ANIMAL CELLS AND SYSTEMS
2024, VOL. 28, NO. 1, 367–380
https://doi.org/10.1080/19768354.2024.2380294

ESCRT-III: a versatile membrane remodeling machinery and its implications in cellular processes and diseases

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ABSTRACT

The endosomal sorting complexes required for transport (ESCRT) machinery is an evolutionarily conserved cytosolic protein complex that plays a crucial role in membrane remodeling and scission events across eukaryotes. Initially discovered for its function in multivesicular body (MVB) formation, the ESCRT complex has since been implicated in a wide range of membrane-associated processes, including endocytosis, exocytosis, cytokinesis, and autophagy. Recent advances have elucidated the ESCRT assembly pathway and highlighted the distinct functions of the various ESCRT complexes and their associated partners. Among the ESCRT complexes, ESCRT-III stands out as a critical player in membrane remodeling, with its subunits assembled into higher-order multimers capable of bending and severing membranes. This review focuses on the ESCRT-III complex, exploring its diverse functions in cellular processes beyond MVB biogenesis. We delve into the molecular mechanisms underlying ESCRT-III-mediated membrane remodeling and highlight its emerging roles in processes such as viral budding, autophagosome closure, and cytokinetic abscission. We also discuss the implications of ESCRT-III dysregulation in neurodegenerative diseases. The versatile membrane remodeling capabilities of ESCRT-III across diverse cellular processes underscore its importance in maintaining proper cellular function. Furthermore, we highlight the promising potential of ESCRT-III as a therapeutic target for neurodegenerative diseases, offering insights into the treatments of the diseases and the technical applications in related research fields.

ARTICLE HISTORY
Received 20 June 2024
Accepted 3 July 2024

KEYWORDS
Autophagy; ESCRT-III; membrane remodeling; MVB; neurodegenerative disease

Introduction

The endosomal sorting complexes required for transport (ESCRT) machinery is a cytosolic protein complex involved in membrane remodeling and scission, and is conserved across a wide range of eukaryotes, from yeast to humans (Hurley 2010; Hurley and Hanson 2010; Samson et al. 2017). The initial investigations into the ESCRT complex were anchored in the formation process of multivesicular bodies (MVBs) in yeast (Katzmann et al. 2001; Babst et al. 2002a). In yeast, the ESCRT complex was identified as a mediator for isolating endosomal membrane proteins into intraluminal vesicles (ILVs) during MVB formation (Babst et al. 2002a). Subsequently, the scope of the roles of the ESCRT complex has expanded beyond MVBs, revealing its significant role in various membrane-associated processes, such as endocytosis, exocytosis, and cytokinesis (Vietri et al. 2020). Given the implications of impaired membrane trafficking in numerous human diseases, the importance of investigating the ESCRT complex has become increasingly apparent (Hurley 2010).

The ESCRT complex comprises ESCRT-0, -I, -II, and –III, along with accessory components. These components are recruited to the endosomes through interactions with proteins and lipids. In the MVB formation process, ESCRT-0 recognizes and gathers ubiquitinated membrane proteins on endosomes, whereas ESCRT-I interacts with ESCRT-0, identifying the targets and serving as a bridge for ESCRT-II (Babst et al. 2002b; Ren and Hurley 2011). ESCRT-II then receives the targets identified by the above components and provides a starting point for ESCRT-III engagement (Babst et al. 2002b; Teo et al. 2004). ESCRT-III, the final complex in the pathway, polymerizes on the membrane surrounding the targets, bending and cutting the membrane to form ILVs for degradation of ubiquitinated proteins (Babst et al. 2002a; Wollert et al. 2009). Among the ESCRT complexes, ESCRT-III acts as a key

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player in membrane remodeling, with various proteins forming higher-order multimers. Numerous studies have revealed that the role of ESCRT-III in membrane remodeling extends beyond MVB formation to encompass a broader range of cellular activities (Vietri et al. 2020). This review focuses on ESCRT-III and investigates its function and relevance in various intracellular activities. In addition, it will delve into the significance of ESCRT-III in disease conditions.

