive review of the recent findings in TRAPP biology.

Keywords TRAPP · COPII vesicle · Autophagy · ER exit sites · Vesicular transport

Introduction

The trafficking of protein transport vesicles requires a process called vesicle tethering, an initial interaction between the incoming vesicle and its native target membrane [1]. In ER-to-Golgi vesicle transport, ER-derived COPII vesicles are tethered by a protein complex called TRAPP [2]. It has been postulated that this complex works in concert with vesicle tethering mediator p115 to bring COPII vesicles to the ERGIC and/or *cis*-Golgi membrane surface in preparation for vesicle fusion [3, 4]. The TRAPP complex was first identified as a protein complex consisting of 7–10 subunits that is bound to Bet3 in yeast [5]. Subsequent biochemical and genetic studies showed that TRAPP has functions in multiple membrane trafficking pathways [6], and other aspects of biology. A summary of the functions of TRAPP in various membrane trafficking pathways, and the evidence for such functions is presented in Fig. 1. In this review, we provide an updated summary of the reported functions of TRAPP and outline challenges we are facing and the directions we take on how one should further study these functions.

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The structures of TRAPP

Structural studies of yeast TRAPP have elucidated the most solid conclusions, although evidence for the structures of mammalian TRAPP complexes is emerging. Figure 2 shows the structures of yeast and mammalian TRAPP complexes identified to date. In yeast, three forms of TRAPP complexes, TRAPPI, II, and III, have been identified [2, 7–9]. TRAPPI contains six subunits, Trs20, Trs23, Trs31, Bet5, two copies of Bet3, and perhaps Trs33 (discussion below). X-ray crystal structures of the six-subunit TRAPPI core reveal that the complex forms a flat and elongated structure [4, 10]. TRAPPII contains all the subunits of TRAPPI plus three additional subunits: Trs65, Trs120, and Trs130. EM structure of this complex showed that TRAPPII is a dimer, consisting of two sets of every

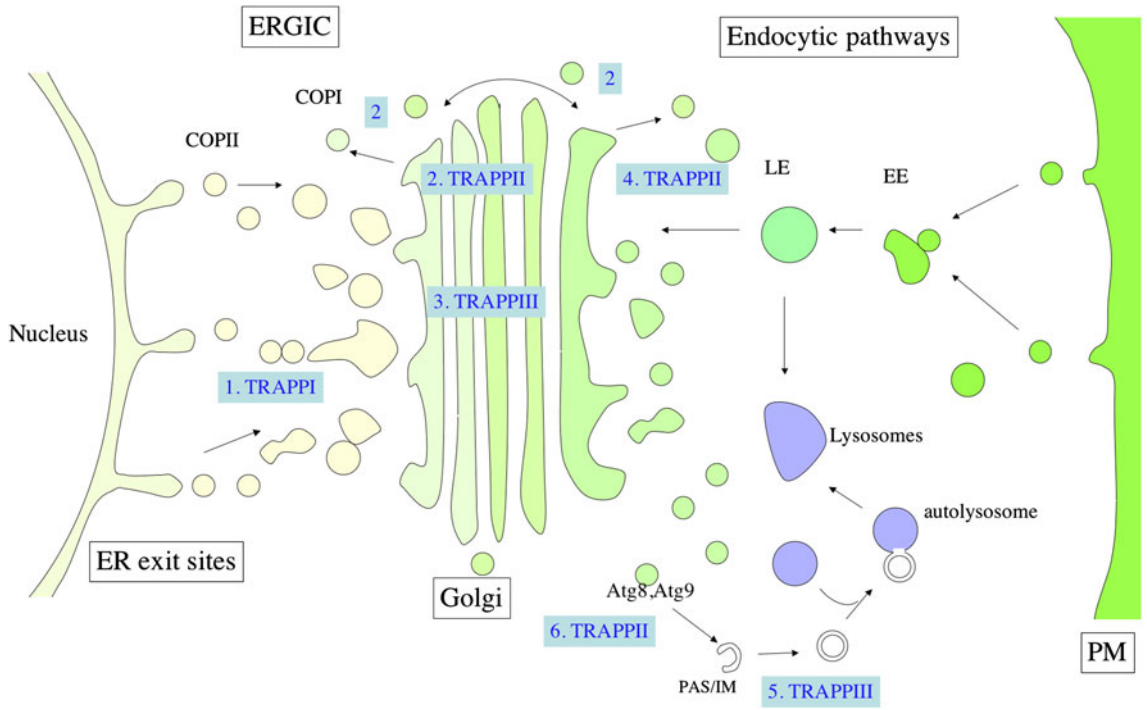

Fig. 1 TRAPP complexes function in various membrane trafficking pathways. TRAPPI tethers COPII vesicles at ERGIC but its role in this part of the vesicular transport may start at the ER exit sites. TRAPPII mediates intra-Golgi traffic, Golgi exit, endosome-to-Golgi traffic, and the trafficking of autophagy proteins Atg8 and Atg9 from Golgi to PAS. TRAPPIII has function in anterograde transport at the Golgi and also regulates autophagy. For each of the functions of TRAPP (numbered in the figure), supporting evidence is listed as follows: *1.* TRAPPC3/Bet3 interacts with Sec23. Many TRAPP subunits are localized in the ERGIC. TRAPPI acts as GEF for Rab1/Ypt1 at ERGIC. RNAi depletion or yeast genetic studies showed blocks in early transport [2, 17, 20, 21, 24, 26, 39]. *2.* TRAPPC9 and TRAPPC10 interact with COPI coat subunit and possible retrograde vesicular transport. Yeast genetic studies on the TRAPPII-specific subunits showed defects in intra-Golgi transport. TRAPPII serves as GEF for Ypt31/32 and plays a critical role in mediating the traffic exiting the Golgi toward the plasma membrane in yeast [2, 9, 17, 53, 85]. *3.* RNAi depletion of TRAPPIII-specific subunit, TRAPPC8, blocked transport at the Golgi. Trs85 mutation slightly impaired anterograde transport at the Golgi [20, 40]. *4.* Yeast Trs120 mutants showed defect in endosome to Golgi traffic [77]. *5.* TRAPPIII-specific subunit Trs85 is required for the localization of Ypt1 to PAS. RNAi depletion of TRAPPC8 demonstrated this subunit (possibly mammalian TRAPPIII) negatively regulates autophagy. TRAPPIII subunits physically interact with other proteins in the autophagic protein network [7, 22]. *6.* Mutations of yeast TRAPPII-specific subunit Trs130 impaired the transport of Atg8 and Atg9 to PAS [40]. *EE* Early endosome, *LE* late endosome, *PAS* pre-autophagosomal structure, *IM* isolation membrane, *PM* plasma membrane, *ER* endoplasmic reticulum, *ERGIC* ER-Golgi intermediate compartment

TRAPP subunit (four for the subunit Bet3). It forms a three-layered structure in three dimensions (Fig. 1 for a schematic drawing of yeast TRAPPII) [11]. The outer layers on both sides contain the TRAPPI cores, connected by Trs120 and Trs130 at either side to form the middle layer, where two Trs65 molecules are located and dimerize in a twofold symmetry. TRAPPIII contains TRAPPI core plus Trs85 [7, 12]. Its structural information has not been obtained to date.

