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Traffic Interchange

Are All Multisubunit Tethering Complexes Bona Fide Tethers?

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Abstract

Since the late 1990s, a number of multisubunit tethering complexes (MTCs) have been described that function in membrane trafficking events: TRAPP I, TRAPP II, TRAPP III, COG, HOPS, CORVET, Dsl1, GARP and exocyst. On the basis of structural and sequence similarities, they have been categorized as *c*omplexes *a*ssociated with *t*ethering *c*ontaining *h*elical *r*ods (CATCHR) (Dsl1, COG, GARP and exocyst) or non-CATCHR (TRAPP I, II and III, HOPS and CORVET) complexes (Yu IM, Hughson FM. Tethering factors as organizers of intracellular vesicular traffic. Annu Rev Cell Dev Biol 2010;26:137–156). Both acronyms (CATCHR and MTC) imply these complexes tether opposing membranes to facilitate fusion. The main question we will address is: have these complexes been formally demonstrated to function as tethers? If the answer is no, then is it premature or even correct to refer to them as tethers? In this commentary, we will argue that the vast majority of MTCs have not been demonstrated to act as a tether. We propose that a distinction between the terms tether and tethering factor be considered to address this issue.

Keywords CATCHR, COG, CORVET, Dsl1, exocyst, GARP, HOPS, tether, TRAPP

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Membrane traffic is a process that ensures the correct complement of proteins and lipids reach the appropriate cellular compartment. It is recognized that a number of different types of protein machinery must act in concert to achieve this by directing vesicular carriers to the correct destination. These factors include SNARE proteins, vesicle coat proteins, Ypt/Rab GTPases and a class of factors referred to as tethers (1). Traditionally, tethers have been classified into two broad groups: (i) coiled-coil proteins and (ii) multisubunit tethering complexes (MTCs) (2,3). On the basis of both structural and sequence similarities between the subunits of some of these complexes, the MTCs have in turn been subcategorized into CATCHR and non-CATCHR complexes (2). Inherent in these acronyms is the presumption that these complexes tether membranes. This raises the question: how strong is the evidence that each of the nine MTCs is a tether in the strict sense of the word? In order to address this question, we will define a tether as a protein or complex that physically links two distinct membranes to each other. These membranes could be two vesicles or two identical organelles such as vacuoles (i.e. homotypic fusion) or a vesicle with a target organelle (i.e. heterotypic fusion). Much of the work on the MTCs has been performed in yeast and we will focus on that system. However, we will also discuss higher eukaryotes when evidence is available.

In many cases, early studies demonstrating the accumulation of vesicles in yeast bearing a mutation in a subunit of one of the MTCs, and the fact that the complexes act upstream of SNARE complex formation, led to the assumption that these complexes are tethers. However, it has never been suggested that, for example,

Sec18p/N-ethylmaleimide-sensitive factor (NSF), mutation of which results in a massive accumulation of transport vesicles, is a tether. The most compelling argument for a tether would be to demonstrate an ability to physically link two membranes together, which can only be accomplished in a reconstituted system. As we will discuss below, that is the case for just two of the MTCs. For the remainder, a tethering function has been inferred using genetic, *in vitro* and cell biological techniques. While the experimental evidence is compelling in some cases, the flaw in these approaches is that an MTC may tether either directly or may simply facilitate tethering by recruiting *bona fide* tethers. Furthermore, given the interaction between these complexes and GTPases, the MTCs may simply function through activated Ypt/Rabs. Hence, it may be at best premature to refer to all of the MTCs as tethers.

