Published in final edited form as:
Traffic. 2012 July ; 13(7): 898–907. doi:10.1111/j.1600-0854.2012.01353.x.

Exorcising the Exocyst Complex

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Abstract

The exocyst complex is an evolutionarily conserved multisubunit protein complex implicated in tethering secretory vesicles to the plasma membrane. Originally identified two decades ago in budding yeast, investigations using several different eukaryotic systems have since made great progress toward determination of the overall structure and organization of the eight exocyst subunits. Studies point to a critical role for the complex as a spatiotemporal regulator through the numerous protein and lipid interactions of its subunits, although a molecular understanding of exocyst function has been challenging to elucidate. Recent progress demonstrates that the exocyst is also important for additional trafficking steps and cellular processes beyond exocytosis, with links to development and disease. In this review, we discuss current knowledge of exocyst architecture, assembly, regulation and its roles in a variety of cellular trafficking pathways.

Exocytosis, or secretion, is the process by which cargo-filled vesicles fuse with the plasma membrane to incorporate proteins and lipids into the plasma membrane and to release molecules into the extracellular space. Exocytic events are often restricted to a distinct region of the plasma membrane, resulting in polarized growth and secretion. The budding yeast *Saccharomyces cerevisiae* has been a critical model system to study the mechanisms of polarized exocytosis and these findings have guided and complemented experiments in multicellular eukaryotes, due to the high conservation of trafficking mechanisms. These studies resulted in the identification of a multitude of proteins and lipids critical for establishing cell polarity and the trafficking of vesicles between cellular membranes.

Exocytic vesicles are generated at the Golgi apparatus and those that function in polarized exocytosis are transported using cytoskeletal tracks and motor proteins to the plasma membrane (1). Vesicle fusion at the target membrane is facilitated by SNARE proteins present on the vesicle and target membranes. Yeast genetic studies identified a number of proteins that are required for a step after vesicle delivery but preceding SNARE-mediated vesicle fusion. Temperature-sensitive mutations in these genes result in an accumulation of vesicles that fail to fuse with the plasma membrane, leading to growth and secretion defects (2, 3). Many of these proteins were later identified as components of an evolutionarily conserved complex and named the exocyst (4), which is the focus of this review. The exocyst is a member of the Complex Associated with Tethering Containing Helical Rods (CATCHR) family (5), of which two other family members are reviewed in this issue (Ungar, COG review; Spang, Dsl review) and the other, GARP, was recently reviewed (6). Several functions have been proposed for these complexes, including tethering vesicles to their target membranes, as well as spatial and temporal regulation of SNARE complex assembly (7–9) (Figure 1).

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For nearly two decades the exocyst has been a major focus of research in a variety of eukaryotic model systems, including the identification of numerous protein-protein interactions, and determination of crystal structures of several subunits (10–12). However, our understanding of the molecular mechanisms of its function is still limited. Additionally, the more we learn about the exocyst complex, the more it becomes clear that the complex is important in multiple stages of membrane trafficking and likely plays more active roles in exocytosis than simply tethering two lipid bilayers (Figure 1). Interactions with SNAREs, SNARE regulators and many key cell signaling molecules, as well as the unique roles of several of its subunits, suggest that the exocyst is a key integrator of many signals and is a spatiotemporal regulator of multiple membrane trafficking processes.

Exocyst architecture

The composition of the exocyst is highly conserved in eukaryotic systems, with eight single-copy subunits: Sec3, Sec5, Sec6, Sec8, Sec10, Sec15, Exo70, and Exo84 (4, 13, 14). Six of the eight subunits were identified in the original *S. cerevisiae* screen for secretory mutants and all but *SEC3* are essential genes in yeast (2, 15). Since the identification of the complex, budding yeast has proved to be a powerful tool for elucidating functional and structural information about the exocyst complex. Moreover, homologues of all the subunits exist in multicellular eukaryotes and the essential role for the complex in growth and development is conserved as well. Null mutants in a number of exocyst subunits result in early lethality in both mice and *Drosophila* indicating a critical role in development (16–18).

The exocyst belongs to the CATCHR family of multisubunit protein complexes, which have low sequence identity but conserved helical bundle structures (see (5, 6, 19) for review). The crystal structures of exocyst subunits display a common motif of tandem helical bundles that form extended rod-like structures. Electron microscopy (EM) studies of the mammalian brain exocyst (20) and biochemical studies (21) predict that the subunits pack together in a side-by-side manner in the assembled holocomplex. The EM images show the glutaraldehyde-fixed exocyst complex in a “Y-shaped” structure, suggesting that the two arms may connect apposing members to mediate its putative tethering function (10, 20). Supporting this idea, electron tomography studies of cell plate formation in *Arabidopsis thaliana* showed “Y-shaped” structures linking vesicles (22).