Structural features of ESCRT-III components

As summarized in Table 1, each component of the ESCRT complex is assigned a different name in yeast and mammals, and even within a single species, multiple nomenclatures are often used interchangeably. This variation in nomenclature frequently needs to be clarified among ESCRT researchers. The nomenclature for mammals was primarily employed in this review. Mammalian ESCRT-III components share the common name of charged multivesicular body protein (CHMP). This nomenclature stems from the structure of the Snf7 family, where ESCRT-III proteins possess an N-terminal α-helix region rich in positively charged amino acids and a C-terminal α-helix region abundant in negatively charged amino acids (Figure 1A) (Horii et al. 2006). This structure typically results in an autoinhibited conformation, in which ESCRT-III proteins fold through interactions between positively and negatively charged regions (Figure 1B) (Lata et al. 2008). When unfolded, each region is exposed outward, activating ESCRT-III proteins and allowing each monomer to gain the ability to form polymers (Lin et al. 2005). In addition, the positively charged regions can easily adhere to negatively charged lipid bilayers, facilitating their role in membrane remodeling (Jukic et al. 2023). A helical structure composed of hydrophobic amino acids at the N-terminal end also interacts with the membrane (Buchkovich et al. 2013). ESCRT-III proteins lacking this helical structure are incapable of membrane remodeling, resulting in impaired MVB formation.

The C-terminal end of the polymerized ESCRT-III possesses a microtubule interacting and trafficking (MIT) domain-interacting motif (MIM), which enables interactions with proteins containing an MIT domain (Figure 1A) (Guo and Xu 2015; Han et al. 2015). In humans, approximately 20 proteins containing an MIT domain have been identified so far, and binding between the MIT and MIM domains occurs in more than seven distinct ways, which is believed to lead to diverse physiological responses mediated by the ESCRT complex (Wenzel et al. 2022). The interaction between the MIM of ESCRT-III and MIT domain-containing proteins has been extensively studied in the VPS4 complex (Han et al. 2015; Pfitzner et al. 2020). Upon binding to the MIT domain of VPS4, polymerized ESCRT-III can be disassembled into monomers through the AAA-ATPase activity of VPS4. This conformational change provides a crucial force for membrane constriction (Adell et al. 2014).

In addition to these fundamental structures, the ESCRT-III components contain regions that interact with other proteins. CHMP4 proteins have a C-terminal region that interacts with the Bro1 domain of ALIX (Morita et al. 2007; McCullough et al. 2008). Through this interaction, ALIX recruits deubiquitinase to ESCRT-III, which induces the removal of ubiquitin from the target. This prevents the disassembly of the ESCRT-III polymer by the VPS4 complex. CHMP7 has a longer amino acid sequence with distantly related domains at

Table 1. ESCRT subunits

Complex	Yeast protein	Mammalian protein	Motifs and domains
ESCRT-0	Vps27	HRS (HGS)	VHS, FYVE, UIM, DUIM, coiled-coil, CBD
	Hse1	STAM1,2	VHS, UIM, SH3, GAT
ESCRT-I	Vps23	TSG101	UEV, PRD, coiled-coil, SBOX
	Vps28	VPS28	VPS28-N, VPS28-C
	Vps37	VPS37A,B,C,D	Mod r, coiled-coil, UEV
	Mvb12	MVB12A,B	MABP, UMA
ESCRT-II	Vps22	EAP30	HD, WH1, WH2
	Vps25	EAP20	WH1, WH2
	Vps36	EAP45	GLUE, HD, WH1, WH2
ESCRT-III	Vps2	CHMP2A,B	ANCHR, Snf7, MIM1, MIM3
	Vps20	CHMP6	Snf7, MIM2
	Vps24	CHMP3	ANCHR, Snf7, MIM4
	Snf7	CHMP4A,B,C	ANCHR, Snf7, MIM
	Vps60	CHMP5	Snf7, MIM5
	Did2	CHMP1A,B	Snf7, MIM
	-	CHMP7	Snf7, MIM1, WH1, WH2
	Ist1	CHMP8 (IST1)	ELYC, Snf7, MIM1, MIM2
AAA-ATPase	Vps4	VPS4A/B (SKD1)	MIT, AAA-ATPase
	Vta1	VTA1 (LIP5, SBP1)	MIT1, MIT2, VSE, VSL
Deubiquitinase	Bro1 (Vps31)	ALIX (AIP1)	Bro1, V domain, PRD

