Review

Assembly and disassembly of the ESCRT-III membrane scission complex

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The ESCRT (endosomal sorting complex required for transport) pathway promotes the final membrane scission step at the end of cytokinesis, assists viral budding and generates multivesicular bodies (MVBs). These seemingly unrelated processes require a topologically similar membrane deformation and scission event that buds membranes/vesicles out of the cytoplasm. The topology of this budding reaction is ‘opposite’ to reactions that bud endocytic and secretory vesicles into the cytoplasm. Here we summarize recent findings that help to understand how the ESCRT machinery, in particular the ESCRT-III complex, assembles on its target membranes, executes membrane scission and is disassembled by the AAA-ATPase Vps4.

1. Introduction

The identification of the endosomal sorting complexes required for transport (ESCRT) in yeast provided the first insight into the molecular mechanism that is required to generate multivesicular bodies (MVBs) [1–3]. MVBs are specialized organelles of the endosomal system that are required for the lysosomal degradation of membrane proteins [4]. They consist of a limiting membrane and small intraluminal vesicles (ILVs). Like all vesicle budding reactions, the formation of intraluminal MVB vesicles requires three distinct steps. First: cargo recognition and sorting. Second: membrane budding. Third: vesicle scission from a donor membrane (endosome). While endocytic and secretory vesicles bud from their donor membranes into the cytoplasm, the budding and scission of the cargo-laden MVB vesicles has the opposite topology. MVB vesicles bud away from the cytoplasm into the lumen of endosomes (Fig. 1). Thereby, cargo proteins and lipids are sequestered inside MVBs and thus removed from the cytoplasm. Fusion of MVBs with the lysosome releases ILVs into the lumen of the lysosome where they are degraded together with their contents. In yeast, the MVB pathway requires the vps (vacuolar protein sorting) class E genes that assemble into five functionally distinct ESCRT complexes (-0, -I, -II, -III and Vps4). Loss of any of these genes interrupts the MVB pathway. MVB vesicles are no longer formed; membrane proteins and lipids, which are degraded via the MVB pathway, accumulate in the so-called class E compartment inside cells [5]. Not surprisingly, ESCRT dysfunction contributes to diseases ranging from neurodegeneration to cancer [6].

Parts of the ESCRT machinery also function during cell abscission at the final stage of cytokinesis and during retroviral budding [7]. These different processes require topologically similar membrane rearrangements that rely on the assembly of the ESCRT-III complex and AAA-ATPase Vps4 complex at the corresponding target membrane (Fig. 1). Somehow, ESCRT-III complexes can pinch off membrane necks and release ‘end-products’ that differ in size: MVB vesicles have a diameter of 25 nm in yeast and 50 nm in mammals. The membrane stalk connecting budding HIV-1 to its host has a diameter of 50–100 nm and mature HIV-1 has an diameter of 120–150 nm [8]. During cytokinesis a 1 μm intracellular bridge is narrowed into a 200 nm constriction zone that is cleaved by ESCRT-III [9,10]. This ‘promiscuity’ sets the ESCRT pathway for membrane scission apart from classical membrane budding events driven by protein coats like clathrin, COP-I, or -II. Their property to form defined ‘protein cages’ that bud membranes, determines a fixed vesicle diameter.

The assembly pathways for ESCRT-III and Vps4 on their respective target membranes appear to be more flexible, allowing the same set of molecules to scission membranes in different biological processes. The following steps are mandatory for ESCRT function:

1. Recruitment and activation of the individual ESCRT-III subunits.
2. Ordered assembly of ESCRT-III filaments.
3. Vps4 mediated disassembly of ESCRT-III filaments into its individual subunits.
2. Recruitment and activation of the individual ESCRT-III subunits