Although the exocyst subunits share structural homology, their surfaces are characterized by unique hydrophobic and electrostatic patterns (23). This diversity of surface properties indicates unique binding interfaces and functions of the individual subunits, either within the complex or individually. Structural studies have been important in characterizing these unique binding sites and interactions (reviewed in (1, 10). In addition to the conserved helical bundles, several exocyst subunits contain additional functional domains. The yeast Sec3 N-terminal region contains a novel Pleckstrin Homology domain in a region demonstrated to interact with $PI(4,5)P_2$ and a number of small GTPases (11, 12). Moreover, mammalian Sec5 and Exo84 were each crystallized in complex with the RalA GTPase, structures that were invaluable in defining the specificity of binding to the GTP-bound form of RalA (24, 25).

Exocyst localization and activation

As expected for a complex involved in polarized vesicle exocytosis, the exocyst is localized to limited regions of the plasma membrane, where it mediates the delivery of lipids and proteins necessary for polarized membrane growth. In yeast, these sites are the tip of the growing bud and the mother-bud neck during cytokinesis (26). Similarly, the *Schizosaccharomyces pombe* exocyst is localized at the division septum during membrane scission (27). Studies in *Drosophila* and mammalian neurons indicate that the exocyst is

found at the ends of neuronal growth cones during neurite branching, as well as at sites of synaptogenesis (28–30). Cell-cell contact sites in polarized epithelial cells and the leading edge of cell motility processes are also sites of exocyst concentration (31, 32). Data is rapidly emerging about the role of the exocyst in plants, where the complex localizes to the growing ends of pollen tubes, root hair tips and the cell plate for division (33, 34). How the exocyst is recruited and maintained at polarized sites is a critical question, and one that has been the focus of much effort since the complex was identified.

Early studies in budding yeast implicated Sec3 as a spatial landmark for exocytosis, as the localization of Sec3-GFP appeared unaffected by disruptions of the secretory pathway, actin, and cell cycle proteins (35). Immunofluorescence of endogenous Sec3 called this result into question, however, and later reports demonstrated that Sec3 is not sufficient to target and/or retain exocyst complexes at sites of secretion (36–38). Consistent with exocyst localization being dependent on secretion and polarized actin, live imaging and fluorescence recovery after photobleaching (FRAP) analyses suggested that six of the eight exocyst subunits arrive at polarized sites on vesicles via transport on actin cables (39). Sec3 and Exo70 were the exceptions in that Sec3-GFP seemed to localize independently of these mechanisms and Exo70-GFP appeared to use both vesicle-independent and -dependent routes to polarized sites. The model proposed that exocyst subunits arriving on vesicles assembled with Exo70 and Sec3 at the plasma membrane, although it is not clear whether the rest of the subunits arrive individually or already assembled together. It remains to be determined if assembly and disassembly of the complex are important for tethering and targeting vesicles; it seems likely that disassembly of the complex must follow to initiate another round of vesicle fusion, but there is no direct evidence yet to suggest whether this occurs *in vivo*.

Exo70 and Sec3 are effectors for Rho GTPases, which are master cell polarity regulators that are localized to the plasma membrane and are critical in polarizing the actin cytoskeleton for vesicle delivery. For a more thorough review of the role of small GTPases in exocytosis, see Wu *et al.*, 2008 (40). The yeast Sec3 N-terminal domain interacts with Rho1, Cdc42 and $PI(4,5)P_2$, while Exo70 binds Rho3, Cdc42 and $PI(4,5)P_2$ (41–46). The GTPase interactions of Exo70 are conserved, as mammalian Exo70 interacts with the Rho protein TC10 (47).

