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Multi-Component Protein Complexes and Golgi Membrane Trafficking

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Several large cytosolic protein complexes with multiple components have been proposed to play key roles in mediating or controlling membrane trafficking. Among these complexes, TRAPP, COG and GARP/VFT have been implicated in multiple steps of Golgi membrane trafficking. The importance of these complexes for Golgi function has been established using *in vitro* biochemical assays and yeast and mammalian somatic cell genetics. Furthermore, mutations in the genes encoding subunits of either TRAPP or the COG complex have been shown to be responsible for human genetic disorders. We here review recent studies exploring the structures and functions of these three oligomeric complexes.

Key words: COG, GARP/VFT, Golgi membrane trafficking, human genetic disorders, TRAPP.

Anterograde and retrograde vectorial vesicular transport of proteins and lipids through the secretory and endocytic pathways requires that vesicles budding from donor membranes target and fuse to specific acceptor compartments. A number of protein complexes have been identified by biochemical and genetic studies to participate in vesicular trafficking at the budding, recognition, tethering/docking, and fusion steps in this multi-step process, although the precise roles played by some of these remains uncertain. Tethering is usually thought to represent the initial contact of a transport vesicle to its target membrane through long, often coiled coil proteins bridging the two membrane. For example, one well characterized protein is GM130, a long coiled coil protein, which plays roles in concert with p115, and giantin. They have been proposed to serve as essential tethering proteins by forming a long elongated complexes that bridge COPI vesicles to the Golgi apparatus (*1*). However, several studies have raised doubts about the role of GM130, because it appears to be dispensable for maintenance of the Golgi structure and transport *in vivo* (*2–4*). In this review, we will focus on three large protein complexes (TRAPP, COG and GARP/VFT) involved in Golgi membrane trafficking, and discuss current models of how they work together with Ypts/Rabs and SNAREs to facilitate vesicular transport.

TRAPP

TRAPP (transport protein particle), the first of these complexes to be discovered, comprises ten distinct subunits. Characterization of TRAPP began with the identification of yeast Bet3p by genetic screening based on a mutation in the *BET1* gene, which encodes a SNARE (*5*). Biochemical approaches using the tagged Bet3 protein resulted in identification of the entire TRAPP complex in both yeast and human cells (*6–8*). Several components of TRAPP are highly conserved between yeast and humans. Yeast TRAPP is stably associated with the Golgi membrane and does not appear to continuously cycle through the ER (*6*, *9*). Yeast *bet3* mutants were used to show that TRAPP influences ER-to-Golgi transport (*5*). Subsequent analysis using an *in vitro* transport assay demonstrated that TRAPP appears to be involved in the attachment of ER-derived vesicles to the Golgi apparatus (Fig. 1) (*9*).

Gel filtration chromatography reveals that there are two forms of TRAPP (TRAPP I and TRAPP II) in yeast cell lysates (*7*). TRAPP II is the complete complex of ten subunits. TRAPP I has only seven of these, including Bet3p but lacking the Trs120p, Trs130p and Kre11p subunits (Fig. 2). Unlike *bet3* mutations that interfere with ER-to-Golgi transport, a mutation in the TRAPP II–specific subunit gene *TRS130*, causes defects in the intra-Golgi transport (*7*). Thus, the two forms of TRAPP may act at different steps in the secretory pathway (Fig. 1). Studies in yeast have established genetic interactions

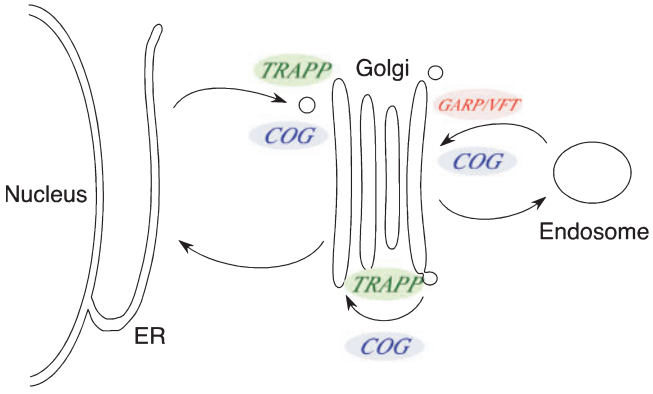

Fig. 1. **Putative roles of the TRAPP, COG and GARP/VFT protein complexes in Golgi membrane trafficking.** See text for details.