CATCHR Complexes

The exocyst complex is composed of eight subunits (Sec3, Sec5, Sec6, Sec8, Sec10, Sec15, Exo70 and Exo84) and was one of the first of the MTCs identified (4). The complex is involved in tethering of vesicles to the plasma membrane (PM) during exocytosis and tethering vesicles at sites of membrane expansion such as at the site of cytokinesis and neurite outgrowth (4–7). Localization studies of the individual subunits have led to the suggestion that Sec3 and Exo70 are recruited to the PM and act as spatial landmarks while the remaining subunits arrive on vesicles (8,9). Assembly of the exocyst at the PM would bring the vesicle and its target membrane into close proximity thereby tethering them. In support of this model Sec3 and Exo70 directly interact with $PI(4,5)P_2$, a phospholipid enriched at the PM, and Sec15 interacts with activated Sec4, a Rab found on PM-destined vesicles (10–13). The tethering activity of the exocyst has not been tested in a reconstituted system and the large size and low solubility of the complex will make this difficult (14). The most direct evidence to date that this complex physically links two membranes comes from images of electron tomography studies of the *Arapidopsis* cell plate during cytokinesis where 'Y'-shaped structures link vesicles prior to homotypic vesicle fusion (15). These structures resemble the exocyst purified from rat brain based on size and shape but it was not confirmed through protein tagging or immuno-labeling experiments whether they truly represent the exocyst and whether this structure is itself performing the tethering reaction.

The COG complex is composed of eight subunits (Cog1-8) arranged into two 'lobes' (16), and is required for retrograde transport through the Golgi (17,18). Consistent with COG acting as a tether for intra-Golgi transport, Cog3 depletion in mammalian cells results in the accumulation of vesicles containing Golgi-resident cargo (18). Tethering of these vesicles to donor Golgi membranes from rat liver was blocked by the addition of anti-Cog3 antibody, further pointing to the COG complex as a tether (19). Further evidence for a tethering function came from a study whereby relocalization of COG4 to the mitochondria resulted in the accumulation of syntaxin 5-containing vesicles to this compartment. The vesicles were attached via fibrous extensions, consistent with a tethering function for COG (20). However, these experiments do not rule out that COG is acting upstream of the actual tethering event and that the true tether was either purified with the vesicle and/or Golgi preparation or relocalized with COG4. In fact, COG subunits interact with a large number of trafficking proteins including SNAREs, Rabs, other tethers, motor proteins and vesicle coat proteins (21). It is clear that COG is essential for retrograde Golgi transport, but there is not yet conclusive evidence that one of its mechanisms of action is to physically tether two membranes.

The Dsl1 complex is the smallest of the MTCs in terms of the number of subunits (Dsl1, Dsl3 and Tip20). The complex is endoplasmic reticulum (ER)-localized via an interaction with the ER proteins Sec20, Ufe1 and Use1. Two of its subunits, Dsl1 and Tip20, interact with components of the COP I coat and either cause or facilitate disassembly of the coat (22,23). Yeast cells with mutations in *tip20* or cells depleted of the Dsl1 protein result in an accumulation of COP I-coated vesicles (24), consistent with the ability of the Dsl1 complex to uncoat these vesicles. Collectively, this has led to an elegant model of Dsl1 tethering (25). However, whether it physically tethers the COP I vesicles to the ER has not been formally demonstrated. The ability to purify a recombinant form of this relatively small complex should allow for testing its tethering function in a reconstituted system.

The GARP complex, consisting of four subunits (Vps51, Vps52, Vps53 and Vps54), has been implicated in traffic between endosomes and the *trans*-Golgi network (TGN) in both yeast and higher eukaryotes (26,27). It is predominantly localized to the TGN where it binds to SNARE proteins as well as to the activated forms of the GTPases Ypt6 and Arl1 (28–31). Similarly to the *in vitro* binding of TRAPP I to COP II vesicles (see below), purified recombinant GARP has been shown to be capable of binding to endosome-derived vesicles (32). Work in both yeast and mammalian cells has identified regions on GARP subunits responsible for this interaction (32,33), although the receptor on the vesicles remains elusive. Nevertheless, simultaneous binding of GARP to both the TGN and endosome-derived vesicles has never been reported.