To understand the functional significance of these interactions, specific temperature-sensitive mutants in yeast were studied. *cdc42-6* and *rho3-V51* alleles display severe growth and secretion defects without disrupting exocyst localization or actin polarization (42, 43). The latter Rho3 effector domain mutation abrogates binding to both Exo70 and the myosin motor Myo2, and recently identified loss-of-function *exo70* mutants mimic the phenotypes of these specifically exocytosis-deficient Rho mutants (43, 48). However, deletion of the N-terminal domain of Sec3 resulted in the mislocalization of only Sec3 with no growth or secretion defects (44). It was possible that this lack of phenotype resulted from a redundant or parallel pathway involving Exo70 and synthetic genetic interactions have been tested extensively. Interestingly, the double mutant, *rho3-V51 sec3*ΔN, shows no synthetic effects on growth, polarity, or localization of any exocytic machinery (36). However, *sec3*ΔN was synthetically lethal in combination with *cdc42-6* arguing that there may be functional overlap between Exo70 and Sec3 through Cdc42, but because *exo70* loss-of-function mutants alone demonstrate similar phenotypes to *cdc42-6* it seems plausible that Exo70 is the primary effector for this GTPase (36, 48).

Interestingly, these mutants can be rescued by GTP-hydrolysis deficient versions of the Rho GTPases, suggesting that the GTPase cycle is not required for their exocytosis-specific functions (36). Small GTPases, such as Cdc42, function both through GTP hydrolysis and hydrolysis-independent mechanisms. Commonly, molecular recognition and timing events

that require binding and release of effectors require hydrolysis of GTP; for example, the Sec4 interaction with the exocyst requires this function (see below). Hydrolysis-independent mechanisms are proposed to be allosteric regulatory events, where binding of the GTPase activates the binding partner through a conformational change (40). Since exocyst interactions with Rho appear to fit this allosteric model, it is possible that these interactions function primarily to activate the exocyst at polarized sites, potentially to accelerate SNARE complex assembly for vesicle fusion.

Because Rho GTPase interactions are not critical for polarized exocyst localization, phospholipid interactions may provide this function. *sec3ΔN* mutants crossed to *exo70* mutants defective in binding to $PI(4,5)P_2$ are severely growth defective or synthetically lethal in yeast, indicating possible redundant functions for these subunits in stabilizing exocyst localization through lipid binding (49, 50). Furthermore, mutations in yeast *MSS4* the kinase that produces $PI(4,5)P_2$, cause diffuse exocyst localization (51). Mammalian Exo70 is also dependent on $PI(4,5)P_2$ binding for its localization and the residues involved in this interaction constitute the most conserved domain on the protein (52). The lipid binding residues in the N-terminal region of Sec3 are also highly conserved among Sec3 homologues (11). Finally, in addition to phospholipid interactions, it is likely that additional factors critical for exocyst localization remain to be identified. The yeast *sec6* mutant alleles, *sec6-49* and *sec6-54* result in mislocalization of all eight exocyst subunits, which remain fully assembled (38). The mutations are in regions suggestive of protein-protein, rather than protein-lipid, interactions. Therefore, these mutants are proposed to be defective in binding to a protein factor that anchors the assembled complex at the plasma membrane.

Exocyst assembly

A key aspect to understanding exocyst function is to determine the mechanism(s) of its assembly and disassembly. Many questions remain unanswered, such as when, where and how many of the subunits assemble together, and if they always stay assembled. Whether the exocyst requires disassembly is unknown, although considering the ~750 kDa size of the complex, disassembly may remove the exocyst as an obstacle for vesicle fusion and/or facilitate recycling of the complex. Hints of functional subcomplexes and monomeric pools of subunits have been observed, but biochemical isolation and characterization of these pools remains elusive, as does the fully assembled complex.

Early biochemical experiments discovered that the eight unique polypeptides of the exocyst form a high molecular weight complex (4, 14). Differential centrifugation, cell fractionation, and immunofluorescence experiments in both yeast and higher eukaryotes indicated that the exocyst subunits are found primarily as a single complex, with both cytosolic and plasma membrane pools (4, 33, 53–57). This is consistent with the localization of all of the exocyst subunits to sites of polarized secretion at the bud tip and mother-bud neck in yeast, and polarized sites of membrane expansion in plant and animal cells. Moreover, in unpolarized epithelial cells, the exocyst subunits Sec6 and Sec8 are primarily cytosolic, but the majority shifts to polarized sites on the plasma membrane upon cell-cell contact (55).

Individual temperature-sensitive mutations in each of the budding yeast exocyst subunits result in the loss of specific combinations of subunits from the complex (54), suggesting that many individual interactions are necessary for maintaining the architecture of the exocyst. Additional work using yeast two-hybrid analyses and *in vitro* binding studies identified weak pairwise binding interactions among the subunits of the exocyst (reviewed in (10, 32)). Structural and biochemical studies of the holocomplex remain an outstanding challenge for the field, to achieve an understanding of how the subunits are pieced together, and details of

assembly and disassembly of the complex. Moreover, it will be interesting to see if these mechanisms are conserved across all eukaryotes.