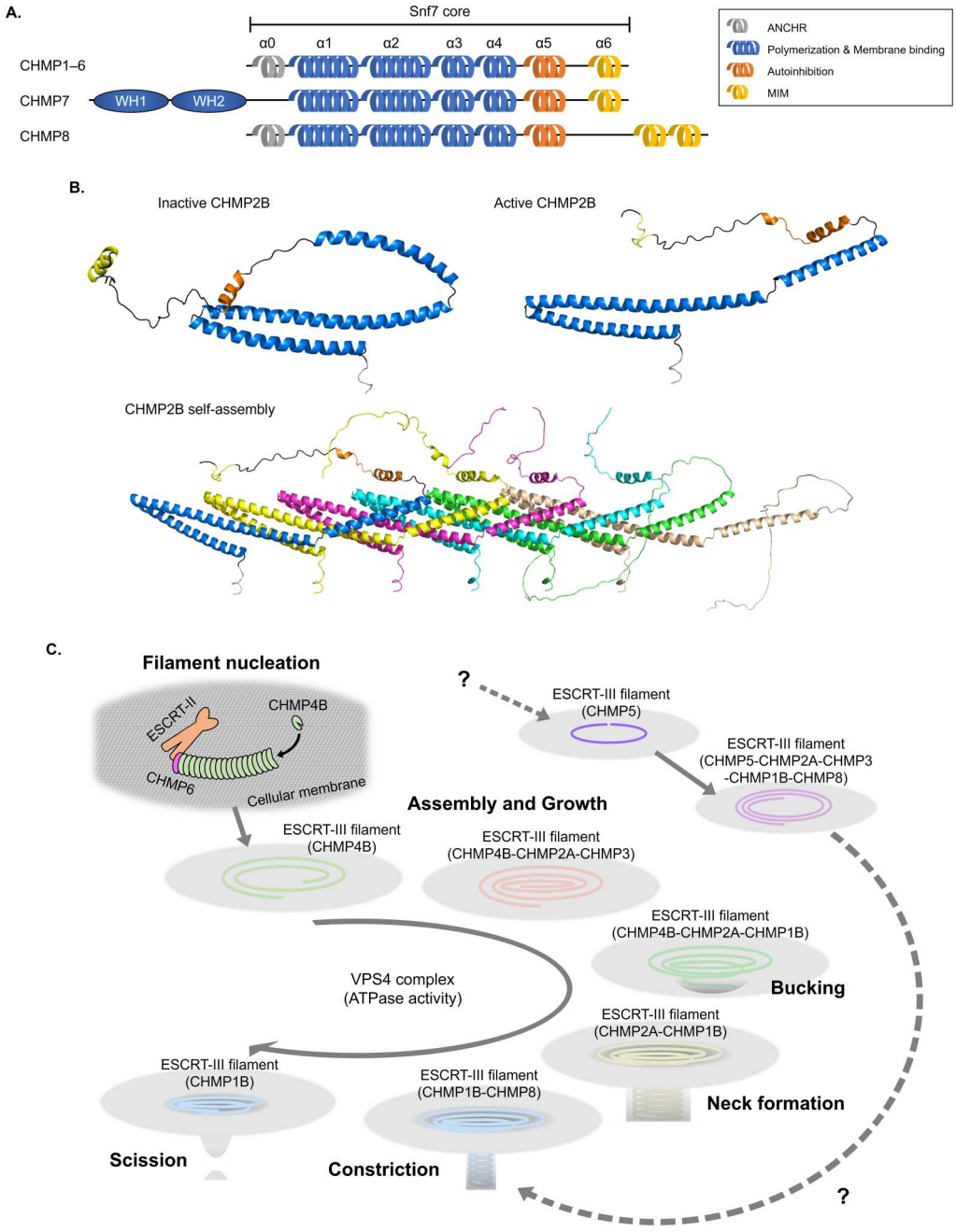

Figure 1. The architecture of ESCRT-III. (A) All CHMP proteins share a Snf7 core region consisting of six α-helices (shown as spirals). The α1-α4 helices (shown as blue spirals) facilitate polymerization and membrane binding via their positive charges, while the α5 helix (shown as orange spirals), bearing negative charges, inhibits polymerization in the cytosol. The α0 helix anchors the protein to the membrane via its hydrophobic residues called the ANCHR motif (shown as grey spirals), and the α6 helix, bearing the MIM (shown as yellow spirals), interacts with MIT domain-containing proteins like VPS4. In addition to the core Snf7 domain, CHMP7 and CHMP8 feature additional motifs and domains: CHMP7 has WH1 and WH2 domains for LEMD2 interaction, while CHMP8 has longer MIM sequences. ANCHR: amphipathic N-terminus containing hydrophobic residues motif; MIM: MIT-interacting motif; WH: winged helix domain. (B) In their cytosolic state, ESCRT-III proteins, such as CHMP2B, adopt a closed conformation mediated by electrostatic interactions between the α1-α4 helices and the negatively charged α5 helix. When the protein opens, the self-assembly region becomes exposed, allowing it to assemble into higher-order multimeric polymers. The 3D models of CHMP2B and CHMP2B assembly were generated using AlphaFold2 and visualized as cartoons using PyMOL. (C) The sequential assembly of the ESCRT-III complex. ESCRT-III polymerization generally initiates with the binding of CHMP6 to ESCRT-II, which induces CHMP4B polymerization. CHMP2A and CHMP3 then join the CHMP4B polymer, and