Discrepancies regarding the structure of TRAPP have also been reported. For example, Trs33 has been reported to be essential for the assembly of TRAPPII, and therefore, it has been regarded as a member of the TRAPPII complex [8, 9, 13]. The less studied TRAPPIII is thought to contain TRAPPI and Trs85. However, using gel filtration Choi et al. [14] have detected at least three independent profiles of TRAPP subunits, including a higher-molecular-weight TRAPP complex containing Trs85. This complex is 4,000 kD and is distinct from TRAPPII or the TRAPPIII proposed by Lynch-Day et al. [7]. Trs130 has two peaks on gel filtration, which correspond to 4,000-kD TRAPP and TRAPPII, respectively. Trs31, a subunit present in all forms of TRAPP, has three peaks corresponding to 4,000-kD TRAPP, TRAPPII, and TRAPPI. Interestingly, the newly identified TRAPP subunit, Tca17, as well as the TRAPPII-specific subunits Trs65 and Trs130, comigrate on gel filtration. These results raise the possibility that TRAPPIII may contain more than just the TRAPPI core plus Trs85. The higher-molecular-weight complex may contain Trs31, perhaps Trs130, and other proteins such as coat proteins, cargo, or regulatory proteins [14]. Its function is unclear at this point. Tca17 is a homolog of Trs20. It

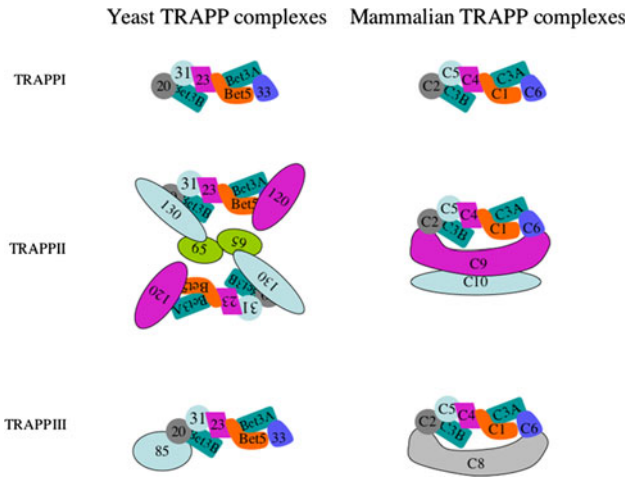

Fig. 2 Structure of TRAPP complexes. Three forms of TRAPP complexes have been revealed from structural studies of the yeast complexes. The structures of mammalian complexes are more preliminary, particularly TRAPPII and TRAPPIII. In both systems, additional proteins have been assigned to TRAPPII or TRAPPIII but not presented in the drawings because the evidence is still preliminary

has been proposed to bind to TRAPPI on the side of the complex opposite of Trs20 as a part of TRAPPII [15, 16]. Whether Tca17 exists in TRAPPII at equimolar or sub-stoichiometric ratio to other subunits and its exact interacting partner within the complex remains to be determined. Nonetheless, it is clear that Tca17 and its mammalian ortholog TRAPPC2L are intimately associated with TRAPP.

The structure of mammalian TRAPP is less well understood. In mammalian cells, initially only one form of TRAPP complex was identified by gel filtration chromatography and co-immunoprecipitation but we begin to believe there are multiple TRAPP complexes co-migrating at a similar molecular weight on gel filtration columns [17, 18]. When endogenous TRAPPC9 was immuno-isolated, TRAPPC10, but not TRAPPC8, was detected, suggesting the mammalian TRAPPC9-containing complex is similar to yeast TRAPPII and contain no TRAPPC8 [12]. The TRAPPC8-containing complex also migrates at similar molecular weight on the gel filtration column ([15] and our unpublished observation). Both TRAPPC9 and TRAPPC8 can interact with TRAPPC2 but not at the same time. Therefore, it is apparent that at least two distinct TRAPP complexes must exist in mammalian cells. Furthermore, TRAPPC2 appears to be the principle subunit that mediates the interaction between the TRAPPI core and TRAPPC8 or TRAPPC9 [12]. Unlike yeast TRAPPII, the mammalian TRAPPII equivalent has TRAPPC2 serving as an adaptor to form different types of TRAPP complex in mammals. Neither yeast nor mammalian TRAPPI requires this subunit for the core complex to serve as the guanine nucleotide exchange factor (GEF) for Rab1/Ypt1 [10], making TRAPPC2 an ideal subunit for its adaptor function.

The complexity of mammalian TRAPP is compounded by the presence of multiple TRAPP homologs, alternatively spliced variants of the large subunits, and novel subunits or binding proteins that are not part of the yeast TRAPP complexes. More and more proteins have been found to interact with the established TRAPP subunits, an observation that brings excitement as well as challenge to the field. There is no simple way to define whether a new binding protein to TRAPP is a functional subunit of the complex. Determining the stoichiometry of the proteins within the TRAPP complex is a good approach to define subunits. However, precise quantification of each subunit within a complex is usually difficult in practice, due to the lack of high-quality antibodies, highly purified TRAPP complex, and the presence of subcomplexes in yeast and mammalian cells alike. Nonetheless, a current perspective of the TRAPP subunits, their homologs, interacting proteins, and the associated biochemical functions, is presented in the Table 1. In particular, both TRAPPC6a and 6b can complex with TRAPPC3, suggesting distinct TRAPP complexes may be present in mammals [19]. Recently, a homolog to TRAPPC3, called TRAPPC3L, has been discovered [15]. A Trs130-related protein, now designated as TRAPPC11, has been proposed to be part of the mammalian TRAPP that form oligomers, much like the yeast TRAPPII [20]. The ortholog of TRAPPC11 is required for general secretion in *Drosophila* [21]. Other novel TRAPP subunits include TTC-15 (now designated as TRAPPC12), which was first identified to be associated with mammalian TRAPP in two independent proteomic studies and has been implicated as a part of the machinery of the autophagy network [22, 23]. The gene product of C5orf44 is distantly related to Trs65 and has, therefore, been proposed to be the mammalian ortholog of Trs65 [14]. This protein can interact with other TRAPP subunits when overexpressed in mammalian cells. How precisely these new subunits are arranged in the mammalian TRAPP and what exactly are their biochemical functions remain to be determined, but it is possible that the large number of TRAPP subunit homologs in mammalian system will create many more combinations of subunit composition, allowing for more diversified functions of mammalian TRAPPs.

Many of the large subunits have been found to have variants caused by alternatively spliced mRNAs. It is very likely that these splicing variants have different tissue distribution and that they are involved in vesicle tethering at their native tissues. Multiple alternatively spliced mRNA variants of TRAPPC10 have been identified in a mammalian cell line, suggesting that the splicing variants may also have distinct functions at the subcellular level. In particular, some of the TRAPPC10 splicing isoforms lack the

Table 1 Information of TRAPP subunits, biochemical functions, and their interacting proteins

TRAPP subunits (yeast/mammals)	Biochemical functions	Interacting proteins identified and other notes
Trs20/TRAPPC2	Part of TRAPPI, not required for Ypt1p/Rab1 GEF activity [4, 10]	Intracellular chloride channel proteins CLIC1, CLIC2 [92]
Homolog:		
TRAPPC2L or Tca 17	As adapter for TRAPPC8 or TRAPPC9 for TRAPPIII or TRAPPII assembly, respectively [12]	Nuclear protein PAM14 [90]
TRAPPC2.19		Transcription factors MBP1, PITX1, SF1 [91]
Trs23/TRAPPC4	Part of TRAPP1, interacts extensively with Ypt1p/Rab1 to catalyze nucleotide exchange [4, 10]	Syndecan-2 [88]
		ERK1/2; TRAPPC4 modulates ERK1/2 nuclear localization
Trs31/TRAPPC5	Part of TRAPPI	–
Trs33/TRAPPC6	Part of TRAPPI	–
Homolog:		
TRAPPC6a, C6b		
Bet3/TRAPPC3	Part of TRAPPI	Auto-acylate at cystein 68 [83]
Homolog:		
TRAPPC3L		
Bet5/TRAPPC1	Part of TRAPPI	–
Trs120/TRAPPC9	Part of TRAPPII	NF-κB signaling pathway molecules NIK, IKK [78]
	Intra-Golgi and endosome-to-Golgi traffic	
	TRAPPC9 links TRAPPC10 to TRAPPCII in mammalian cells [12]	Dynactin subunit p150^{Glued} [56]
		Rabin8 [42]
	Potentiate NF-κB transactivation	COPI coat subunit γ-COP [17]
	Binds to p150^{Glued}	
	Binds to γ-COP	
Trs130/TRAPPC10	Part of TRAPPII	COPI coat subunit γ-COP [17]
	Intra-Golgi and endosome-to-Golgi traffic	Och 1 transcription is activated by Trs130 deletion [87]
		Genetic interaction with Arf1 and Ypt31 [86]
Trs65/C5orf44	Part of TRAPPII, required for dimerization of two sets of TRAPP in yeast	Gea2 [85]
Trs85/TRAPPC8	Part of TRAPPIII	–
	Play a role in autophagy	
	ER-to-Golgi traffic in mammalian cells	
TRAPPC11 (C40rf41)	Part of mammalian TRAPP	–
TRAPPC12 (a.k.a. TTC-15, CGI-87)	Part of mammalian TRAPP	Binds to TECPR-1 in autophagy network proteomic study [22]

domain that interacts with other TRAPP subunits, suggesting that these isoforms may function as a free subunit independently (Sidney Yu, unpublished observation).