Exocyst subcomplexes

The existence of subcomplexes or monomeric free pools would lead to a greater array of functional possibilities and mechanisms for exocyst regulation. Assembly of the subunits into the full octameric complex at the proper place and time would ensure the spatiotemporal specificity of a vesicle tethering event. Indeed, it has been proposed that a subset of subunits arrives on vesicles and assembles with the remaining subunits waiting at the plasma membrane, thus mediating a connection between membranes (39). Although the exocyst subunits predominantly co-migrate when examined by centrifugation and gel filtration studies, the broad distributions and trailing peaks for some exocyst subunits suggest that some of the subunits may exist in free pools outside of the complex (53, 57). Additionally, localization studies in *Drosophila melanogaster* indicate that specific exocyst subunits exhibit unique localization patterns during oogenesis, development and adulthood, suggesting that the subunits might not always function as a single entity (18).

Cell fractionation studies in mammalian cells also provide strong evidence for subcomplexes. Ral GTPases function in trafficking, but are unique to metazoan systems. Activated RalA and RalB are associated with secretory vesicles (58) and each binds to two exocyst subunits: Sec5 and Exo84, which are predicted to be in separate subcomplexes by cell fractionation (59, 60). Recent studies also showed that Ral GTPases interact with Exo84 and Sec5 in distinct subcellular locations, with Sec5 at the plasma membrane and Exo84 associated with vesicles (61, 62). It seems likely that there would be a greater need for functional subcomplexes in mammalian systems, where different combinations of subunits could respond to a complex array of signals.

Despite a number of studies suggesting that subcomplexes of exocyst subunits exist, the isolation or reconstitution of these has proven challenging, likely due to the weak pairwise interactions between the subunits (21, 23). Weak interactions are likely to be functionally important for cooperative assembly and disassembly of the complex. More sensitive quantitative techniques for detection of these subcomplexes, as well as robust activity assays, will be important for determining their physiological relevance. Furthermore, identification of specific mutants that disrupt intra-exocyst interactions is crucial to tease apart the functions of individual subunits, the complex as a whole, and to understand which subunits are critical for stabilization of exocyst structure.

Vesicle recognition and regulation of assembly by GTPases

Rab GTPases are the largest group of the Ras superfamily of small GTPases, with 11 Rab proteins in yeast and over 60 in humans. They are important regulators at all stages of trafficking, particularly through interactions with vesicle motility machinery (see below), tethering factors, and other regulatory molecules (63). The yeast exocyst subunit Sec15 interacts with the GTP-bound Rab protein Sec4 on vesicles, presumably for specific secretory vesicle recognition; furthermore, functional Sec4 is required for proper exocyst localization and stable assembly (53, 54, 64). It is not yet known whether the Sec4-GTP-Sec15 interaction only facilitates exocyst subunit delivery on vesicles, or if it plays a more active role in assembly/disassembly of the complex.

Exocyst interactions with Rab GTPases are conserved in higher eukaryotes as well. In both mammals and *Drosophila* Sec15 interacts with the Rab GTPase Rab10; this interaction appears to be important for endocytic recycling (65–67). Additionally, interactions with Rab8 and Rab11 function in trafficking from the Golgi and recycling endosome to the

plasma membrane, as well as to the base of the primary cilium during ciliogenesis (68). It will be interesting to determine if these Rab GTPases function similarly to Sec4 in regulation of the exocyst complex.

The interaction of RalA with two different exocyst subcomplexes in metazoans may also be functionally important for exocyst assembly. The reduction of RalA expression results in decreased association of Sec10 with Sec6, each being a component of separate Exo84 and Sec5 subcomplexes (59). Additionally, release of the Ral-exocyst interactions may be triggered by phosphorylation events (69), possibly leading to dissociation of the exocyst from vesicles or disassembly of the complex.

Exocyst Functions

Tethering

Tethering is defined as the initial, long-distance connection between the vesicle and the target membrane (7, 70).The act of tethering would capture and stabilize vesicles before fusion, thus indirectly facilitating SNARE-docking and fusion (Figure 1). Tethering factors take the form of either long coiled-coil proteins or multisubunit protein complexes, which interact with proteins and/or lipids on both the vesicle and target membranes (9).