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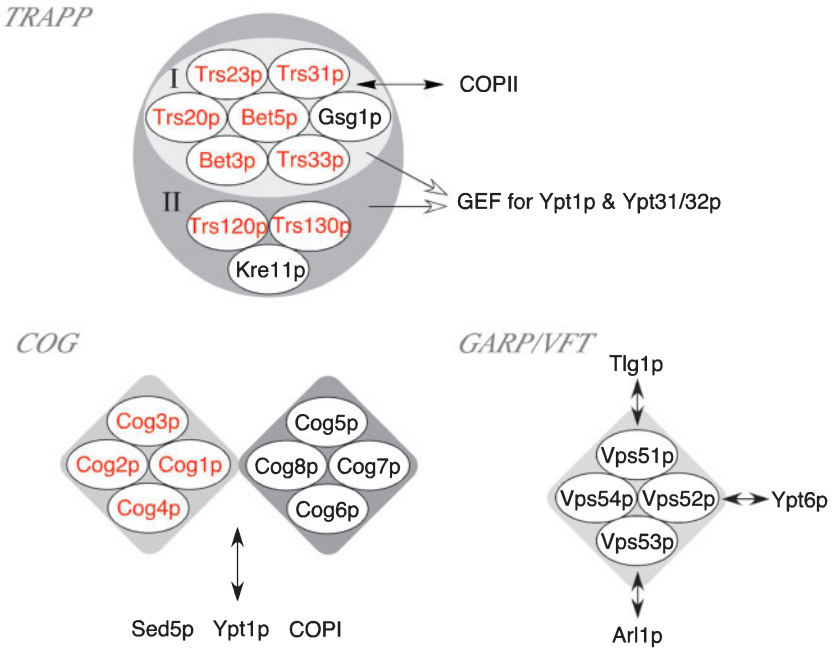

Fig. 2. **Organization of the subunits in the TRAPP, COG and GARP/VFT complexes.** The shaded diamonds and ovals represent sub-complexes which have been identified by biochemical and/or genetic analyses. There are two forms of TRAPP (I and II) that appear to function in distinct steps of secretory pathway (Sacher *et al.*, 2001) (see Fig. 1). The white and black arrows indicate enzymatic activities or physical interactions, respectively. In the GARP/VFT complex, the single subunits directly interacting with the small GTPase and SNARE proteins by an *in vitro* binding assay are indicated by double-headed arrows (Vps51p-Tlg1p, Vps52p-Ypt6p and Vps53p-Arl1p) (*53*, *54*, *61*). The name of each subunit known in the budding yeast *S. cerevisiae* has been used. The red letters indicate the gene products required for cell growth in yeast.

between TRAPP and several components of the secretory pathway [*e.g. YPT1*, SNAREs (*BET1* and *SEC22*) or *USO1*] (*5*, *10*) and *in vitro* studies support the model in Fig. 1. The purified TRAPP I, but not TRAPP II, complex binds to ER-derived COPII vesicles generated by an *in vitro* transport system (*7*), suggesting that the TRAPP II–specific subunits, Trs120p, Trs130p and Kre11p, interfere directly or indirectly with TRAPP binding to COPII vesicles. The binding to the COPII vesicles is independent of factors including Ypt1p, COG and Uso1p. Moreover, the addition of non-hydrolyzable GTP analogue, GTPγS, inhibits COPII-binding of TRAPP I (*7*). Because non-hydrolyzable GTP is known to stabilize coat proteins on vesicles, among its many other effects, TRAPP I binding may be linked to COPII vesicle uncoating, raising the possibility that TRAPP I may participate in the targeting and/or attachment of ER-derived vesicles to the Golgi.

Biochemical analyses indicated that both forms of TRAPP have the ability to facilitate exchange of nucleotides on the small GTPases Ypt1p , a yeast homologue of mammalian Rab1, and Ypt31/32p (*7*, *11*, *12*). Overexpression of *YPT1* represses growth defects of the *bet3-1* and *bet5-1* mutants (*5*, *10*). Increasing gene dosage of either *YPT31* or *YPT32* suppresses lethality resulting from deletion of TRAPP II–specific genes (*TRS120* and *TRS130*), but not the common subunit genes (*13*, *14*), suggesting that the guanine nucleotide exchange activity of TRAPP II may be especially important for the Ypt31/32p GTPases *in vivo*. Indeed, the Trs130p-containing TRAPP II complex and Ypt31/32p co-precipitate from yeast cell lysates (*11–13*). Thus, each form of TRAPP may interact with distinct small GTPases *in vivo* and thus may influence distinct steps in trafficking.