2.1. Molecular architecture of the ESCRT-III subunits

In yeast, the ESCRT-III complex consists of four core subunits, Vps20, Snf7, Vps24 and Vps2 and three accessory components Did2, Vps60 and Ist1 [3,11–13]. They have 12 mammalian homologues: CHMP6 (Vps20), CHMP4A,B,C (Snf7), CHMP3 (Vps24), CHMP2A,B (Vps2) CHMP5 (Vps60), Chmp1A,B (Did2), CHMP7 and Ist1. The homologous ESCRT-III core subunits are relatively small (221–241 amino acids) proteins and probably adopt a common molecular architecture (Fig. 2) [14,15,16]. Yet, their function is not redundant. Their positively charged N-terminal region consists of two helices (α1, α2) that form a 70 Å hairpin structure important for membrane binding and homo- or hetero-dimerization. This hairpin together with α3 and α4 forms an asymmetric anti-parallel four-helix bundle. The C-terminal acidic region (α5 and α6) is negatively charged and constitutes an autoinhibitory region. The intramolecular interaction of helix α5 with the N-terminal hairpin keeps the protein inactive in the cytoplasm [17,18]. The C-terminus also harbors the so-called MIT (microtubule-interacting and transport)-interacting motif (MIM) for interaction with Vps4 [19–21]. Each ESCRT-III subunit has one MIM1 (Vps2, Vps24, Did2), one MIM2 (Vps20, Snf7, Vps60) or both (Ist1). Each ESCRT-III subunit cycles between an inactive cytoplasmic monomer, and its active state as part of a membrane bound ESCRT-III filament (Fig. 2). The activation of a subunit requires a series of intramolecular conformational changes that release autoinhibition, stabilize membrane interactions, enable interaction with other ESCRT-III molecules (homo- or hetero-oligomerization) and expose the MIM domain (Fig. 2). Three different pathways are known to activate ESCRT-III assembly on different target membranes.
2.2. Recruitment of ESCRT-III to endosomes: the MVB-ESCRT pathway

The MVB pathway is essential for the degradation of ubiquitinated membrane proteins. All five ESCRT complexes are required and follow a sequential recruitment to endosomes that is initiated by the ESCRT-0 complex (Fig. 1) [22,23]. The Y-shaped ESCRT-III complex induces the activation of the first ESCRT-III subunit, Vps20 [1,24,25]. Two copies of Vps25 that form the arms of the ‘Y’, provide certain geometry since each activates one Vps20 subunit. Activated Vps20 then might nucleate the assembly of two ESCRT-III filaments [26,27]. ESCRT-0 and -II are only required for the assembly of ESCRT-III on endosomes.

2.3. Recruitment of ESCRT-III to the Midbody: the cytokinetic ESCRT pathway

A final membrane abscission step at the end of cytokinesis physically separates two daughter cells. Abscission requires the recruitment of the ESCRT-I complex, Alix, all ESCRT-III subunits and Vps4 (Fig. 1). The centrosomal protein CEP55 initiates ESCRT assembly at the midbody [28,29]. It recruits Alix (a Bro1 domain containing factor) and Tsg101 (ESCRT-I) into two cortical rings (diameter of app. 1 μm) to either side of the midbody via its ESCRT- and ALIX-binding region (EBAR) [30]. ESCRT-I and Alix then trigger the assembly of long ESCRT-III filaments that extend form the midbody into the constriction zone [9,10].

Members of the crenarcheal kingdom that lack the homologues of tubulin (FtsZ) and actin (MreB) proteins, use the ESCRT-III - Vps4 system for binary cell division [31,32]. A protein called CdvA localizes first to membranes at the site of cell division and recruits the first ESCRT-III subunit (Saci,1373) to membranes [33]. Subsequently, the remaining three ESCRT-III subunits assemble into cortical filaments at the site of cytokinesis. The mode of Vps4 recruitment to ESCRT-III is conserved and occurs prior to abscission [19]. The conservation of the ESCRT-III-Vps4 system in prokaryotes points to its function as the minimal membrane remodeling machinery.

2.4. Recruitment of ESCRT-III to the plasma membrane: the retromer ESCRT pathway

HIV and other retroviruses require ESCRT-I, Alix, a specific subset of ESCRT-III subunits (Chmp4 and Chmp2) and Vps4 to bud out of infected cells (Fig. 1) [34]. Two late domains in HIV-Gag hijack ESCRT-I (by mimicking the Hrs–Tsg101 interaction) and Alix to the plasma membrane [35–37]. Alix accumulates together with Gag at budding sites [38]. Only when Gag assembly was complete, ESCRT-I and Alix initiated ESCRT-III assembly [39,40]. Thus, during HIV budding ESCRT-I, Chmp4, Chmp2 and Vps4 function at budding sites prior to virus release.

Taken together three specific adaptors (ESCRT-0, Cep55 and Gag) initiate distinct ESCRT pathways to activate the assembly of ESCRT-III filaments at defined target membranes.