Despite their classification as tethers, many of these proteins and complexes, such as the exocyst, have not been experimentally shown to perform this function, with the exception of the long coiled coil tethers, TRAPP (71), and (72). One landmark experiment demonstrated that Uso1, a coiled coil tether implicated in ER to Golgi trafficking of COPII vesicles, and the GTPase Ypt1, were sufficient to anchor vesicles at the Golgi and this function was physically separable from SNARE-mediated fusion (70). Tethering has also been shown for other coiled coils and a few of the multisubunit tethers, but most are challenging to test experimentally (5). Demonstration of tethering by the exocyst complex awaits *in vitro* reconstitution experiments; the large sizes and low solubilities of the eight subunits are a significant challenge for purification of the holocomplex, or for reconstituting an assembled and functional complex *in vitro*. Not only would an *in vitro* assay be valuable for demonstrating tethering, but would also be able to distinguish between tethering and a direct effect on SNARE complex assembly and fusion. Other possible approaches include the use of super high resolution imaging for observing tethering of vesicles *in vivo* and powerful electron microscopy techniques such as that previously used to observe homotypic vesicle fusion during cytokinesis in *Arabidopsis* (22).

SNARE regulation

In addition (or alternatively) to tethering, the recognition of exocytic vesicles by the exocyst may directly ensure the fidelity of secretion by activating specific SNARE complex assembly. For example, the yeast exocyst subunit Sec6 binds to the exocytic plasma membrane SNARE Sec9 both *in vitro* and *in vivo* and this interaction inhibits the *in vitro* assembly of the plasma membrane SNARE complex (57, 73). Sec9 binding to Sec6 is incompatible with Sec6-exocyst interactions, suggesting that assembly of the exocyst would lead to release of Sec9 for SNARE complex assembly (57). Additionally, an interaction between Sec6 and the SNARE regulatory protein Sec1 (74) was recently identified, and was suggested to recruit and/or stabilize Sec1 at sites of secretion (57); together, the exocyst and Sec1 may function to spatially and temporally control SNARE assembly. *In vitro* reconstitution of SNAREs with purified exocyst complexes, and other regulators, such as Rab and Rho GTPases, Sec1 and Sro7/77 (75), will be necessary to determine the effect of the exocyst on SNARE assembly and membrane fusion.

SNARE regulation may be a general feature of many tethering complexes. HOPS, the vacuolar tethering complex, binds to SNARE complexes and proofreads vacuolar SNARE pairing (76, 77). Similarly, COG binds to SNAREs and increases the stability of intra-Golgi SNARE complexes, possibly preventing disassembly and promoting fusion. It is unclear whether COG may have an effect on the rate of SNARE complex assembly; Dsl1has a slight stimulatory effect on Golgi to endoplasmic reticulum SNARE complex assembly *in vitro* and GARP promotes the assembly of trans-Golgi network SNARE complexes (6, 78, 79). As the mechanistic details for these functions are explored further, it will be interesting to discover whether all the tethering complexes function similarly in SNARE complex regulation, or if there are interesting organelle-specific (or species-specific) differences.

Diverse cellular functions

In contrast to the traditional view of the exocyst as a simple tether of secretory vesicles to the plasma membrane, the complex has been implicated in a great variety of cellular processes (Figure 1). The common theme seems to involve exocyst-mediated localization of membrane-bound vesicles or compartments to specific target sites at the appropriate time. For example, at least three yeast exocyst subunits (Sec3, Sec5, and Sec8) have been implicated in ER inheritance, potentially by anchoring the cortical ER at the bud tip where the exocyst is localized (80). A later study also identified an interaction between yeast Sec6 and Rtn1, a protein important for ER reticulation, with Rtn1 potentially serving as an exocyst receptor on the ER (81). Several studies implicate the exocyst in prospore membrane formation during meiosis in budding yeast (82, 83).

In higher eukaryotes, the exocyst subunits are expressed in all tissue types analyzed thus far (14). Similar to the phenotype in yeast, exocyst mutants or knock-downs in more complex organisms are associated with cell growth and developmental defects, as has been shown in mouse, plant, and *Drosophila* model systems (16–18, 84). The function of the exocyst in growth and secretion in many cell types reflects its critical role in tethering and SNARE-mediated fusion of exocytic vesicles. Furthermore, as suggested by its bud neck localization in budding yeast, the exocyst also appears to direct vesicles to the midbody during cytokinesis in mammalian cells (85). In addition, the exocyst has been shown to be important for endocytic recycling in animal cells (26, 86). Highly specialized secretory pathways, such as the insulin-stimulated delivery of the glucose transporter Glut4 in adipocytes, also require functional exocyst complexes (47, 87).