The functions of TRAPP

TRAPPI as COPII tether

TRAPPI binds to COPII vesicles in vitro. The subunit TRAPPC3 was localized to the ER exit sites in mammalian cells and is required for COPII vesicle tethering in vitro [24]. It was previously demonstrated to be essential for function of the early secretory pathway in mammalian cells [25]. Subsequently, Bet3/TRAPPC3 was shown to bind to Sec23 specifically in both yeast and mammalian systems [26]. The binding of COPII vesicles by TRAPPI was inhibited by the presence of excess recombinant Bet3/TRAPPC3 in both systems. These observations not only confirm TRAPPI as a COPII vesicle tether but also pinpoint the interaction to Bet3/TRAPPC3 and Sec23. Since the X-ray crystal structure of TRAPPI (yeast and mammalian) revealed two copies of Bet3/TRAPPC3 (designated as Bet3A and Bet3B, Fig. 2) occupying both ends of an elongated, rod-like structure, it has been proposed that the two copies of TRAPPC3 may bring together two COPII vesicles to facilitate their subsequent homotypic vesicle fusion [10]. We do not think this is a likely mechanism

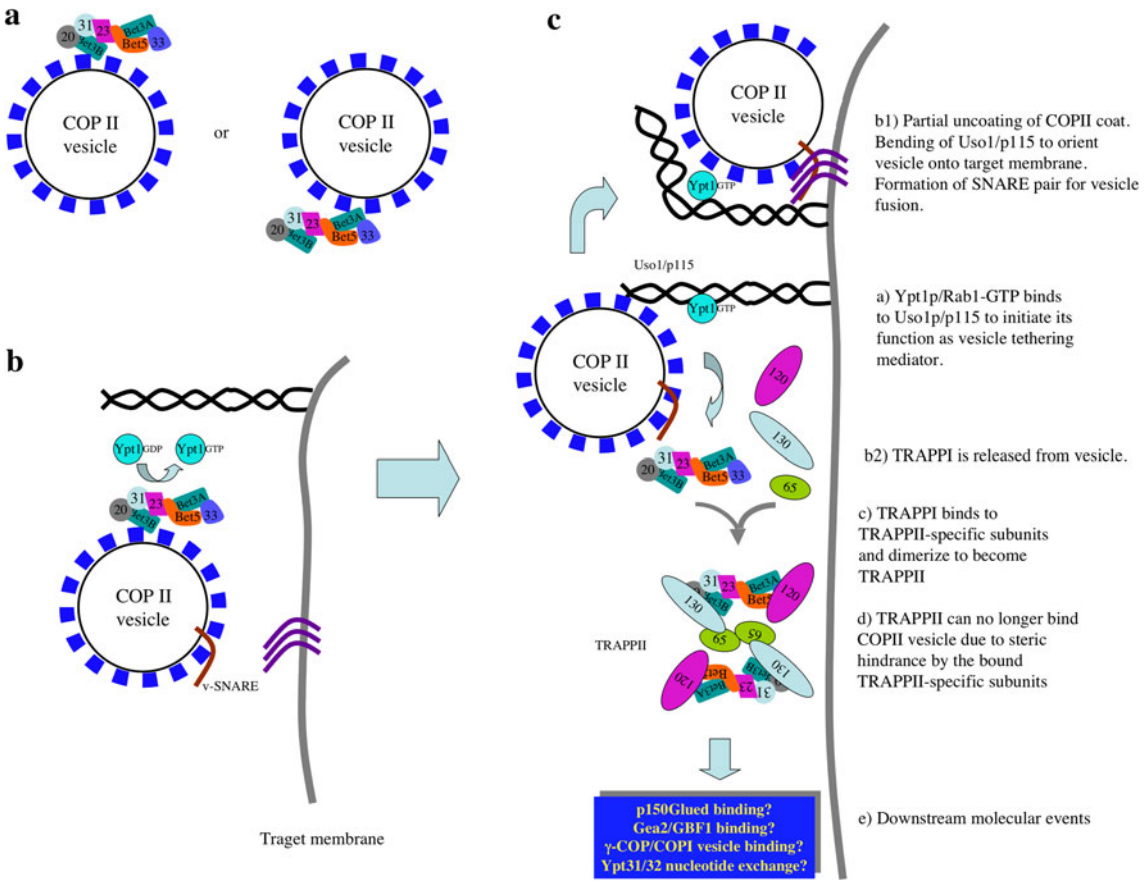

Fig. 3 Hypothetic model of how TRAPP tethers COPII vesicles. **a** TRAPPI binds to COPII vesicle via Bet3/TRAPPC3 and Sec23 interaction. The interaction is mediated either by Bet3B away from where Ypt1/Rab1 binds, or by Bet3A on the same side of Ypt1/Rab1 interaction. **b** When COPII vesicle approaching the target membrane, Ypt1/Rab1 exchange is catalyzed by TRAPPI. **c** (a) Ypt1/Rab1-GTP interacts with tethering mediator Uso1/p115. (b1) Uso1/p115 brings COPII vesicle to close proximity to the target membrane. Partial uncoating of COPII vesicle and SNARE pair occur to facilitate fusion. (b2-d) TRAPPI is released from COPII vesicle and TRAPPII-specific subunits are assembled onto TRAPPI to become TRAPPII. The complex dimerizes; and (e) performs downstream TRAPPII specific functions

because both the yeast and mammalian TRAPPI core have the same subunit arrangement but yeast COPII vesicles fuse heterotypically to the *cis*-Golgi, suggesting the presence of two Bet3/TRAPPC3 in the structure should not be regarded as structural characteristic needed for homotypic fusion. Since TRAPPI, but not TRAPPII, can bind the COPII vesicle [2], the interaction between Bet3/TRAPPC3 and Sec23 must be blocked by the presence of TRAPPII-specific subunits. We propose the binding of Sec23 is located either in Bet3B on the side of the TRAPPI complex that accommodates the TRAPPII-specific subunits, or in a part of Bet3A that also interacts with Trs120 (Fig. 3a). The molecular events taking place during the tethering of a COPII vesicle may happen as follows: Through the interaction between Bet3/TRAPPC3 and Sec23, TRAPPI is assembled onto COPII vesicle. When the COPII vesicle approaches the target membrane, the vesicle-bound TRAPPI activates Ypt1/Rab1 via nucleotide exchange activity (Fig. 3b). GTP-bound Ypt1/Rab1 binds to the tethering mediator Uso1/p115, which brings the vesicle close to target membrane in preparation of fusion (Fig. 3c, a, b1). At this stage, TRAPPI is released from the COPII vesicle (Fig. 3c, b2). It can bind to TRAPPII-specific subunits, dimerize to form TRAPPII (Fig. 3c, c), and performs TRAPPII-specific functions, including the interactions with $p150^{Glued}$, molecules functioning in COPI vesicles like GBF1 and γ-COP, and serving as GEF for Ypt31/32/Rab11 (Fig. 3c, d–e). To account for how homotypic tethering and fusion occur in mammalian COPII vesicles, we imagine the "target membrane" depicted in Fig. 3b, c as just another COPII vesicle. While COPII vesicles may not contain all the constituents of the *cis*-Golgi or ERGIC membrane, p115, ER/Golgi SNAREs and other proteins essential to the tethering process are present on COPII vesicles and are required for homotypic COPII tethering and fusion [27, 28].

