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The Secret Life of Tethers: The Role of Tethering Factors in SNARE Complex Regulation

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Trafficking in eukaryotic cells is a tightly regulated process to ensure correct cargo delivery to the proper destination organelle or plasma membrane. In this review, we focus on how the vesicle fusion machinery, the SNARE complex, is regulated by the interplay of the multisubunit tethering complexes (MTC) with the SNAREs and Sec1/Munc18 (SM) proteins. Although these factors are used in different stages of membrane trafficking, e.g., Golgi to plasma membrane transport vs. vacuolar fusion, and in a variety of diverse eukaryotic cell types, many commonalities between their functions are being revealed. We explore the various protein-protein interactions and findings from functional reconstitution studies in order to highlight both their common features and the differences in their modes of regulation. These studies serve as a starting point for mechanistic explorations in other systems.

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SNARE COMPLEXES

Transfer of protein and lipid cargo between distinct cellular compartments in eukaryotes is achieved through the use of membrane-bound vesicles. These vesicles bud from a donor compartment, are trafficked to and then fuse with their target membrane. Several conserved protein families have evolved to control these various processes, with specificity for particular trafficking pathways. The core of the membrane fusion apparatus is the SNARE complex (Jahn and Scheller, 2006); to facilitate fusion, each set of membranes has a distinct subset of SNARE proteins—t-SNARE proteins on the target membrane, and v-SNARE proteins on the vesicle membrane. Formation of this extremely stable SNARE complex is sufficient to overcome the energy barrier to membrane fusion, and is sufficient for fusion in simplified *in vitro* systems (Weber et al., 1998; Brünger et al., 2015). Additionally, mutations in individual SNARE proteins, changes in SNARE protein levels, and changes in SNARE complex assembly all result in various cellular and organismal defects from yeast through humans, indicating the necessity of these proteins in all stages of trafficking (Johnson et al., 2008; Garcia-Reitböck et al., 2010; Kama et al., 2011).

The regulated fusion of vesicles at proper target membranes requires specific recognition factors on both membranes. Several lines of evidence indicate that SNAREs alone are not sufficient for specificity. First, SNAREs can form stable, fusion-competent non-cognate complexes *in vitro* (Fasshauer et al., 1999; Yang et al., 1999; McNew et al., 2000; Bethani et al., 2007; Furukawa and Mima, 2014). Secondly, at least for exocytosis, protein localization is not sufficient to promote specific SNARE pairing, as many SNAREs are not specifically restricted to sites of

active membrane fusion (Brennwald et al., 1994; Jahn and Südhof, 1999). Furthermore, SNAREs need to traffic through the secretory pathway to reach their final destination, and encounter many cognate and non-cognate SNAREs along the way. When this process is not properly controlled, e.g., failing to inhibit SNARE complexes prior to trafficking, the proteins can form non-fusogenic complexes early in the secretory pathway (Medine et al., 2007). Therefore, to prevent premature or inappropriately localized fusion, SNARE proteins must be tightly controlled. Many syntaxin t-SNARE family members contain an autoinhibitory domain that prevents premature complex assembly (Weimbs et al., 1997; Nicholson et al., 1998; Munson et al., 2000; Dietrich et al., 2003). This and other mechanisms of inhibition and subsequent activation are likely provided by the protein families that are properly localized at sites of fusion, such as the Sec1/Munc18 (SM) proteins and the tethering factors.