Defective TRAPP is responsible for the human X-linked disease spondyloepiphyseal dysplasia tarda (SEDL) (*15–17*). Spondyloepiphyseal dysplasia is one of a large group of genetic disorders of bone growth (*18*) characterized by disproportionate short stature with short neck and trunk, barrel chest, degenerative joint disease and absence of systemic complications (*19–21*). The human SEDL gene encodes a 140 amino-acid protein that is a functional counterpart of the yeast TRAPP subunit Trs20p. SEDL can complement the lethality of yeast *trs20* deletion mutants (*15*, *16*). The human SEDL gene product, called Sedlin, has been demonstrated to form a protein complex with human homologues of other TRAPP subunits (*8*). It seems likely that mutations in SEDL would disrupt the secretion of type II collagen and other key components of articular cartilage, and thus contribute to the dysplasia of the large joints seen in spondyloepiphyseal dysplasia tarda. It is somewhat surprising that mutations expected to result in a loss of function of SEDL (*22*) result in only the progressive, relatively tissue specific and limited defects seen in spondyloepiphyseal dysplasia tarda. Perhaps expression of one of its numerous pseudogenes may partially complement mutation in the X-linked SEDL gene (*17*).

COG

The COG (conserved oligomeric Golgi) complex contains eight subunits (COG-1–COG-8), five of which are highly conserved from yeast to humans (*23*, *24*). The genes for COG subunits were initially discovered independently in mammalian and yeast systems by several groups not aware that these subunits were components of a common complex. Thus, the subunits were given diverse names (Table 1). Only recently has a uniform nomenclature been established (*24*). Characterization of COG began with the identification of mammalian somatic cell mutants (ldlB [COG-1 mutation] and ldlC [COG-2 mutation]) (*25*, *26*) and the cloning of the COG-2 gene (*27*). The COG-1 and COG-2 mutants exhibit defects in the receptor-mediated endocytosis of low density lipoprotein (LDL) due to abnormal Golgi processing of the oligosaccharides on the LDL receptor. The *sec34* (COG-3)

Table 1. **COG subunits in yeast and mammals.**

Subunit	Previously used mammalian nomenclature	Yeast (*S. cerevisiae*)	References
COG-1	IdlBp	Cod3p/Sec36p/Tfi1p/Idb11p	*23–25*, *29*, *36*, *37*, *46*
COG-2	IdlCp	Sec35p	*23–25*, *27*, *28*, *31*
COG-3	hSec34p	Sec34p/Grd20p	*23*, *24*, *28*, *32–34*, *38*, *39*
COG-4	hCod1p	Cod1p/Sgf1p/Sec38p/Tfi3p	*23*, *24*, *35–37*
COG-5	GTC-90	Cod4p	*23*, *24*, *30*
COG-6	hCod2p	Cod2p/Sec37p/Tfi2p	*23*, *24*, *36*, *37*
COG-7	None	Cod5p	*23*, *24*, *48*
COG-8	nDor1p	Dor1p	*23*, *24*

and *sec35* (COG-2) mutants in yeast were subsequently isolated in a genetic screen to identify components involved in transport from the ER to the *trans*-Golgi network (TGN) (*28*). At about the same time, mammalian COG-2 was shown to be a component of a large peripheral Golgi complex whose size and Golgi-association are dependent on COG-1 (*27*, *29*). Walters *et al.* (1998) (*30*) identified a protein called GTC-90 (COG-5) as a component of an ~800 kDa multi-protein complex, named GTC (Golgi transport complex), because of its ability to stimulate an *in vitro* intra-Golgi transport assay . Subsequent independent and nearly simultaneous biochemical and genetic studies by several groups identified all eight COG subunits in yeast (*31–37*) and mammals (*24*, *38*, *39*). Some of the COG subunits exhibit partial sequence similarities (*e.g.*, in N-terminal coiled-coil domains) to components of the GARP/VFT and exocyst complexes (*23*, *40*). The COG subunits fall into two functionally and structurally distinct groups (COG-1 to COG-4 and COG-5 to COG-8) (*23*, *24*). EM images of the purified mammalian COG complex indicate that COG is composed of two similarly sized globular subcomplexes connected by short extensions, raising the possibility that the distinct groups of COG subunits compose distinct domains within the COG complex.