A subsequent study indicates that TRAPPI binds to Sec23 at the same site as Sar1 does, suggesting the COPII

tethering occurs only after Sar1 has been released from the coat upon GTP hydrolysis [3]. The site can be phospho-regulated by Hrr25, the yeast homolog of casein kinase Iδ (CKIδ). It has been proposed that the Golgi-associated CKIδ regulates the uncoating of COPII vesicles at the target membrane to ensure no back fusion of nascent COPII vesicles with the ER. The role of CKIδ in the early secretory pathway may not be as simple as proposed, particularly in mammalian cells. In mammals, there are at least five homologs of CKI. CKIδ and ε belong to a sub-family and are the closest ortholog to yeast Hrr25. CKIα, δ and ε have been reported to participate in Wnt signaling [29]. CKIδ and, to a lesser degree, CKIε are involved in the regulation of the circadian cycle [30]. As the activities of CKIs are heavily influenced by other signaling activities in homeostasis and development, it is difficult to image that CKI is needed for the uncoating of COPII vesicles in every budding and fusion cycle. Therefore, unlike the situation in yeast, perhaps mammalian CKI regulates COPII vesicle transport at a global level. Its kinase activity toward Sec23 might remove the phorsphorylated pool of Sec23 from taking part in COPII budding. Therefore, an additional layer of regulation on the early vesicular transport is installed at the steps of COPII budding and tethering, so that the constitutive secretory pathway can be coordinated with the overall physiological conditions in a multicellular organism. The status of the circadian cycle, the stages of body development and tissue differentiation, and possibly other homeostatic events all have an effect on the activity of the constitutive secretory pathway. Of note, it has long been observed that membrane trafficking is strongly influenced by the circadian cycle. The densities of synaptic vesicles at the nerve termini, internal granulated vesicles and other endomembranes, e.g., the Golgi, in tissues such as suprachiasmatic nucleus and pinealocytes, change rhythmically according to the status of light–dark cycle [31–34]. In plants, the Arf1 ortholog is transcriptionally regulated by circadian cycle [35]. These findings have established a circadian effect on various aspects in membrane trafficking, but provide no clue whether such an effect is direct or via the actions of other circadian-regulated hormones. The observation that CKIδ regulates the COPII vesicle transport may represent the first evidence of a direct regulation by circadian cycle. Furthermore, the role of CKIδ in the early secretory pathway is not limited to the COPII vesicle transport because CKIδ also phosphoregulates the membrane binding of ARFGAP1 [36], one of the Golgi-localized GTPase-activating proteins for ARF1. ARF1 is a small GTPase essential to the formation of COPI-coated vesicles [37]. Furthermore, CKIδ also phosphoregulates actin foci dynamics, most likely via ARFGAP1 ([38] and Sidney Yu, unpublished observation).

TRAPP is a GEF for Rab1/Ypt1 and Ypt31/32

All three forms of yeast TRAPP have GEF activity toward Ypt1, the yeast homolog of Rab1 [7, 39]. However, only TRAPPII, but not TRAPPI or TRAPPIII, has GEF activity toward Ypt31/32 [9, 40]. Supported by solid genetic and biochemical data, these investigators showed that when TRAPPI is converted to TRAPPII, the specificity of the Rab also changed from Ypt1 to Ypt31/32 [9, 13, 40]. This notion remains controversial [41]. Recent studies on EM structure of TRAPPII revealed that the TRAPPII-specific subunits are located away from the Ypt1 binding site on TRAPPI. A co-complex of TRAPPII and Ypt1 observed under EM suggests the TRAPPII-specific subunits provide no steric hindrance to prevent Ypt1 from interacting with TRAPPI core [11]. As there is no evidence to demonstrate that the specificity conversion from Ypt1 to Ypt31/32 comes from the TRAPPII-specific subunits, it is quite possible that there might be other associated factor(s) that provide(s) the specificity conversion, i.e., blocking Ypt1 from TRAPPI and helping Ypt31/32 to bind to the TRAPPII-specific subunit(s). Since in the studies suggesting that TRAPPII is specific for Ypt31/32, GST-tagged TRAPP subunits were introduced to yeast cells and Rab exchange assays were performed using a preparation of TRAPP complex purified by GST pull-down [9], associated factor(s) besides the TRAPPII complex may have been brought down to serve as specificity conversion factor. We propose there must either be additional factor(s) that change the Rab specificity of TRAPPII so that it can serve as Ypt31/32 GEF or the associated factor is in fact the GEF for Ypt31/32. An example of a TRAPPII-specific subunit being associated with a Rab GEF has been reported [42]. In zebrafish, assembly of ciliary vesicles at the centrosome requires a number of molecules including TRAPPC9, Rabin8 and Rab11 [42]. TRAPPC9 binds to Rabin8, the GEF of Rab8. Furthermore, Rabin8 interacts with Rab11, the ortholog of Ypt31/32.

Mammalian TRAPP isolated by immunoprecipitation using antibodies against TRAPPC9 or TRAPPC10 was able to demonstrate GEF activity toward Rab1 [17]. The activity is relatively weak compared to a bacterial gene product DrrA/SidM that also serves as a GEF for Rab1 [43]. Nonetheless, the GEF activity of mammalian TRAPP toward Rab1 is functionally significant as Rab1-GTP interacts with tethering mediator p115, which in turn recruits SNAREs for vesicle fusion [27, 28].

Involvement of TRAPP in autophagy

Trs85 has been implicated in autophagy in yeast [44, 45]. Subsequent study has identified the TRAPPIII complex, a

complex distinct from TRAPPI and TRAPPII, as the form of TRAPP that specifically mediates the effect on autophagy. TRAPPIII directs Ypt1 to the pre-autophagosomal structure (PAS) [7]. In mammalian cells, Rab1 is required for autophagy, as the overexpression of constitutively active Rab1 promotes and its dominant negative mutant inhibits autophagy [46]. Rab1 is localized with autophagic vesicles that do not contain hydrolytic enzymes. A major concern for these observations is that Trs85 and its mammalian ortholog TRAPPC8 are also involved in early secretory pathway. While a relationship between TRAPP and autophagy is unquestioned, the inter-related roles of Trs85/TRAPPC8 on these two processes are difficult to dissect. In yeast, although Trs85 deletion did not have pronounced effect on the early secretory pathway [7], a Trs85 deletion strain containing a tagged version of Bet3 was synthetically impaired for early vesicle transport [2]. Further, Trs85 deletion in a different genetic background produced a secretion defect ([40]. Overall, it appears that yeast strains with Trs85 deleted are very close to the threshold of having a secretion defect, implying that Trs85 functions in the early secretory pathway. It is, therefore, premature to designate TRAPPIII or Trs85 as autophagy- or secretion-specific at present. Second, it is well known that defects in the early secretory pathway also result in defects in autophagy. Mutants of Sec12, Sec23, and Sec24 are also defective in autophagy in addition to their well-characterized functions on early vesicle transports [47, 48]. On the other hand, in mammalian cells, depletion of a number of TRAPP subunits, including TRAPPC8 and TRAPPC12, impairs ER-to-Golgi transport [20]. Both subunits have been implicated in mammalian autophagy [22]. Recently, a TRAPPII-specific subunit, Trs130, has also been demonstrated to play a role in the Cvt pathway and starvation-induced autophagy (Zou et al., in revision). This effect is mediated by Ypt31/32, which was previously shown to take part in yeast autophagy [49]. Therefore, TRAPPII may exert its effect on autophagy through its functions in the endosome and *trans*-Golgi. Overall, we think that TRAPP may play a role in autophagy but it remains to be determined whether the effect is specific or just an indirect consequence of impaired secretion.

Involvement of TRAPP in microtubule-related processes

Accumulating evidence indicates that TRAPP is involved in such microtubule-related processes as cytokinesis, ciliogenesis, and dyneine/dynactin-mediated vesicle movement. In all cases, the subunit TRAPPC9 appears to be the first subunit reported to be involved in these processes. Its exact role, however, is not clear at this stage.

Cytokinesis

It has been well documented that cytokinesis requires a number of molecules important in membrane trafficking because active delivery of membrane to the boundaries of the dividing cells is a necessary step for cytokinesis [50, 51]. In *Drosophila* male meiotic cells, cytokinesis is dependent on the gene product of brunelleschi [52], subsequently revealed to be the *Drosophila* ortholog of Trs120/TRAPPC9 [52]. dTRAPPC9 genetically interacts with dRab11 and dPI4Kβ. Both proteins are required for the proper localization of dRab11 to the cleavage furrow in spermatocytes. Interestingly, spermatocytes are the only tissue affected in brunelleschi mutants, suggesting the involvement of dTRAPPC9 in cytokinesis is tissue-specific and may require spermatocyte-specific factor(s). Although the precise relationship between TRAPPC9 and PI4Kβ has not been elucidated, these molecules, together with the yeast ortholog of Rab11, Ypt31/32, are required for the normal function and the integrity of Golgi structure in yeast [53].