SM PROTEINS

The SM proteins are a family of SNARE regulators with diverse and (at times) seemingly contradictory functions (Carr and Rizo, 2010; Archbold et al., 2014). Many different protein-protein and genetic interactions were identified for each of the four SM family members (Sec1/Munc-18, Vps45, Sly1, and Vps33). SM proteins interact with SNAREs using a number of different binding modes, often utilizing more than one binding mode simultaneously. The functional consequences of these interactions include regulating protein levels of partner SNAREs, promoting SNARE assembly and downstream membrane fusion, chaperoning/stabilizing the autoinhibited conformation of syntaxin prior to SNARE complex assembly, and working with the Sec17/Sec18 (NSF/SNAP) SNARE disassembly machinery to protect cognate SNARE complexes from disassembly prior to fusion (Carr et al., 1999; Sato et al., 2000; Bryant and James, 2003; Kennedy et al., 2004; Deák et al., 2009; Hashizume et al., 2009; Struthers et al., 2009; Lobingier and Merz, 2012; Lobingier et al., 2014). Most SM proteins also interact with tethering complexes, either transiently or as a stoichiometric component of the intact complex (discussed below). The most compelling mechanistic details of SM protein function were published recently, for the vacuolar fusion SM protein Vps33 (a component of the HOPS tethering complex): a pair of crystal structures suggested that if Nyv1 (v-SNARE) and Vam3 (t-SNARE) interact simultaneously with Vps33, these SNARE proteins would be correctly aligned to initiate zipping of the SNARE complex (Baker et al., 2015).

TETHERING COMPLEXES

SNARE complex assembly and fusion are also regulated by the multisubunit tethering complexes (MTCs; Bröcker et al., 2010; Yu and Hughson, 2010; Hong and Lev, 2014). The MTCs are compartment-specific complexes proposed to promote the initial interaction between a vesicle and its target membrane via interactions with lipids and proteins on both membranes. These interactions are critical to promote specific vesicle fusion at the proper target destinations. Most steps of membrane

trafficking are associated with an MTC (**Figure 1**), and while these complexes differ in subunit composition and number they each interact with the same families of proteins—Rab GTPases, SM proteins, coat proteins, and SNAREs (**Table 1**). Many MTCs also interact with the specific Guanine nucleotide Exchange Factor (GEF) for their GTPases. These complexes function upstream of SNARE assembly and vesicle fusion, resulting in vesicle accumulation at their sites of fusion upon disruption of MTCs. Although we focus on the MTCs in this review, the long coiled-coil tethers have also been implicated in SNARE complex regulation (Cheung and Pfeffer, 2016).

Despite differences in overall complex architecture, a subset of tethering complexes was defined based on the structures of the individual subunits—the Complexes Associated with Tethering Containing Helical Rods (CATCHR) family (Yu and Hughson, 2010). As the name suggests, the proteins in these complexes are composed of long rods of stacked helical bundles. The similar bundle topology of each subunit suggests divergent evolution from an ancient ancestor (Sivaram et al., 2006; Croteau et al., 2009; Yu and Hughson, 2010; Klinger et al., 2013). The remaining “non-CATCHR” complexes have a more diverse subunit composition; however, they still share many of the same protein family interactions, suggesting a common mechanism of action across all of the complexes.