their assembly, along with CHMP1B, drives membrane curvature formation. Subsequently, CHMP4B dissociates from the polymer, allowing for the reshaping of the membrane into a neck-like structure. The detachment of CHMP2A and the recruitment of CHMP8 induce further constriction of the membrane neck, eventually leading to scission. This sequential assembly and disassembly process is driven by the AAA-ATPase activity of the VPS4 complex. Interestingly, CHMP5 can initiate ESCRT-III assembly independently of CHMP4B, but its precise physiological function remains unclear.

the N-terminal end than the other CHMPs (Figure 1A) (Horii et al. 2006). Upon binding to the nuclear membrane protein LEM domain nuclear envelope protein 2 (LEMD2), CHMP7 unfolds into its active form and generates a polymer ring, initiating ESCRT-mediated nuclear envelope reformation (von Appen et al. 2020). CHMP8, also known as increased sodium tolerance 1 homolog (IST1), possesses two MIMs that enable it to bind to VPS4 with a higher affinity than other CHMPs (Dimaano et al. 2008; Guo and Xu 2015). Therefore, CHMP8 was initially thought to inhibit the AAA-ATPase activity of the VPS4 complex by forming CHMP8-VPS4 heterodimers (Dimaano et al. 2008; Guo and Xu 2015). However, recent in vitro studies have shown that CHMP8 and CHMP1B interact reciprocally to form stable scaffolds that mediate membrane severing, either cooperatively with or independently of VPS4 (Pfitzner et al. 2020; Cada et al. 2022). These findings indicate that the exact role of CHMP8 in membrane scission needs to be further investigated to clarify the mechanisms involved.