3. Assembly of the ESCRT-III filament

ESCRT-III function requires the polymerization of its subunits into filaments with defined structure and stoichiometry. Individual ESCRT-III subunits can oligomerize into ring-like or helical filaments and tubes in vitro and in vivo, which may indicate structural and functional properties of the membrane scission competent complex. First evidence for the formation of ESCRT-III filaments was provided by over-expression of Snf7 (Chmp4) [42]. Snf7 assembled into flat ring-like filaments at the plasma membrane. The binding of ATPase deficient Vps4 (a substrate traps that blocks ESCRT-III disassembly [43]) to these Snf7 filaments, changed their morphology and generated Snf7 tubes that projected out of the cytoplasm, pushing the plasma membrane outward. In vitro, ESCRT-III subunits polymerize in a concentration dependent manner. Snf7 assembled into rings and sheets. Vps24 assembled into a two intertwined helical filaments [44]. Vps24 and Vps2 formed 1:1 hetero- oligomeric tubes of 50–100 nm in diameter that narrow into a closed dome at one end [45]. Ist1 assembled into large homo-polymeric tubes with a diameter of app. 700 nm. Chmp1 (Did2) polymerized into tubes with a diameter of app. 200 nm [15]. Despite the self-assembly properties of most subunits it is clear that ESCRT-III filaments require a defined order of subunit assembly.

3.1. ESCRT-III assembly during MVB sorting

ESCRT-III assembly on endosomes requires ESCRT-II mediated activation of Vps20 [1]. Two steps result in full activation of Vps20 (Fig. 2). First: the N-terminal myristoyl residue together with the positively charged N-terminus probably serve as the primary targeting signals that direct Vps20 to endosomes. Membrane binding may induce a conformational change that facilitates the interaction with Vps25 (ESCRT-II) [25,46]. Second: binding of helix x1 to Vps25 could displace helices α5/α6, thereby releasing autoinhibition [26,47]. Activated Vps20 (helix α2) could then nucleate Snf7 filaments in a ratio of approximately 1:10-20 molecules of Vps20 to Snf7 [48]. The Snf7 homo-oligomer is the major ESCRT-III component on endosomes. Snf7 homo-oligomerization is capped by Vps24. Subsequent recruitment of Vps2 completes the ESCRT-III filament [1,3,48]. The same order of ESCRT-III assembly with similar stoichiometry was used to reconstitute MVB vesicle formation in vitro [46,49,50]. When larger ESCRT-III filaments were generated, either by over-expression of Snf7 or by delaying Vps4 mediated disassembly, viewer but larger MVB vesicles were formed [26,13,51,52]. Hence the size of the ESCRT-III filament contributes to MVB vesicle formation. Additionally, ESCRT-III filaments could sequester MVB cargo by forming a ring-like fence [48]. Bro1-Doa4 mediated cargo de-ubiquitination occurs at this stage without the risk of cargo escaping the MVB sorting process. Once inside the ESCRT-III ring, cargo is committed to enter the intraluminal vesicle (Figs. 1 and 3). Consistently, binding of Bro1 to Snf7 delays disassembly of ESCRT-III filaments, thereby coordinating cargo de-ubiquitination and ESCRT-III function [52]. Hence, ESCRT-III filaments may have a dual role during MVB sorting: membrane budding/scission and cargo sequestration.

3.2. ESCRT-III assembly during cytokinesis

All 12 ESCRT-III subunits appear to contribute to cytokinesis, with Chmp6 (Vps20) being least important [53]. Mechanistically, it is not well understood how ESCRT-III assembly is activated at the midbody. ESCRT-II is not required for cytokinesis. Instead, Alix could activate Chmp4 (Snf7) directly. The interaction of the Bro1 domain with the autoinhibitory C-terminus of Chmp4 (Snf7) may facilitate the release of autoinhibition and activate ESCRT-III assembly [54]. Alix dimers could even activate the assembly of two Snf7 filaments, in analogy to the Y-shaped ESCRT-II complex. Alternatively, Alix could ‘cross-link’ and thereby stabilize two Snf7 filaments [55]. Ultra-structural analysis revealed that the ESCRT-III subunits organize into long helical filaments of 17 nm in diameter that span a distance over 1 μm (Fig. 1). Once ESCRT-III filaments reach the constriction site, GFP-Vps4 accumulates at the site of membrane scission. Ten minutes later, membrane abscission takes place [10]. ‘Cytokinetic’ ESCRT-III filaments consist and scission membranes of large dimensions (0.2–1 μm), maybe therefore they are longer and more stable when compared to those for MVB sorting or HIV budding [10,9].
3.3. ESCRT-III assembly during HIV budding