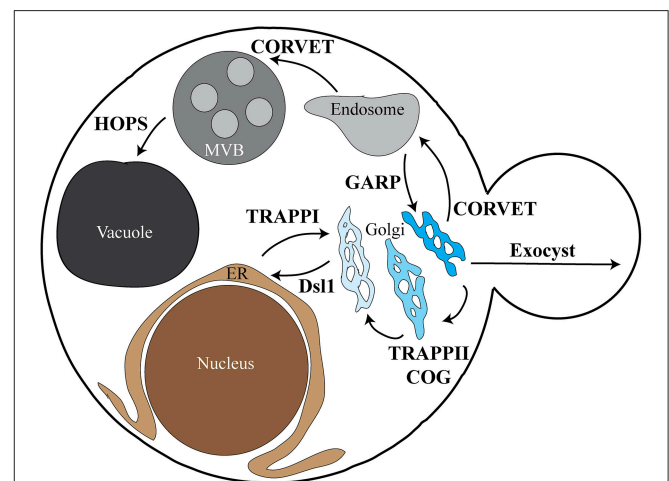


FIGURE 1 | Overview depicting MTC localization in yeast. The various subcellular locations and trafficking pathways in yeast are depicted, along with the tethering complexes associated with each pathway. The TRAPPI complex is involved in ER to cis-Golgi traffic, with the Dsl1 complex required for retrograde Golgi to ER traffic. The TRAPPII and COG complexes are involved in retrograde Golgi traffic between the various Golgi compartments. CORVET functions in both trans-Golgi to early endosome trafficking and early endosome to MVB/late endosome trafficking. The HOPS complex is required for MVB/late endosome to vacuole/lysosome vesicle fusion. Early endosome to Golgi recycling requires the GARP complex, while Golgi to plasma membrane trafficking requires the exocyst complex. Each of the pathways depicted have associated SNARE proteins; the tether-SNARE interactions discussed in this review are outlined in **Table 1**. The role of TRAPPIII in autophagosome formation is not shown. ER, endoplasmic reticulum; MVB, multivesicular body/late endosome.

TABLE 1 | Summary of MTC-SNARE interactions.

| Function | Tethering complex | SNARE Interaction | References |
|---|-------------------|--|--|
| Localization of MTC/SNAREs | HOPS | Vam7 | Wang et al., 2003 Zick and Wickner, 2013 |
| | COG | Unknown partners | Oka et al., 2004 Willett et al., 2013a |
| | Exocyst | Sn2 | Shen et al., 2013 |
| Protect SNARE complex from disassembly | HOPS | Pre-fusion SNARE complexes | Collins et al., 2005 Collins and Wickner, 2007 Xu et al., 2010 |
| | HOPS | Properly assembled SNARE complexes | Starai et al., 2008 |
| | COG* | Assembled SNARE complexes | Shestakova et al., 2007 |
| | Exocyst* | Assembled SNARE complexes | Dubuke et al., 2015 |
| | GARP* | Assembled SNARE complexes | Siniossoglou and Pelham, 2002 |
| Promote SNARE assembly/Stabilize SNARE proteins | COG | Unknown partners | Fotso et al., 2005 Oka et al., 2004 Shestakova et al., 2007 |
| | GARP | Unknown partners | Siniossoglou and Pelham, 2002 |
| | Dsl1 | Unknown partners | Meiringer et al., 2011 |
| Unknown Function(s) | CORVET | Pep12 (t-SNARE) | Subramanian et al., 2004 |
| | | Assembled SNARE complexes | Balderhaar et al., 2013 |
| | Dsl1 | Sec22/Sec20 | Kraynack et al., 2005 |
| | GARP | Tlg1 | Conibear et al., 2003 Siniossoglou and Pelham, 2001 |
| | | SNARE domains of Stx6, Stx16 and Vamp4 | Pérez-Victoria and Bonifacino, 2009 |

The functional implications of the various tether-SNARE interactions in yeast and mammalian cells are summarized. The * indicates an extrapolation of the functional consequence of the interaction for that tethering complex based on similar interactions in other stages of trafficking. For COG, GARP, and Dsl1, functional effects of SNARE interactions were observed, but the specific SNAREs involved have not been identified. Conversely, other specific interactions with SNAREs were identified for CORVET, Dsl1, and GARP, but the functional consequences of those interactions are currently unknown.

DSL1 COMPLEX

The CATCHR family Dsl1 complex is localized at the ER and is required for specific recognition of COPI coated retrograde Golgi-derived vesicles prior to fusion with the ER (Andag et al., 2001; Reilly et al., 2001). This complex is the smallest of all known tethering complexes with only three core subunits—Dsl1, Tip20, and Dsl3/Sec39 in yeast (Ren et al., 2009; Spang, 2012) and NAG, RINT1, and ZW10 (NRZ) in mammals (Tagaya et al., 2014). Although the Dsl1 complex is small, it participates in many of the same interactions as the other MTCs. Interestingly the complex does not appear to interact with GTPases on either membrane. Instead, the Dsl1 subunit interacts with the COPI coat of the incoming vesicle, while the Dsl3 and Tip20 subunits interact with SNARE proteins on the target membrane (Zink et al., 2009). While the switching action of a GTPase may not be used to modulate the interaction with the vesicle, the un-coating of the vesicle may provide a similar mechanism for proceeding to SNARE complex assembly (Zink et al., 2009). The complex also interacts with the SM protein Sly1, which functions at the Golgi, although the role of this interaction is unknown (Kraynack et al., 2005).