Trs120/TRAPPC9 has also been implicated in cytokinesis in plants. Endosome-derived vesicles failed to assemble into a cell plate in dividing cells in Arabidopsis carrying a mutation in Trs120/TRAPPC9 [54]. Although the precise mechanism in cytokinesis in plant cells must be distinct from that of mammalian cells, the accumulation of vesicles at the site of cleavage is a necessary process, so that sufficient plasma membrane is available to divide the daughter cells. It is likely that Trs120/TRAPPC9 plays a role in the tethering of these vesicles during cytokinesis in plants and animals alike.

Ciliogenesis

Another close relationship between TRAPPC9 or TRAPPII and Rab11 is found in the process of ciliogenesis. Rabin8 and Rab11 are required for the formation of ciliary vesicles. The membrane assembly of primary cilia requires a number of proteins including Rab8, its GEF Rabin8, upstream GTPase Rab11 and certain TRAPP subunits [42, 55]. Rab11 activates Rabin8, which catalyzes the nucleotide exchange for Rab8. Rabin8 interacts with TRAPPC9 and Rab11 via distinct domains within the protein [42], although the exact relationship between TRAPPC9 and Rab11 has yet to be elucidated in this context. TRAPP is required in this process because siRNA depletion of TRAPP subunits, e.g., TRAPPC9, TRAPPC10, andTRAPPC3, impaired the centrosomal localization of Rabin8 and therefore ciliogenesis. As has been the situation in yeast and the cytokinesis, the simultaneous involvement of both TRAPPII and Rab11/Ypt31/32 has been a recurrent theme.

Table 2 Physiological functions of TRAPP in multicellular organisms

TRAPP subunits (yeast/mammals)	Mutants or genetic diseases in multicel organisms
Trs20/TRAPPC2	X-Linked spondyloephiphyseal dysplasia tarda [64–73] (multiple epiphyseal abnormalities, early onset of osteoarthritis, short trunk and barrel-shaped chest, platyspondyly)
Trs33/TRAPPC6	Hypomorphic TRAPPC6a causes pigmentation defect in mutant mice [82]
Trs120/TRAPPC9	Intellectual disability with neonatal microcephaly [74–76]
	Brunelleschi mutant in *Drosophila* [52] (defect in cytokinesis in male meiotic cells)
TRAPPC11 (C4orf41)	Foie gras mutant in zebrafish [79, 80] (steatosis and hepatomegaly in mutant fish; ER stress, accumulation of lipid droplets in mutant hepatocytes)

The physiological functions of TRAPP in multicellular organisms are inferred from the phenotypes of the TRAPP mutants or the clinical presentations of the genetic lesions found in TRAPP subunit gene loci

p150^{Glued}/vesicle trafficking

Overexpression of TRAPP subunits disrupts astral microtubule arrays in mammalian cells [56]. All of the TRAPP subunits, when overexpressed, disrupt astral arrays to a varying degree, resulting in a circular array instead. This effect is mediated by a novel interaction between a subunit of dynactin p150^{Glued} and TRAPPC9 [56]. Dynactin has been implicated in various aspects of membrane trafficking including the movement of COPII from ER to Golgi [57]. The cargo-binding domain of p150^{Glued} physically interacts with Sec23 and Sec24. TRAPPC9 reportedly binds to p150^{Glued} on the same domain at higher affinity [56]. Overexpressing TRAPPC9 reduced the colocalization between endogenous p150^{Glued} and Sec23, and depletion of TRAPPC9 increased the colocalization. It has been well established that cytoplasmic dynein is required for the movement of vesicles from the ER to Golgi [58, 59], and p150^{Glued} is a subunit of dynactin that increases the processivity of the dynein motor [60]. p150^{Glued} binds directly to COPII coat subunits Sec23 and Sec24 and mediates the movement of COPII vesicles. The precise mechanism of how p150^{Glued} executes this is not clear [61]. TRAPPC9 is localized to the ERGIC, the target membrane for COPII vesicles [56]. The observation that TRAPPC9 can "outmuscle" Sec23 and Sec24 for the interaction with p150^{Glued} suggests that TRAPPC9 may mediate the movement of COPII vesicles that have been tethered at, or just fused with, the ERGIC. Complete uncoating of COPII coat is not a pre-requisite for the subsequent fusion step [3, 62]. In fact, COPII coat subunits have been observed partially localized to the ERGIC [63].

Physiological functions of TRAPP

Often mutations that severely interfere with the function of genes essential to basic cellular functions result in early embryonic lethality. For many genes, functional redundancy due to the existence of multiple homologs ensures the well-being of the individual. However, mutations that only slightly compromise these essential genes can have functional consequences in specific physiological settings. Often, the elucidation of disease mechanisms not only affirms the importance of the gene toward a cellular function but also provides new insight that stimulates further research. Good examples that illustrate this concept are the mutations found in TRAPP subunits in humans. A summary of the pathological and physiological functions of TRAPP based on either the phenotypes of TRAPP subunit mutant animals or the clinical conditions of human individuals having genetic lesions in TRAPP subunits is presented in Table 2. Since these phenotypes are far milder than the biochemical functions of TRAPP would have predicted, we believe functional redundancies must have play a role in limiting the severity of the TRAPP mutant phenotypes. Detailed discussions are presented in the following.

X-linked spondyloepiphyseal dyslasia tarda (SEDT)

SEDT is a genetic disease associated with the onset of osteoarthrosis [64]. Mutations in TRAPPC2 (human Trs20) have been identified in these patients, and therefore, TRAPPC2 was independently named sedlin [65]. In humans, the homologs of TRAPPC2 can be found at three chromosomal loci. TRAPPC2 was the first identified disease gene for SEDT and is located on the X chromosome [65]. However, the same sequence is duplicated on chromosome 19. Initially regarded as a pseudogene, the locus from chromosome 19 can be expressed and, therefore, has been named TRAPPC2.19 [15, 66]. The ortholog of Tca17 is called TRAPPC2-like protein or Sedlin-like protein (TRAPPC2L or SEDLP, respectively) [15, 52]. Given the secretory function of TRAPPC2, it has been speculated that defective secretion of collagen could be the cause of the abnormal skeletal development in SEDT patients [67], but the exact molecular mechanism of why mutations in TRAPPC2 can cause such a defect has not been elucidated.

It has been hypothesized that the loss of TRAPPC2 function in SEDT patients is compensated by its homologs, SEDLP/TRAPPC2L or TRAPPC2.19. Therefore, the loss of TRAPPC2 function shows a much milder clinical expression. Of note, most of the disease-causing mutations isolated result in truncation of the protein [68–72]. The partially translated mutant protein is not stable and ends up in the degradation pathway. So far, there are only five missense mutations identified [68, 73], three of which (S73L, F83S, V130D) cause protein misfolding and invoke proteosome-mediated degradation [73]. The D47Y mutation did not cause protein misfolding but this mutation impairs the interaction between TRAPPC2 and TRAPPC9 or TRAPPC8 [12]. Therefore, it is very likely the formation of mammalian TRAPPII and TRAPPIII must have been impaired in chondrocytes, resulting in a mild defect in general secretion. When reaching a developmental stage where rapid secretion of collagen or protein hormones by chondrocytes is needed, cells defective in TRAPPII and/or TRAPPIII simply cannot meet the demand for general secretion, resulting in a clinical expression as SEDT. So far, it remains unclear why other tissues that demand heavy secretion are not affected by the TRAPPC2 mutation.