The precise role or roles of COG in Golgi function and membrane trafficking remain to be established. Roles for COG in three distinct activities in the secretory pathway have been proposed: (i) protein sorting on exit from the ER (*41*, *42*), (ii) attachment and/or targeting of ER-derived vesicles to the Golgi (*31*, *32*, *34*), (iii) retention and/or retrieval of Golgi-localized proteins (Fig. 1) (*33*, *37*, *43*). Evidence for an influence of COG on sorting from the ER came from an *in vitro* budding assay that showed the sorting of GPI-anchored proteins from other secretory proteins is defective in the *sec34* (COG-3) and *sec35* (COG-2) mutants (*41*, *42*). It is not yet clear if the observed effects are due to a direct effect of COG on the ER or to secondary effects of Golgi-localized COG. Yeast *cog* mutants have been identified in a screen for abnormalities in vesicle accumulation and defects in ER to Golgi transport (*28*). An *in vitro* ER-to-Golgi transport assay indicated that COG is dispensable for formation of the ER-derived vesicles (*31*, *32*). The influence of COG on targeting and/or attachment of ER-derived vesicles to the Golgi has been examined using *in vitro* assays, with the consequences of *cog* mutations on targeting and/or attachment apparently dependent on the alleles of the *cog* mutations used in the assays (*31*, *32*, *37*). Neither transport of secretory and membrane proteins (*e.g.*,VSV-G) from the ER to the plasma membrane nor normal endocytic cycling are substantially disrupted in the mammalian COG-1 and COG-2 mutants (ldlB and ldlC), despite the dramatically reduced association of the other COG subunits with the Golgi in these mutants (*24*, *44*, Oka, T. and Krieger, M., unpublished observations). Apparent discrepancies in activities attributed to COG that have been reported to date will most likely be resolved as the detailed molecular mechanisms underlying COG function are revealed by further studies. Additional support for a role of COG in membrane trafficking comes from the findings of genetic and/or physical interactions between COG and numerous components of the yeast and/or mammalian secretory systems, including the vesicle coat COPI (*e.g.*, epsilon-COP, Ret2p, Sec21p, Sec26p and Sec27p), vesicle docking and fusion components [SNAREs (Sec22p, Bet1p, Ykt6p, Gos1p (GOS-28 homologue), Sed5p, Snc2p), small GTPases (Ypt1p, Arl1p, Ypt6p GTP/GDP exchange factor: Ric1p), Sec1/munc-18–like SM (Sly1p), alpha-SNAP (Sec17p)], and the putative tethering protein Uso1p (p115 in mammals) (*23*, *31–37*, *43*). In particular, COPI proteins, Ypt1p and Sed5p (a yeast homologue of mammalian syntaxin-5) have been shown to co-precipitate with some of COG subunits (*36*). Yeast COG also interacts with the Golgi associated, golgin-like protein Grp1p/Rud3p (*32*, *34*, *35*, *45*).

The first indication that COG can have global influence on Golgi function was the discovery that there were pleiotropic defects in the synthesis of oligosaccharides on most glycoproteins (both *N*- and *O*-linked) and glycolipids in the mammalian ldlB (COG-1) and ldlC (COG-2) mutants (*26*). The global defects in glycoconjugate synthesis in mammalian COG mutants appears to be due, at least in part, to the mislocalization and/or instability of some of the proteins responsible for glycoconjugate synthesis (*e.g.*, glycosyl transferases such as mannosidase II) that are normally distributed in distinct cisternae of the Golgi (*43*). As expected from the earlier analysis of the mammalian mutants, yeast *cog* mutants have more recently been shown to exhibit defects in glycosylation of mannoproteins and invertase, a secretory protein, (*23*, *46*, *47*). Indeed, mislocalization of the two Golgi mannosyltransferases, Och1p and Mnn1p, has been confirmed in the *sec34* (COG-3) mutants (*47*) and the TGN protein Kex2p is missorted to the vacuole in the same mutants (*33*). These findings suggest that COG is necessary for retention and/or retrieval of Golgi-localized proteins to maintain normal Golgi functions. The ability of COG to stimulate an in vitro intra-Golgi transport assay in the presence of NSF, SNAPs and p115 (*30*) further supports the proposal that COG influences a variety of functions of

the Golgi by controlling intra- or inter-Golgi membrane trafficking pathways.