GARP COMPLEX

The Golgi Associated Retrograde Protein (GARP) complex is a CATCHR family MTC (Bonifacino and Hierro, 2011) required for protein sorting at the late Golgi (Conibear and Stevens, 2000). This complex functions in mammalian cells in two forms—GARP containing Vps54, and EARP containing syndetin. EARP is involved in the recycling endocytic pathway (Schindler et al., 2015).

GARP is another small tethering complex, containing only 4 core subunits. As observed for most MTCs, GARP interacts with a Golgi-localized GTPase, and GARP subunits interact with vesicles through interactions with an as yet unidentified protein (Siniossoglou and Pelham, 2001; Siniossoglou, 2005). Similarly, no physical interaction has been identified between GARP subunits and an SM protein, although a synthetic genetic interaction was identified between the Vps53 subunit and Sly1 (VanRheenen et al., 2001). GARP also has not been shown to physically interact with any GEFs, but several studies identified synthetic genetic interactions between components of GARP and the Ric1/Rgp1 dimeric GEF (Tong, 2004; Costanzo et al., 2010; Hoppins et al., 2011).

COG COMPLEX

The Conserved Oligomeric Golgi (COG) complex is necessary for retrograde transport between Golgi compartments, and is one of the best studied CATCHR complexes. It is composed of 8 subunits that form two separate “lobes” connected through the COG1 and COG8 subunits (Willett et al., 2013b). Additionally, depletion of various COG subunits results in an accumulation of vesicles at the Golgi (Wuestehube et al., 1996; Zolov and Lupashin, 2005). Results from cell-free systems suggested that COG can tether vesicles prior to fusion, supporting a direct role in tethering (Cottam et al., 2013).

To provide its tethering function, both the yeast and mammalian COG complexes interact with small GTPases on both the vesicle and target membranes (Suvorova et al., 2002; Fukuda et al., 2008; Yu et al., 2008; Miller et al., 2013). The COG4 subunit also interacts with the SM protein Sly1 (Laufman et al., 2009), and several COG subunits genetically interact with the GEF Ric1 (Tong, 2004; Schuldiner et al., 2005; Costanzo et al., 2011; Hoppins et al., 2011).

EXOCYST COMPLEX

The exocyst complex is the CATCHR-family MTC proposed to recognize and tether secretory vesicles to the plasma membrane (Heider and Munson, 2012; Wu and Guo, 2015). Similar to COG, the exocyst is composed of 8 subunits that form two separate “modules” connected by multiple protein-protein interactions (Heider et al., 2016). Temperature-sensitive yeast exocyst mutants result in vesicle accumulation in the bud, supporting a tethering role upstream of vesicle fusion with the plasma membrane (Novick et al., 1980; Grote et al., 2000).

The exocyst shares many similar interactions with other MTCs, including interactions with lipids and Rab/Rho family GTPases on the vesicle and plasma membranes, although tethering has not yet been directly demonstrated (Adamo et al., 1999; Guo et al., 1999; Zhang et al., 2001, 2008; He et al., 2007; Baek et al., 2010; Wu et al., 2010; Yamashita et al., 2010; Brunet and Sacher, 2014). The exocyst also interacts with the SM protein Sec1 through its Sec6 subunit (Wiederkehr et al., 2004; Morgera et al., 2012). Furthermore, the exocyst interacts with Sec2, the GEF for the vesicle-specific GTPase Sec4, through its Sec15 subunit (Medkova et al., 2006).