The exocyst is required for many other types of membrane expansion, including ciliogenesis, tubulogenesis and cell migration in mammalian systems (31, 32, 68) (Figure 1). Due to its promotion of cell growth, cell migration, and its interactions with Ral GTPases, the exocyst has been linked with cancer progression and metastasis (31, 88). In one example, the secretion of matrix metalloproteinases (MMPs) in tumor cell invadopodia requires exocyst-mediated exocytosis (89, 90). Furthermore, the exocyst-mediated exocytic pathway has also been shown to play a role in bacterial pathogenesis; the exocyst is co-opted by the bacteria *Salmonella* to promote its invasion of intestinal epithelial cells (91). The exocyst also has roles in host survival responses—several studies have linked exocyst function to various aspects of the innate immune response (92, 93).

The newest facet to exocyst function was discovered through the study of the involvement of the GTPase RalB in autophagosome biogenesis (62). RalB triggers its exocyst binding partner Exo84 to serve as a platform for the assembly of the autophagy induction complex and vesicle formation machinery. It will be interesting to see whether the exocyst's role in autophagy is yet another aspect of its tethering/membrane fusion activities, or a novel function for the complex or its subunits.

In contrast to these various roles for the exocyst, several secretory processes appear not to be dependent on wild-type levels of exocyst function. In *Schizosaccharomyces pombe* for example, severely reduced levels of Sec8 protein blocked septum cleavage with only a modest effect on cargo secretion and no significant effect on polarized growth (27). It is possible that exocyst function is rate-limiting during cytokinesis and not growth, but recent results suggested the presence of parallel actin-dependent and exocyst-dependent secretory pathways in *S. pombe* (94). Additionally, *Drosophila* Sec5 mutants suggested a requirement for the exocyst during neuronal development, but not for synaptic vesicle fusion (17). This specialized system may have evolved additional mechanisms to mediate the fine-tuned release of synaptic vesicles. However, Sec8 was found on purified mammalian synaptic vesicles, so it is possible that the exocyst could be required for synaptic transmission in other animals (95).

Cytoskeleton interactions: role in vesicle transport?

Yeast post-Golgi vesicles are transported from the trans-Golgi network to the plasma membrane along actin filaments using the type V myosin motor Myo2. The Rab GTPases Ypt31/32 and Sec4 both associate with post-Golgi vesicles and bind to Myo2, but not simultaneously, as they exchange during the progression of vesicle transport (96). Due to this GTPase shuffling, it seems unlikely that Rabs would be the sole interactors maintaining the cytoskeletal connection of the vesicle. Indeed, it was recently shown that the cargo-binding domain of Myo2 is structurally homologous to the exocyst subunits (97) and this domain of Myo2 directly binds to Sec15; abrogation of the Myo2-Sec15 interaction leads to growth and secretion defects in yeast (96). Immunoprecipitation of Myo2 pulls down all of the exocyst subunits, suggesting association with the full complex, although it is unclear whether this occurs during vesicle transport or upon arrival at sites of secretion (96). The function of this interaction is unclear, however, as disruption of exocyst assembly and function by a variety of mutants does not lead to defects in vesicle delivery to polarized sites (2). More specific mutant alleles of Sec15 and Myo2 may be required to tease apart this molecular mechanism.

In mammalian systems, vesicles are transported from the Golgi by microtubules and their associated kinesin motors to cortical actin networks at the plasma membrane. Numerous approaches have demonstrated an interaction between the exocyst complex and microtubules; furthermore, Exo70 was shown to inhibit the polymerization of tubulin *in vitro* (98). The exocyst or one or more of its subunits may play a role as adaptors in the connection of vesicles to microtubules, analogous to its proposed role in actin-based transport in yeast. Moreover, it was proposed that the exocyst may be needed to release vesicles from microtubules to the actin networks (98). There is no mechanistic understanding yet for the role of the exocyst in these processes but the interactions provide important clues that the exocyst is involved in multiple stages of trafficking including vesicle transport up through SNARE complex assembly.