TRAPPC9-associated intellectual disability

Intellectual disability (ID) with microcephaly is sometimes associated with genetic lesions in TRAPPC9/Trs120 [74–76]. Individuals identified with such mutations have partial deletion of the TRAPPC9 at the carboxyl terminus. These mutant proteins no longer have the portion of the molecule that interacts with TRAPPC2 and TRAPPC10 [38], suggesting that the assembly and function of TRAPPII must have been compromised in these patients. In SEDT patients, the mutant TRAPPC2 can be compensated by TRAPPC2L and TRAPPC2.19 in most other tissues. Unlike the situation in SEDT patients, there is no obvious homolog for TRAPPC9, and the function of mutant TRAPPC9 found in ID individuals is probably not compensated. This phenomenon not only raises doubt that mammalian TRAPPII is essential for secretion but also creates a dilemma for the current view of the mammalian TRAPP as a single biochemical entity. If the mammalian TRAPP is the TRAPPII equivalent but still functions as a COPII vesicle tether, this essential function must be compromised in the TRAPPC9-associated ID individuals. If so, the tissues affected due to impaired early vesicle transport should have been more wide-spread and the effects more severe. The fact that individuals with TRAPPC9 mutations are normal in most tissues except neurons suggests that the function of TRAPP as a COPII tether must be normal in these individuals. In other words, the TRAPPI function is not affected in these individuals. Therefore, it is logical to assume that the genetic lesion in TRAPPC9 only affects TRAPPII, which, reportedly, plays roles in intra-Golgi or endosome-to-Golgi traffic in yeast [2, 77]. Distinct forms of mammalian TRAPP complexes must exist, just like the situation in yeast, with each form of TRAPP having specific functions. In TRAPPC9-associated ID individuals, the TRAPPI function is not affected while the non-vital TRAPPII function is slightly affected in certain neurons. Of note, TRAPPC9 has also been found to interact with the NF-κB signaling pathway [78]. It has also been shown that this pathway is slightly affected in TRAPPC9-mutant patient fibroblasts [74]. The precise function of TRAPPC9 or TRAPPII in neurodevelopment is currently unknown.

Other functions

Foie gras The zebrafish foie gras mutant develops steatosis and hepatomegaly, among other developmental defects 5 days after fertilization [79]. The mutant hepatocytes showed accumulation of lipid droplets and dilated ER. The pathological state is mediated by ER stress, as the depletion of ATF6, a key mediator of the unfolded protein response in the ER, can partially rescue the steatosis phenotype [80]. Excessive protein unfolding in the ER lumen will trigger a response that increases, via transcriptional regulation, the abundance of ER membrane and the machinery essential for protein folding within this organelle [81]. Such a process, called the unfolded protein response, is intimately related to ER stress. The foie gras mutant gene encodes TRAPPC11, a distantly related protein to TRAPPC10. The mechanism of how TRAPPC11 regulates ER stress and lipid metabolism in hepatocytes remains to be determined. As the ER is the major organelle for lipid synthesis, any defect caused by the protein vesicle trafficking pathway may affect the lipid metabolism and/or cause ER stress.

Pigmentation and melanosome biogenesis A mouse strain with mosaic hypopigmentation was created by a proviral integration at a site near TRAPPC6a [82]. This event reduced expression of TRAPPC6a mRNA in mutant mice to about 1 % of that in normal mice. Defective melanosomes were observed in the retinal pigmented epithelium in the mutant mice. The question of how directly TRAPPC6a participates in melanosome biogenesis and the mechanism of how TRAPPC6a plays a role in this novel and unexpected function awaits further investigation.

Other protein interactions and potential functions Various TRAPP subunits have been implicated in many cellular functions and the precise roles require further characterization. Bet3/TRAPPC3 has the ability to self-acylate at cysteine 68 [83]. The need for such lipid modification is

unknown, but potentially this effect helps dimeric Bet3/TRAPPC3 localized to the Golgi membrane [84]. TRAPPC9 and TRAPPC10 have been demonstrated to bind to the COPI coat subunit γ-COP in the COS cell overexpression system [17]. This interaction was later confirmed in yeast [85]. The GEF for Arf1, Gea2, was also shown to interact with TRAPPII [85]. Yeast two-hybrid assays demonstrated that Trs65 binds directly with Gea2. Furthermore, TRAPPII failed to interact with Gea2 in a Trs65 deletion strain. Whether Trs65 binds directly to Gea2 needs further investigation because there is the potential caveat that the deletion of Trs65 could reduce the stability of Trs130 [13]. Nonetheless, the interaction between TRAPPII and Gea2 appears solid and the functional relationship between TRAPPII and COPI components has been documented [86, 87]. These data, though preliminary, raise the possibility that the transport of COPII and COPI vesicles are coordinated. The tethering factor for COPII could somehow regulate COPI vesicles.

Besides the interaction between TRAPPII and the proteins of the COPI system, other TRAPP subunits have also been reported to have binding proteins. TRAPPC4 binds to Syndecan-2, a molecule implicated in stimulating the formation of dendritic spines in hippocampal neurons [88]. Recently, TRAPPC4 is also reported to interact with the kinase ERK1/2 and modulate the nuclear localization of ERK1/2 [89]. TRAPPC2 has been demonstrated to interact with a number of proteins including transcription factors [90, 91], and ion-channel proteins [92]. TRAPPC9 was implicated in potentiating the NF-κB signaling pathway leading to an increase of the NF-κB transactivation by interacting with IKK and NIK [78]. These reports point to the potentially exciting and novel functions of TRAPP subunits in the nucleus, but effort must be made to clarify whether such effect is direct and its functional significance must be further investigated.

Conclusions

As is the case for most scientific research, there are unexpected discoveries in TRAPP research. It is safe to say that, since the discovery of TRAPP almost 15 years ago, the structures and functions of TRAPP have been expanding in ways that were not expected by any of the researchers in this field. As we gradually open up the Trapper Keeper for TRAPP, each piece of discovery is filled with something novel, unexpected, and often puzzling. Our challenge ahead is to find the answer.

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References

1. Whyte JRC, Munro S (2002) Vesicle tethering complexes in membrane traffic. J Cell Sci 115:2627–2637
2. Sacher M, Barrowman J, Wang W, Horecka J, Zhang Y et al (2001) TRAPP I implicated in the specificity of tethering in ER-to-Golgi transport. Mol Cell 7:433–442
3. Lord C, Bhandari D, Menon S, Ghassemian M, Nycz D et al (2011) Sequential interactions with Sec23 control the direction of vesicle traffic. Nature 473:181–186
4. Kim Y-G, Raunser S, Munger C, Wagner J, Song Y-L et al (2006) The architecture of the multisubunit TRAPP I complex suggests a model for vesicle tethering. Cell 127:817–830
5. Sacher M, Yu J, Barrowman J, Scarpa A, Burston J et al (1998) TRAPP, a highly conserved novel complex on the *cis*-Golgi that mediates vesicle docking and fusion. EMBO J 17:2494–2503
6. Sacher M, Kim Y-G, Lavie A, Oh B-H, Segev N (2008) The TRAPP complex: Insights into its architecture and function. Traffic 9:2032–2042
7. Lynch-Day MA, Bhandari D, Menon S, Huang J, Cai H et al (2010) Trs85 directs a Ypt1 GEF, TRAPPIII, to the phagophore to promote autophagy. Proc Natl Acad Sci 107:7811–7816
8. Tokarev AA, Taussig D, Sundaram G, Lipatova Z, Liang Y et al (2009) TRAPP II complex assembly requires Trs33 or Trs65. Traffic 10:1831–1844
9. Morozova N, Liang Y, Tokarev AA, Chen SH, Cox R et al (2006) TRAPPII subunits are required for the specificity switch of a Ypt-Rab GEF. Nat Cell Biol 8:1263–1269
10. Cai Y, Chin HF, Lazarova D, Menon S, Fu C et al (2008) The structural basis for activation of the Rab Ypt1p by the TRAPP membrane-tethering complexes. Cell 133:1202–1213
11. Yip CK, Berscheminski J, Walz T (2010) Molecular architecture of the TRAPPII complex and implications for vesicle tethering. Nat Struct Mol Biol 17:1298–1304
12. Zong M, X-g Wu, Chan CWL, Choi MY, Chan HC et al (2011) The adaptor function of TRAPPC2 in mammalian TRAPPs explains TRAPPC2-associated SEDT and TRAPPC9-associated congenital intellectual disability. PLoS ONE 6:e23350
13. Liang Y, Morozova N, Tokarev AA, Mulholland JW, Segev N (2007) The role of Trs65 in the Ypt/Rab guanine nucleotide exchange factor function of the TRAPP II complex. Mol Biol Cell 18:2533–2541
14. Choi C, Davey M, Schluter C, Pandher P, Fang Y et al (2011) Organization and assembly of the TRAPPII complex. Traffic 12:715–725
15. Scrivens PJ, Shahrzad N, Moores A, Morin A, Brunet S et al (2009) TRAPPC2L is a novel, highly conserved TRAPP-interacting protein. Traffic 10:724–736
16. Montpetit B, Conibear E (2009) Identification of the novel TRAPP associated protein Tca17. Traffic 10:713–723
17. Yamasaki A, Menon S, Yu S, Barrowman J, Meerloo T et al (2009) mTrs130 Is a component of a mammalian TRAPPII complex, a Rab1 GEF that binds to COPI coated vesicles. Mol Biol Cell 20:4205–4215
18. Sacher M, Barrowman J, Schieltz D, Yates JRI, Ferro-Novick S (2000) Identification and characterization of five new subunits of TRAPP. Eur J Cell Biol 79:71–80
19. Kummel D, Oeckinghaus A, Wang C, Krappmann D, Heinemann U (2008) Distinct isocomplexes of the TRAPP trafficking factor coexist inside human cells. FEBS Lett 582:3729–3733