HOPS AND CORVET COMPLEXES

The non-CATCHR Homotypic Fusion and Vacuolar Protein Sorting (HOPS) Complex and Class C Core Vacuolar/Endosomal Tethering (CORVET) complexes are required for early endosomal homotypic fusion, early to late endosomal fusion, and vacuolar/lysosomal fusion. These subcellular compartments and tethering complexes can be purified; therefore, these trafficking steps can be reconstituted *in vitro* and are well-characterized (Conradt et al., 1992; Haas, 1995; Stroupe et al., 2006, 2009; Hickey and Wickner, 2010; Ostrowski et al., 2010; Plemel et al., 2011; Balderhaar et al., 2013). They are also the only tethering factors shown to be *bona fide* tethers (Brunet and Sacher, 2014).

The architectures of HOPS and CORVET are composed of a shared core of four subunits; the two additional subunits promote binding to specific Rab GTPases (Price et al., 2000; Seals et al., 2000; Peplowska et al., 2007). Unlike other tethering factors, HOPS/CORVET incorporate the SM protein (Vps33) into the complex rather than recruiting it as needed (Seals et al., 2000). It is through this subunit that many of the SNARE interactions occur. One of the HOPS-specific subunits appears to function as a GEF for Ypt7 in yeast, and the HOPS complex interacts with the Ccz1/Mon1 GEF (Wurmser et al., 2000; Nordmann et al., 2010); however, in mammalian systems no evidence of GEF activity has been detected (Peralta et al., 2010). These interaction similarities suggest that HOPS and CORVET, although distinct in structure from other MTCs, share conserved functions (Bröcker et al., 2012).

TRAPP COMPLEXES

The Transport Protein Particle (TRAPP) complexes, of which there are three identified in yeast, are putative tethering factors that function in ER to Golgi transport (TRAPPI), intra-Golgi trafficking (TRAPP II), and autophagosome formation (TRAPP III; Barrowman et al., 2010; Kim et al., 2016). The TRAPP complexes share the least sequence and structural similarity with the other tethering complexes (Cai et al., 2008). They interact with coat proteins, and specific subunits appear to differentiate ER-derived COPII coated vesicles from the Golgi-derived COPI coated vesicles (Sacher et al., 2001). Additionally, TRAPPI and TRAPP II can function as a GEF for Ypt1, a small Rab GTPase found on ER-derived vesicles and required for fusion with the Golgi (Wang et al., 2000). However, no interactions have been identified between TRAPP and either an SM protein or SNARE proteins/complexes, suggesting that it may function differently than other MTCs.

MTC-SNARE COMPLEX INTERACTIONS

Interactions between tethering factors and SNARE complexes have been observed for almost all trafficking steps (Table 1), and generally serve to promote formation of proper and stable SNARE complexes (Hong and Lev, 2014; Kuhlee et al., 2015). However, detailed mechanistic studies are needed to understand how these interactions regulate SNARE complex assembly, and the functional roles these interactions play in intracellular trafficking. Furthermore, the relationships between tethers and SM proteins in SNARE regulation remain to be elucidated.

One role for the MTC:SNARE interaction is in promoting MTC localization, SNARE protein localization, or both. For example, HOPS recruitment by the SNARE Vam7 maintains proper HOPS localization at sites of vacuole fusion, and loss of Vam7 membrane binding results in reduced HOPS enrichment (Wang et al., 2003). Secondly, HOPS is required to recruit the SNARE Vam7 to sites of fusion after disassembly of post-fusion SNARE complexes; these two interactions together result in a positive feedback of recruitment of the various fusion machinery (Zick and Wickner, 2013). For intra-Golgi trafficking,

knockdown of individual COG subunits in mammalian cells leads to changes in SNARE localization (Oka et al., 2004). Similarly, relocalization of the COG complex results in a redistribution of Golgi-destined vesicles, suggesting that COG recruits proper vesicles to their sites of fusion (Willett et al., 2013a). In polarized yeast exocytosis, a cluster of point mutations in the v-SNARE protein Snc2 (Snc2-M2) disrupts an interaction between the exocyst subunit Sec6 and Snc2, resulting in a mild exocyst polarization defect (Shen et al., 2013).