Conclusions

The recent years have shown an explosion in studies of exocyst function, in yeast and in many *Drosophila* plant, and mammalian cell types. These advances argue that the exocyst is more than just a tethering complex, and that it has many roles in multiple stages of vesicle trafficking. A common theme arising from all model systems is the role of the exocyst at many sites in the cell as a spatiotemporal regulator of membrane trafficking. It is well-suited to these functions, having eight subunits characterized by unique sets of interacting partners, with multiple layers of regulation available (Table 1).

Recent work links the exocyst with disease and bacterial pathogenesis in mammalian systems. The key to understanding the role of the exocyst in these processes will be deeper mechanistic examination of exocyst function using structural and quantitative biochemical studies of the octameric complex, putative subcomplexes and their binding partners. Further insight is provided by mutational analyses, especially in yeast, to isolate the functions specific to particular subunits within and outside of the complex. These studies will complement localization and *in vivo* functional assays in multicellular organisms, where genetic techniques are more challenging. Finally, although classified as a tethering complex, no direct evidence for tethering has been experimentally demonstrated; development of tethering and other *in vitro* activity assays presents the greatest challenge to advance our understanding of the molecular details of exocyst complex function.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank Chavela Carr, Heidi Hehnly and members of the Munson laboratory for critical reading of this manuscript. Research in the Munson lab is supported by the National Institutes of Health Grant GM068803.

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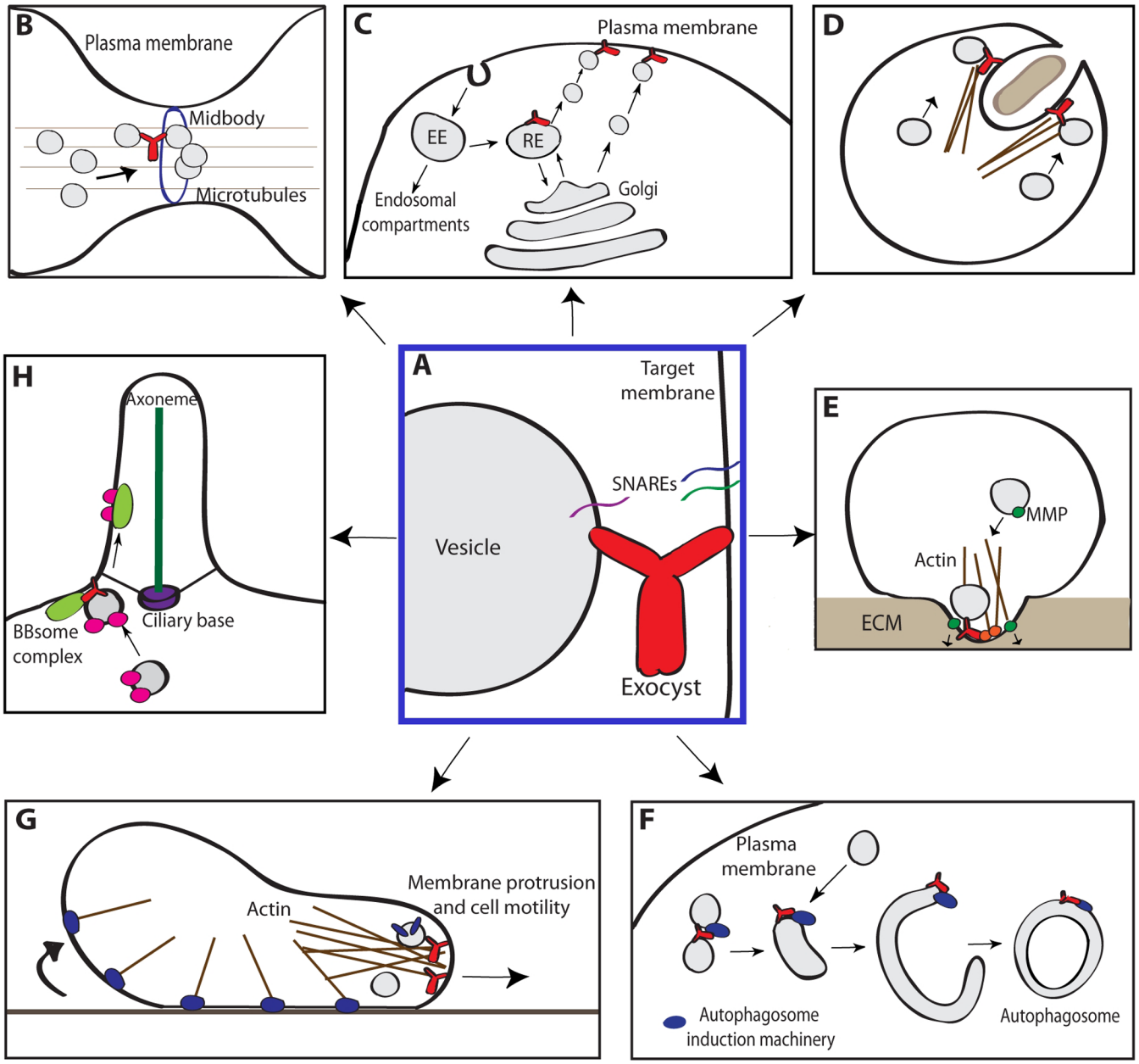