Only Chmp4 and Chmp2, but not Chmp3 (Vps24) are absolutely required for HIV budding [56], suggesting that distinct ESCRT-III filaments execute membrane scission during MVB sorting and cytokinesis. Like in cytokinesis, the mechanism underlying Chmp4 activation is unclear, but may also involve Alix mediated activation of Chmp4. GFP-Chmp4 and GFP-Vps4 were recruited for 35–120 s to budding sites. Two to five Vps4 complexes assembled at each budding site prior to viral release [41]. Dominant-negative Vps4 or depletion of Chmp2 (Vps2), which is required for the recruitment of Vps4, stabilizes ring like striations in the necks of the arrested viral buds (Fig. 1) [40,56]. Upon depletion of Chmp4 (Snf7), these rings were no longer detectable, indicating that they correspond to ESCRT-III filaments that need to be disassembled prior to HIV release.

Overall, it seems possible that three activation pathways result in the assembly of specific ESCRT-III filaments, each with different subunit requirements, length and dynamics. It is currently unknown how the assembly, the stoichiometry and the dynamics of these ESCRT-III filaments are controlled.

4. ESCRT-III disassembly

4.1. The Vps4 complex

From archaean to humans, Vps4 releases ESCRT-III subunits from endosomes into the cytoplasm. Vps4 is a mechano-enzyme of the type I AAA (ATPase associated with a variety of cellular activities) ATPases family. In the cytoplasm Vps4 is an inactive protomer (mono/dimer) [43]. Vps4 protomers assemble on ESCRT-III filaments into the active dodecameric complex consisting of two stacked hexameric rings with a central pore [57]. The N-terminal MIT (microtubule interacting and transport) domain is required for ESCRT-III interaction. MITs are asymmetric three-helical bundles that bind directly to MIMs of each ESCRT-III subunits. Sterically, one MIT domain could bind two ESCRT-III subunits simultaneously, one with MIM1, the other with MIM2 [19,21,58]. A flexible linker region connects the MIT domain to the single AAA-domain. Like all AAA-ATPase Vps4 converts the energy from ATP hydrolysis into mechanical power to disassemble the ESCRT-III filament.

4.2. Vps4 recruitment to ESCRT-III filaments

A recruitment complex regulates the assembly of Vps4 on ESCRT-III. Its central component is Vps2, which functions together with Did2 and Ist1. Vps2 is the last core subunit added to the ESCRT-III filament and thereby provides a timer for filament disassembly [3,48]. Vps4 assembly may include 12 different, partially redundant, protein–protein interactions with this recruitment complex [59]. At first, the MIT domain of Vps4 contacts the MIM of Vps2 which is supported by Did2 and Ist1 [11–13,59]. Vps4 complex assembly proceeds by binding to the cofactor Vta1 [60]. Dimers of Vta1 stabilize the Vps4 complex and enhance its ATPase activity, finally resulting in a dodecameric Vps4 complex bound to three [61] or six Vta1 dimers [62]. Vta1 contains two MIT domains of which only MIT2 binds to Vps60. Thus in theory, the Vps4-Vta1 complex could interact simultaneously with 24 ESCRT-III subunits [62]. Alternatively, Vta1 may crosslink different Vps4 complexes to generate Vps4 arrays on ESCRT-III [63]. The interaction of Vps4 with ESCRT-III subunits increases ATP hydrolysis, suggesting that the Vps4 complex could function like a substrate-activated enzyme [64,65].

4.3. Vps4 mediated disassembly of the ESCRT-III complex

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In addition to the interaction of MIT with MIMs which guide Vps4 recruitment, the pore of Vps4 dodecamer together with the acidic regions surrounding the MIMs of ESCRT-III contribute to the disassembly reaction [65]. Once assembled, the Vps4-Vta1 complex appears to remain stable for some time, suggesting that Vps4 could progressively disassemble ESCRT-III filaments [66]. Mechanistically, ATP hydrolysis driven motions of Vps4 could translocate ESCRT-III subunits through the central pore [67]. Alternatively, Vps4 might use ATP to act as a molecular crowbar and change ESCRT-III subunit conformation just enough for release from the filament. During each process, Vps4 ATPase activity is
required to reset ESCRT-III subunits to the inactive, autoinhibited state to ready them for a new round of ESCRT-III filament formation (Fig. 2). The exact molecular mechanism of Vps4 mediated ESCRT-III disassembly and its role in membrane remodeling and scission is unclear.