Another possible role for these interactions is in the protection of pre-fusion cognate SNARE complexes. HOPS competes with the disassembly machinery (Sec17/Sec18) for binding to the assembled SNARE complex and preferentially binds to trans-SNARE complexes that bridge the membranes; this protects the pre-fusion SNARE complex from premature disassembly (Collins et al., 2005; Collins and Wickner, 2007; Xu et al., 2010). Other evidence for this protective role is that HOPS prevents fusion between vacuolar compartments with non-cognate SNARE complexes, suggesting that it may “proofread” the SNARE complex prior to fusion (Starai et al., 2008). Similarly, COG binds more tightly to the assembled SNARE complex than the individual SNAREs, although a direct protective role remains to be shown (Shestakova et al., 2007). Recently, we showed that the exocyst subunit Sec6 has a tighter affinity for the Sec9:Sso1:Snc2 ternary complex than the Sec9:Sso1 binary complex (Dubuke et al., 2015); it will be interesting to see if exocyst can also proofread exocytic SNARE complexes.

In some cases, the MTCs were shown to be important for SNARE function, although the specific MTC:SNARE interactions are currently unknown. Knockdown of individual COG subunits in mammalian cells leads to an increase in uncomplexed SNAREs, and a decrease in overall SNARE protein stability (Oka et al., 2004; Fotso et al., 2005; Shestakova et al., 2007). Also in mammalian cells, SNARE assembly is reduced when GARP is depleted (Siniossoglou and Pelham, 2002). Similarly, in yeast, functional Dsl1 subunits are required for formation of the assembled t-SNARE complex, and stimulate SNARE complex assembly *in vitro* (Ren et al., 2009; Meiringer et al., 2011). These functional consequences leave open the major question of the mechanism(s) by which the various MTCs are regulating their cognate SNARE proteins.

Finally, for many of these complexes, the individual interactions were identified but not the function of these interactions in trafficking. CORVET interacts with

endosomal/vacuolar SNARE proteins and SNARE complexes through the Vps33 subunit (Subramanian et al., 2004; Balderhaar et al., 2013). The Dsl1 complex interacts with t-SNARE proteins on the ER, potentially in lieu of interactions with small GTPases, and its mammalian counterpart NZR interacts with various ER-localized SNARE proteins (Kraynack et al., 2005; Meiringer et al., 2011; Tagaya et al., 2014). The GARP complex interacts with the N-terminal regulatory domain of the syntaxin homolog Tlg1, as well as the SNARE domains of several mammalian Golgi SNAREs. The mammalian GARP homolog also interacts with the assembled SNARE complex (Siniossoglou and Pelham, 2001, 2002; Conibear et al., 2003; Pérez-Victoria and Bonifacino, 2009).

Each of the “modes” of SNARE regulation by the MTCs suggests a common theme—the MTCs generally have a positive influence on cognate SNARE complex assembly. However, each mode is characterized in only a few trafficking pathways, and often only part of the information is known (e.g., binding interactions vs. functional consequences) without elucidation of the full story. Are these specific modes common across all of the trafficking pathways? Are there additional modes, waiting to be identified? How do the MTCs collaborate with the SM proteins to control the SNAREs? In many cases, experimental groundwork exists in terms of purified complexes and binding partners, indicating that quantitative *in vitro* functional assays are likely possible. Similarly, powerful genetic tools are becoming commonplace enough to begin teasing apart mechanisms in mammalian cells and other organisms that were previously characterized only in yeast. The function of the MTCs and SNAREs is an intriguing question, and by combining results from different pathways and organisms we can begin to understand the complicated interplay between these protein families in all stages of trafficking.

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All authors listed, have made substantial, direct, and intellectual contribution to the work, and approved it for publication.

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