20. Scrivens PJ, Noueihed B, Shahrzad N, Hul S, Brunet S et al (2011) C4orf41 and TTC-15 are mammalian TRAPP components with a role at an early stage in ER-to-Golgi trafficking. Mol Biol Cell 22:2083–2093
21. Wendler F, Gillingham AK, Sinka R, Rosa-Ferreira C, Gordon DE et al (2010) A genome-wide RNA interference screen identifies two novel components of the metazoan secretory pathway. EMBO J 29:304–314
22. Behrends C, Sowa ME, Gygi SP, Harper JW (2010) Network organization of the human autophagy system. Nature 466:68–76
23. Gavin A-C, Bosche M, Krause R, Grandi P, Marzioch M et al (2002) Functional organization of the yeast proteome by systematic analysis of protein complexes. Nature 415:141–147
24. Yu S, Satoh A, Pypaert M, Mullen K, Hay JC et al (2006) mBet3p is required for homotypic COPII vesicle tethering in mammalian cells. J Cell Biol 174:359–368
25. Loh E, Peter F, Subramaniam VN, Hong W (2005) Mammalian Bet3 functions as a cytosolic factor participating in transport from the ER to the Golgi apparatus. J Cell Sci 118:1209–1222
26. Cai H, Yu S, Menon S, Cai Y, Lazarova D et al (2007) TRAPPI tethers COPII vesicles by binding the coat subunit Sec23. Nature 445:941–944
27. Bentley M, Liang Y, Mullen K, Xu D, Sztul E et al (2006) SNARE status regulates tether recruitment and function in homotypic COPII vesicle fusion. J Biol Chem 281:38825–38833
28. Allan B, Moyer B, Balch W (2000) Rab1 recruitment of p115 into a cis-SNARE complex: programming budding COPII vesicles for fusion. Science 289:444–448
29. Price MA (2006) CKI, there's more than one: casein kinase I family members in Wnt and Hedgehog signaling. Genes Dev 20:399–410
30. Cheong JK, Virshup DM (2010) Casein kinase 1: complexity in the family. Int J Biochem Cell Biol 43:465–469
31. Cronlein J, Reuss S, Vollrath L (1990) Investigations on day-night differences of vesicle densities in synapses of the rat suprachiasmatic nucleus. Neurosci Lett 114:167–172
32. Mukai S, Matsushima S (1980) Effect of continuous darkness on diurnal rhythms in small vesicles in sympathetic nerve endings of the mouse pineal-quantitative electron microscopic observations. J Neural Transm 47:131–143
33. Kachi T (1979) Demonstration of circadian rhythm in granular vesicle number in pinealocytes of mice and the effect of light: semi-quantitative electron microscopic study. J Anatomy 129:603–614
34. Pevet P, Kuyper M (1978) The ultrastructure of pinealocytes in the golden mole (*Amblysomus hottentotus*) with special reference to the granular vesicles. Cell Tissue Res 191:39–56
35. Memon A, Hwang S, Deshpande N, Thompson GJ, Herrin D (1995) Novel aspects of the regulation of a cDNA(Arf1) from chlamydomonas with high sequence identity to animal ADP-ribosylation factor 1. Plant Mol Biol 29:567–577
36. Yu S, Roth MG (2002) Casein kinase I regulates membrane binding by ARF GAP1. Mol Biol Cell 13:2559–2570
37. Roth MG (1999) Snapshots of ARF1: implications for mechanisms of activation and inactivation. Cell 97:149–152
38. Siu KY, Yu MK, Wu X, Zong M, Roth MG et al (2011) The non-catalytic carboxyl-terminal domain of ARFGAP1 regulates actin cytoskeleton reorganization by antagonizing the activation of Rac1. PLoS ONE 6:e18458
39. Wang W, Sacher M, Ferro-Novick S (2000) TRAPP stimulates guanine nucleotide exchange on Ypt1p. J Cell Biol 151:289–296
40. Zou S, Liu Y, Zhang X, Chen Y, Ye M, et al (2012) Genetic analysis of exocytic Ypt/Rab GTPases and TRAPP subunits. Genetics (in press)
41. Barrowman J, Bhandari D, Reinisch K, Ferro-Novick S (2010) TRAPP complexes in membrane traffic: convergence through a common Rab. Nat Rev Mol Cell Biol 11:759–763
42. Westlake CJ, Baye LM, Nachury MV, Wright KJ, Ervin KE et al (2011) Primary cilia membrane assembly is initiated by Rab11 and transport protein particle II (TRAPPII) complex-dependent trafficking of Rabin8 to the centrosome. Proc Natl Acad Sci 108:2759–2764
43. Zhu Y, Hu L, Zhou Y, Yao Q, Liu L et al (2010) Structural mechanism of host Rab1 activation by the bifunctional Legionella type IV effector SidM/DrrA. Proc Natl Acad Sci 107:4699–4704
44. Nazarko TY, Huang J, Nicaud J-M, Klionsky DJ, Sibirny AA (2005) Trs85 is required for macroautophagy, pexophagy and cytoplasm to vacuole targeting in *Yarrowia lipolytica* and *Saccharomyces cerevisiae*. Autophagy 1:37–45
45. Meiling-Wesse K, Epple UD, Krick R, Barth H, Appelles A et al (2005) Trs85 (Gsg1), a component of the TRAPP complexes, is required for the organization of the preautophagosomal structure during selective autophagy via the Cvt pathway. J Biol Chem 280:33669–33678
46. Carlos Martín Zoppino F, Damián Militello R, Slavin I, Álvarez C, Colombo MI (2010) Autophagosome formation depends on the small GTPase Rab1 and functional ER exit sites. Traffic 11:1246–1261
47. Reggiori F, Wang C-W, Nair U, Shintani T, Abeliovich H et al (2004) Early stages of the secretory pathway, but not endosomes, are required for Cvt vesicle and autophagosome assembly in Saccharomyces cerevisiae. Mol Biol Cell 15:2189–2204
48. Ishihara N, Hamasaki M, Yokota S, Suzuki K, Kamada Y et al (2001) Autophagosome requires specific early Sec proteins for its formation and NSF/SNARE for vacuolar fusion. Mol Biol Cell 12:3690–3702
49. Geng J, Nair U, Yasumura-Yorimitsu K, Klionsky DJ (2010) Post-Golgi sce proteins are required for autophagy in Saccharomyces cerevisiae. Mol Biol Cell 21:2257–2269
50. Simon G, Prekeris R (2008) Mechanisms regulating targeting of recycling endosomes to the cleavage furrow during cytokinesis. Biochem Soc Transact 36:391–394
51. Finger FP, White JG (2002) Fusion and fission: membrane trafficking in animal cytokinesis. Cell 108:727–730
52. Robinett CC, Giansanti MG, Gatti M, Fuller MT (2009) TRAPPII is required for cleavage furrow ingression and localization of Rab11 in dividing male meiotic cells of Drosophila. J Cell Sci 122:4526–4534
53. Sciorra VA, Audhya A, Parsons AB, Segev N, Boone C et al (2005) Synthetic genetic array analysis of the PtdIns 4-kinase Pik1p identifies components in a Golgi-specific Ypt31/rab-GTPase signaling pathway. Mol Biol Cell 16:776–793
54. Qi X, Kaneda M, Chen J, Geitmann A, Zheng H (2011) A specific role for Arabidopsis TRAPPII in post-Golgi trafficking that is crucial for cytokinesis and cell polarity. Plant J 68:234–248
55. Yoshimura S, Egerer J, Fuchs E, Haas A, Barr F (2007) Functional dissection of Rab GTPases involved in primary cilium formation. J Cell Biol 178:363–369
56. Zong M, Satoh A, Yu MK, Siu KY, Ng WY et al (2012) TRAPPC9 mediates the interaction between p150Glued and COPII vesicles at the target membrane. PLoS ONE 7:e29995
57. Watson P, Forster R, Palmer KJ, Pepperkok R, Stephens DJ (2005) Coupling of ER exit to microtubules through direct interaction of COPII with dynactin. Nat Cell Biol 7:48–55
58. Scales SJ, Pepperkok R, Kreis TE (1997) Visualization of ER-to-Golgi transport in living cells reveals a sequential mode of action for COPII and COPI. Cell 90:1137–1148