Figure 1. Exocyst functions in a variety of processes in single- and multicellular eukaryotes

A) The exocyst is proposed to form an initial connection between vesicle and target membrane through interactions with proteins and lipids on both surfaces. The interactions may bring the vesicle close enough to promote SNARE complex formation and vesicle fusion and/or the exocyst may play an active role in regulating SNARE assembly. B) The exocyst localizes to the site of cytokinesis to direct and tether vesicles at these sites, leading to formation of a new membrane and facilitating abscission. C) During polarized secretion, the exocyst tethers both exocytic vesicles generated at the Golgi apparatus and vesicles that are being recycled to the plasma membrane from the recycling endosome (RE=Recycling Endosome; EE=Early Endosome). D) An invading pathogen mediates its entry into the cell by hijacking host cell processes including the exocyst complex, to polarize the cytoskeleton and vesicle delivery for membrane ruffling and macropinocytosis. E) The exocyst

colocalizes with IQGAP1 (orange) in invadopodia, directing the growth of invasive processes and the delivery of matrix metalloproteinases (MMPs) that degrade the extracellular matrix (ECM). F) Exo84 and a possible subcomplex of exocyst subunits interact with autophagosome induction machinery (blue), promoting the formation of the autophagosome. The exocyst may function to tether vesicles or tubules to each other leading to the production of this compartment. G) The exocyst interacts with lipids and proteins to localize to the leading edge of migrating cells, promoting the outgrowth of the leading edge and delivering focal adhesion (blue) components recycled from the rear. H) The exocyst directs membrane and protein delivery to the ciliary base to promote ciliogenesis and the BBsome complex shuttles proteins into the cilium beyond the diffusion barrier. For references, see the text and Table 1.

Table 1

Exocyst protein interactions reveal roles for the complex in a variety of basic and complex eukaryotic cellular processes.

Cellular Process	Interactor	Exocyst Partner	Kingdom	References
Bud site selection	Iqg1	Sec3	Fungi	(99)
Endoplasmic reticulum structure	Rtn1	Sec6	Fungi	(81)
SNARE complex regulation	Sec9 and Sec1	Sec6	Fungi	(57, 73)
Post-Golgi vesicle transport	Myo2	Sec15	Fungi	(96)
Cell polarity	Sro7/Sro77	Exo84	Fungi	(75)
Cell polarity	ICR1	Sec3	Plant	(100)
Exocyst disengagement from Ral GTPase	Protein Kinase C	Sec5	Animal	(69)
Cytokinesis	Centriolin	Sec15	Animal	(85)
GLUT4 trafficking	TC10	Exo70	Animal	(47)
Ciliogenesis	Rab8 and Rab11	Sec15	Animal	(68)
Invadopodia function, MMP secretion	IQGAP1	Sec3 and Sec8	Animal	(89)
Cancer, cell migration	RalA/RalB	Sec5 and Exo84	Animal	(31, 59, 60)
Cell migration	aPKCs	unknown	Animal	(101)
Actin polymerization and cell migration	ARPC1 of Arp2/3 complex	Exo70	Animal	(102)
Directional cell migration	PIPKIγi2	Exo70 and Sec6	Animal	(103)
Neuronal and epithelial cell polarity	RalA/RalB	Sec5 and Exo84	Animal	(30, 55)
Tight junction establishment and function	RalA/RalB	Sec5 and Exo84	Animal	(61)
Innate immunity signaling	TBK1	Sec5	Animal	(92, 93)
Salmonella invasion	SipC	Exo70	Animal	(91)
Autophagy induction	Beclin/ULK1/VPS34	Exo84	Animal	(62)