The Non-CATCHR Complexes

The TRAPP I and II complexes were among the first of the MTCs to be identified and structurally characterized. Several studies suggested that TRAPP complexes act as tethers. Purified TRAPP I was able to bind to a crude preparation of ER-derived transport vesicles *in vitro* (34). This same study showed that depletion of TRAPP from an *in vitro* assay that reconstitutes ER-to-Golgi transport resulted in an increase in membranes presumed to represent transport vesicles. To act as a *bona fide* tether, one would expect the TRAPP complexes to interact with both Golgi- and vesicle-localized proteins. Indeed, both TRAPP I and II interact with components of the COP II and COP I vesicle coats, respectively (35,36). Although one study suggested that TRAPP I physically tethers COP II vesicles during heterotypic fusion (36), the reaction was performed with cytosol and not with reconstituted components. Therefore, a direct role for TRAPP I in the tethering function cannot be concluded. In yeast and mammalian cells, TRAPP can be found on Golgi membranes or the ER–Golgi intermediate compartment although a Golgi receptor (protein or lipid) are yet to be identified (37–41). On the basis of the aforementioned membrane interactions it has been assumed that TRAPP acts as a tether and it is included in discussions of MTCs. But the ability to simultaneously bind to vesicles and Golgi membranes or to physically link two vesicles has never been conclusively demonstrated. To date, the only measurable function of the TRAPP complexes is their ability to act as a guanine nucleotide exchange factor (GEF) for Ypt1/Rab1 (34,41–43). Interestingly, activated Rab proteins themselves have been reported to function as tethers (44) raising the possibility that the role of TRAPP in vesicle tethering may be indirect. Clearly, TRAPP is involved in the tethering process as mutations in genes encoding TRAPP subunits in yeast result in an accumulation of ER-derived vesicles (34,45), but whether this is a direct function of the complex or indirect by its role as a GEF remains unknown.

The HOPS and CORVET complexes are related in that they share a core of four subunits (Vps11, Vps16, Vps18 and Vps33) and each has two distinct subunits: Vps39/Vam6 and Vps41 for HOPS, Vps3 and Vps8 for CORVET (46). The HOPS complex functions in homotypic vacuolar fusion while CORVET functions earlier in the endocytic pathway (46). Homotypic vacuolar fusion has been fully reconstituted *in vitro* (47–49). Therefore, unlike most of the other MTCs discussed herein, a role for HOPS in tethering two membranes, in this case two vacuoles, together has been demonstrated. HOPS binds to activated Ypt7 through both its Vps39 and Vps41 subunits (50,51). These subunits are found on either end of the extended HOPS structure (52) and could therefore mediate the interaction between two membranes (vacuoles) following activation of Ypt7 by the Mon1-Ccz1 GEF. The CORVET complex has been modeled on the HOPS structure and its unique subunits Vps3 and Vps8 occupy the same location as the HOPS subunits Vps39 and Vps41 (53). Like the HOPS-specific subunits, the CORVET subunits Vps3 and Vps8 bind to the activated GTPase Vps21 (54) and CORVET has been shown to tether vacuoles *in vitro* (55). It is noteworthy that the CORVET complex used in this study was purified directly from yeast and it remains formally possible that a co-purifying protein that contributes to tethering was present. Nonetheless, this study suggests a model of tethering that is similar to that of HOPS. Both complexes also interact with SNARE proteins and have been suggested to function in a post-tethering event (55–57). Thus, both HOPS and CORVET are the only two MTCs that have been shown to fulfill the criteria for a *bona fide* tether, which represents just one of their functions.

Conclusion

A common theme among many of the complexes discussed is their interaction with Ypt/Rab proteins. As Rabs are also involved in the tethering process, teasing apart the role of these complexes in tethering is not trivial. Indeed, the tethering function for some MTCs is more compelling than for others. Assumptions based on the function of one complex cannot necessarily be extended to any of the others. Even for the related TRAPP complexes, if one is shown to be a *bona fide* tether, the assumption that the other complexes are also tethers cannot be made until the precise mechanism of tethering is known. For example, the Bet3 subunit in the TRAPP core binds to a component of COP II vesicles and it is not unreasonable to speculate that this region of Bet3 is masked in TRAPP II. Thus, a completely different function may be performed by TRAPP II. On the basis of the literature discussed herein, it is clear that the majority of MTCs have not yet been definitively demonstrated to act as tethers. However, all MTCs have been shown to function in the tethering process. We suggest that researchers consider the complexes yet to be assigned a tethering function as 'tethering factors' rather than tethers. The distinction between tether and tethering factor is that the former performs the tethering function while the latter is simply involved in the process by organizing other factors essential for tethering. Should these complexes not be demonstrated to act as tethers, a change in the MTC acronym may be warranted.

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