5. Contribution of Vps4 to ESCRT-III mediated membrane scission

Several models on how ESCRT-III could execute membrane scission have been postulated recently [68,69]. It is common to all models that ESCRT-III subunits are not consumed in the budding reaction, since they are not localized inside the buds but remain at bud necks. Two major paradigms exist for ESCRT-III mediated membrane scission: The ‘ESCRT-III only’ and the ‘ESCRT-III-Vps4’ models (Fig. 3A).

5.1. The ‘ESCRT-III-only’ model for membrane scission

The model predicts that the assembly of ESCRT-III is sufficient for membrane scission (Fig. 3A, left panel). In vitro reconstitution experiments suggest that Vps20, Snf7 and Vps24 are scission competent ESCRT-III subunits. Vps2 and Vps4 are only required for repeated rounds of membrane scission [49,50]. All ESCRT-III subunits interact with membranes via their positively charged N-termini [14], thus their membrane binding could couple filament assembly to membrane deformation. Circular ESCRT-III filaments could form ever-narrowing spirals in the neck of a growing vesicle. Due to the interactions of the filament with the membrane, the necks could be constricted to a size below a critical threshold (2 nm) that would favor scission [70]. Alternatively, the ‘dome model’ proposes, that membrane scission involves the assembly of Vps24 and Vps2 into a dome-shaped hetero-polymer, which functions as a scaffold that forces its surrounding membrane into extreme curvature for scission [71,45]. Yet, Vps2 is not required for membrane scission in vitro [50] and Vps24 is dispensable for HIV budding [56], suggesting that either other ESCRT-III subunits could form a similar ‘dome’ or a dome may not be required at this stage of the budding process. Vps4 would function after membrane scission. The energy of ATP hydrolysis would be invested to reset the autoinhibition of ESCRT-III subunits. The autoinhibited ESCRT-III proteins could store this energy in the cytoplasm and release it upon membrane scission (Fig. 3B, right panel).

5.2. The ‘ESCRT-III Vps4’ model

In vivo experiments suggest that Vps4 mediated disassembly of ESCRT-III filaments actively participates in membrane remodeling and scission (Fig. 3A, right panel). Vps4 is recruited to viral bud sites and to the midbody prior to membrane scission. Loss of the ESCRT-III accessory proteins, Ist1 and Did2, which regulate Vps4 function, results in an increase in MVB vesicle diameter [13,51]. Modulating Snf7 oligomer stability by the over-expression of the Bro1-domain, delayed Vps4 mediated ESCRT-III disassembly and caused in the accumulation of budding intermediates that did not yet detach from the limiting membrane of the endosome [52]. Blocking of Vps4 activity resulted in the formation of ring like ESCRT-III filaments within the necks of arrested viral buds. The mechanism of Vps4 activity on ESCRT-III remains unclear. Maybe Vps4 acts like a winch, pulling in and successively removing one ESCRT-III subunit at the time, thereby gradually shrinking the diameter of the ESCRT-III filament and constricting the membrane (‘purse string’ model) (Fig. 3B, left panel) [46]. Alternatively, ESCRT-III filaments/domes may have already narrowed the neck to a critical diameter. The recruitment of Vps4 into the dome would allow for multiple simultaneous interactions between Vps4 and ESCRT-III subunits. By binding as many ESCRT-III subunits as possible, the substrate dependent ATPase activity of Vps4 would become maximal. The sudden disassembly of the ESCRT-III dome would relax the strain on the bent membrane and thereby trigger scission (Fig. 3B, right panel).

6. Perspective

It is clear that ESCRT-III and Vps4 constitute a ‘minimal’ membrane scission machinery. Yet major questions regarding the underlying molecular mechanism remain unclear: How are membranes scissed? How is ESCRT-III filament stoichiometry regulated? How does Vps4 disassemble ESCRT-III filaments? Answers to these questions are required to understand this fundamental membrane scission process.

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