59. Presley JF, Cole NB, Schroer TA, Hirschberg K, Zaal KJM et al (1997) ER-to-Golgi transport visualized in living cells. Nature 389:81–85
60. Schroer TA (2004) DYNACTIN. Annu Rev Cell Dev Biol 20:759–779
61. Watson P, Stephens DJ (2006) Microtubule plus-end loading of $p150^{Glued}$ is mediated by EB1 and CLIP-170 but is not required for intracellular membrane traffic in mammalian cells. J Cell Sci 119:2758–2767
62. Trahey M, Hay JC (2010) Transport vesicle uncoating: it's later than you think. F1000 Biol Rep 2:47
63. Tang BL, Peter F, Krijnse-Locker J, Low SH, Griffiths G et al (1997) The mammalian homolog of yeast Sec13p is enriched in the intermediate compartment and is essential for protein transport from the endoplasmic reticulum to the Golgi apparatus. Mol Cell Biol 17:256–266
64. Savarirayan R, Thompson E, Gecz J (2003) Spondyloepiphyseal dysplasia tarda. Eur J Hum Genet 11:639–642
65. Gedeon AK, Colley A, Jamieson R, Thompson EM, Rogers J et al (1999) Identification of the gene (SEDL) causing X-linked spondyloepiphyseal dysplasia tarda. Nat Genet 22:400–404
66. Gecz J, Hillman MA, Gedeon AK, Cox TC, Baker E et al (2000) Gene structure and expression study of the SEDL gene for spondyloepiphyseal dysplasia tarda. Genomics 69:242–251
67. Sacher M (2003) Membrane traffic fuses with cartilage development. FEBS Lett 550:1–4
68. Lin Y, Rao S, Yang Y (2008) A novel mutation in the SEDL gene leading to X-linked spondyloepiphyseal dysplasia tarda in a large Chinese pedigree. Zhonghua Yi Xue Yi Chuan Xue Za Zhi 25:150–153
69. Fiedler J, Merrer ML, Mortier G, Heuertz S, Faivre L et al (2004) X-linked spondyloepiphyseal dysplasia tarda: novel and recurrent mutations in 13 European families. Human Mutat 24:103
70. Bar-Yosef U, Ohana E, Hershkovitz E, Perlmuter S, Ofir R et al (2004) X-linked spondyloepiphyseal dysplasia tarda: a novel SEDL mutation in a Jewish Ashkenazi family and clinical intervention considerations. Am J Med Genet Part A 125A:45–48
71. Matsui Y, Yasui N, Ozono K, Yamagata M, Kawabata H et al (2001) Loss of the SEDL gene product (Sedlin) causes X-linked spondyloepiphyseal dysplasia tarda: identification of a molecular defect in a Japanese family. Am J Med Genet 99:328–330
72. Christie PT, Curley A, Nesbit MA, Chapman C, Genet S et al (2001) Mutational analysis in X-linked spondyloepiphyseal dysplasia tarda. J Clin Endocrinol Metab 86:3233–3236
73. Choi MY, Chan CCY, Chan D, Luk KDK, Cheah KSE et al (2009) Biochemical consequences of sedlin mutations that cause spondyloepiphyseal dysplasia tarda. Biochem J 423:233–242
74. Philippe O, Rio M, Carioux A, Plaza J-M, Guigue P et al (2009) Combination of linkage mapping and microarray-expression analysis identifies NF-κB signaling defect as a cause of autosomal-recessive mental retardation. Am J Human Genet 85:903–908
75. Mochida GH, Mahajnah M, Hill AD, Basel-Vanagaite L, Gleason D et al (2009) A truncating mutation of TRAPPC9 is associated with autosomal-recessive intellectual disability and postnatal microcephaly. Am J Human Genet 85:897–902
76. Mir A, Kaufman L, Noor A, Motazacker MM, Jamil T et al (2009) Identification of mutations in TRAPPC9, which encodes the NIK- and IKK-β-binding protein, in nonsyndromic autosomal-recessive mental retardation. Am J Human Genet 85:909–915
77. Cai H, Zhang Y, Pypaert M, Walker L, Ferro-Novick S (2005) Mutants in trs120 disrupt traffic from the early endosome to the late Golgi. J Cell Biol 171:823–833
78. Hu W-H, Pendergast JS, Mo X-M, Brambilla R, Bracchi-Ricard V et al (2005) NIBP, a novel NIK and IKKβ-binding protein that enhances NF-κB activation. J Biol Chem 280:29233–29241
79. Sadler KC, Amsterdam A, Soroka C, Boyer J, Hopkins N (2005) A genetic screen in zebrafish identifies the mutants vps18, nf2 and foie gras as models of liver disease. Development 132:3561–3572
80. Cinaroglu A, Gao C, Imrie D, Sadler KC (2011) Activating transcription factor 6 plays protective and pathological roles in steatosis due to endoplasmic reticulum stress in zebrafish. Hepatology 54:495–508
81. Walter P, Ron D (2011) The unfolded protein response: from stress pathway to homeostatic regulation. Science 334:1081–1086
82. Gwynn B, Smith R, Rowe L, Taylor B, Peters L (2006) A mouse TRAPP-related protein is involved in pigmentation. Genomics 88:196–203
83. Kummel D, Walter J, Heck M, Heinemann U, Veit M (2010) Characterization of the self-palmitoylation activity of the transport protein particle component Bet3. Cell Mol Life Sci 67:2653–2664
84. Kim Y-G, Sohn E, Seo J, Lee K, Lee H et al (2005) Crystal structure of bet3 reveals a novel mechanism for Golgi localization of tethering factor TRAPP. Nat Struct Mol Biol 12:38–45
85. Chen S, Cai H, Park S-K, Menon S, Jackson CL et al (2011) Trs65p, a subunit of the Ypt1p GEF TRAPPII, interacts with the Arf1p exchange factor Gea2p to facilitate COPI-mediated vesicle traffic. Mol Biol Cell 22:3634–3644
86. Zhang C, Bowzard J, Greene M, Anido A, Stearns K et al (2002) Genetic interactions link ARF1, YPT31/32 and TRS130. Yeast 19:1075–1086
87. Yamamoto K, Jigami Y (2002) Mutation of TRS130, which encodes a component of the TRAPP II complex, activates transcription of OCH1 in Saccharomyces cerevisiae. Curr Genet 42:85–93
88. Ethell IM, Hagihara K, Miura Y, Irie F, Yamaguchi Y (2000) Synbindin, a novel syndecan-2-binding protein in neuronal dendritic spines. J Cell Biol 151:53–68
89. Zhao S-L, Hong J, Xie Z-Q, Tang J-T, Su W-Y et al (2011) TRAPPC4-ERK2 interaction activates ERK1/2, modulates its nuclear localization and regulates proliferation and apoptosis of colorectal cancer cells. PLoS ONE 6:e23262
90. Liu X, Wang Y, Zhu H, Zhang Q, Xing X et al (2010) Interaction of Sedlin with PAM14. J Cell Biochem 109:1129–1133
91. Jeyabalan J, Nesbit MA, Galvanovskis J, Callaghan R, Rorsman P et al (2010) SEDLIN forms homodimers: characterisation of SEDLIN mutations and their interactions with transcription factors MBP1, PITX1 and SF1. PLoS ONE 5:e10646
92. Fan L, Yu W, Zhu X (2003) Interaction of Sedlin with chloride intracellular channel proteins. FEBS Lett 540:77–80