The similarities in the pleiotrophic Golgi-associated glycosylation defects in COG-1 and COG-2 deficient CHO cells (*26*) and the fibroblasts of some patients with Congenital disorders of glycosylation (CDG) of previously unknown etiology led us and our colleagues to propose that some cases of CDG may be due to COG-deficiency (*48*). CDG arise because of a variety of defects in the biogenesis of glycoconjugates (*49*). CDG patients often share clinical characters such as mental retardation, seizures, hypotonia, liver malfunctions, coagulopathy and dysmorphia. Recently, the defects in two sibling with CDG of previously unknown etiology have been shown to be due to mutation in the *COG7* gene (*48*). Fibroblasts from these patients exhibit pleiotrophic glycosylaton defects (*e.g.*, lower glycoconjugate sialylation) and reductions in Golgi sugar transporter activities. It seems possible that mutations in other COG subunits will account for additional cases of CDG. Curiously, flies (*Drosophila melanogaster*) with homozygous mutations in their COG-5 gene (four-way-stop, *fws*) are viable (*50*). The principle gross phenotype exhibited is male sterility due to dramatic alterations in cellular and subcellular morphology during spermatogenesis, including disruption in the formation and/or stability of the Golgi-based spermatid acroblast.

GARP/VFT

The GARP (Golgi-associated retrograde protein)/VFT (Vps fifty three) complex consists of four subunits (Vps51p–Vps54p) (*51–54*). The genes coding for GARP/VFT were originally identified as yeast mutants defective in vacuolar protein sorting (Vps) (*51*, *55*). The tetrameric GARP/VFT protein complex was isolated as an effector of yeast Ypt6p, a homologue of mammalian Rab6 (*52–54*). Some components of the complex show partial sequence similarities to subunits of either COG or the exocyst. Several GARP/VFT homologues have been found in worms, flys, mammals and plants (*56*, *57*), suggesting that the complex is highly conserved. Analyses of yeast vps mutants have revealed that GARP/VFT is required for retrograde transport of Golgi-localized proteins from the endosome to the Golgi apparatus (Fig. 1) (*51*, *54*), consistent with the finding that GARP/VFT via Vps52p directly binds to Ypt6p, which appears to be essential in membrane trafficking between the late Golgi and endosome (Fig. 2) (*58–60*). In addition, the Vps51p subunit of GARP/VFT directly interacts with the N-terminal region of Tlg1p (*52*, *54*), which is a t-SNARE involved in recycling of proteins from early endosomes to the Golgi apparatus. Another small GTPase Arl1p, a yeast homologue of human ARL1, interacts with GARP/VFT *via* Vps53p in a GTP-dependent manner (Fig. 2) (*61*). Arl1p also binds to the GRIP domains of golgins, Golgi-associated large coiled-coil proteins, to target them to the Golgi membrane (*61*, *62*). Golgins with GRIP domains are believed to be involved in membrane trafficking of tubulovesicular structures of the *trans*-Golgi network (*63–66*), suggesting that GARP/VFT may function in concert with the golgins. GARP/VFT has been also reported to be required for cytoplasm to vacuole targeting (Cvt) of yeast aminopeptidase I (*67*).

Conclusion

A number of cytosolic proteins including Ypts/Rabs, coiled-coil proteins and oligomeric protein complexes (TRAPP, COG and GARP/VFT) has been shown to play important roles in membrane trafficking. In controlling vesicular transport to, within and from the Golgi apparatus and the organelles with which it communicates, the TRAPP, COG and GARP/VFT complexes and their individual subunits play important, but not always essential, roles in the secretory pathway. In addition to using the classic approaches of biochemistry and yeast and somatic mammalian cell genetics to understand how these complexes participate in membrane trafficking, the analysis of the effects of disruptions in their activities in complex organisms (flies and humans) can be expected to provide further insight into the molecular mechanisms of their activities and their contributions of animal physiology and human disease.

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