Assembly and disassembly of ESCRT-III complex

ESCRT-III proteins exist in an inactive state in the cytosol; however, when assembled into polymers, they can form a structure capable of bending and severing membranes. This intricate assembly process was elegantly demonstrated in a recent study using purified yeast homolog proteins and lipid layers (Pfitzner et al. 2020). The assembly and disassembly of the ESCRT-III complex occur through sequential recruitment and continuous turnover of subunits directed by VPS4 activity (Figure 1C). The assembly of ESCRT-III proteins is initiated by CHMP6, which interacts with the ESCRT-II complex. CHMP6 nucleates into a seed-like lipid structure and accelerates CHMP4B polymerization on the membrane (Yorikawa et al. 2005). Notably, CHMP4B filaments exhibit a superior ability to bind to flat membranes compared with other ESCRT-III proteins (Bertin et al. 2020). The tension generated by the assembled CHMP4B polymer spiral induces a negative curvature in the membrane (Lee et al. 2015). Subsequently, CHMP2A-CHMP3 heterodimers are recruited to the CHMP4B polymer, generating a new spiral during polymerization (Effantin et al. 2013; Sandrin and Sundquist 2013; Pfitzner et al. 2020). With the addition of CHMP1A or CHMP1B to the assembly, the ESCRT-III spiral acquires a new level of tension, further bending the membrane inward (Pfitzner et al. 2020). Notably, heteropolymers composed of CHMP2A-CHMP3 dimers exhibit a more stable assembly on curved membranes than flat membranes, unlike homopolymers composed of CHMP4B (Bertin et al. 2020). From the spiral structure, CHMP4B is dissociated by VPS4, resulting in a tube-like structure with a diameter of approximately 22 nm as tension is released (Pfitzner et al. 2020). CHMP8 ultimately joins the complex by binding to CHMP1A or CHMP1B. Disassembly of the ESCRT-III complex commences with dissociating the CHMP2A-CHMP3 dimer from the complex by VPS4. As the CHMP2A-CHMP3 dimer dissociates, the neck contracts to form a tube with a diameter of approximately 12 nm (Pfitzner et al. 2020). Further contraction occurs as VPS4 disassembles CHMP8. Upon the disassembly of CHMP1A or CHMP1B, the neck collapses, isolating cargoes into ILVs. Membrane manipulation by ESCRT-III occurs as each component assembles and is subsequently disassembled by VPS4 (Adell et al. 2014; Pfitzner et al. 2020). The disassembled CHMP proteins return to the cytosol in an inactive state and are recycled for other ESCRT-III-mediated membrane remodeling events (Cada et al. 2022).

The assembly of the ESCRT-III complex typically occurs as mentioned above, but occasionally involves the participation of other ESCRT-III proteins in the assembly process. Recent research suggests that CHMP5 can be a foundation for the ESCRT-III spiral assembly by replacing CHMP4B (Figure 1C) (Pfitzner et al. 2023). Unlike CHMP4B, CHMP5 forms a single-stranded circular polymer structure on the lipid membrane instead of a flat spiral structure. This structure, generated independently of CHMP4B, allows not only the attachment of CHMP2A-CHMP3 dimers but also the simultaneous assembly of CHMP1A or CHMP1B with CHMP2A-CHMP3 dimers. In addition, ESCRT-III polymers initiated by CHMP5 exhibit slower disassembly kinetics than those initiated by CHMP4B. The assembly of the ESCRT-III complex by combinations of different ESCRT-III subunits is thought to be due to their involvement in various intracellular membrane remodeling processes. Although CHMP4B and CHMP5 are functionally distinct, both are involved in lysosomal repair (Pfitzner et al. 2023). However, CHMP5 is not involved in nuclear envelope reformation. Instead, CHMP7 initiates ESCRT-III assembly during this process. Through its interaction with LEMD2, CHMP7 assembles to form an O-ring, which is a pivotal step in nuclear membrane restructuring (von Appen et al. 2020). Therefore, the assembly sequence of ESCRT-III polymers can vary depending on the participating ESCRT-III subunits, enabling the diverse properties of ESCRT-III polymers to adapt to the membrane remodeling processes in which they are involved.

Diverse functions of ESCRT-III

Numerous biochemical and genetic studies have demonstrated that the ESCRT complex serves as a crucial regulator of various membrane remodeling processes through the dynamic assembly and disassembly of ESCRT subcomplexes. Among the ESCRT subcomplexes, ESCRT-III is a key functional component that mediates the formation of membrane-binding spirals, which induce membrane deformation and scission (Saksena et al. 2009; Adell et al. 2014; Chiaruttini et al. 2015; Mierzwa et al. 2017). Extensive studies have elucidated the mechanism by which ESCRT-III complexes dynamically interact with membranes, cargo, and each other to facilitate membrane deformation and drive membrane scission. Here, we discuss the involvement of ESCRT-III proteins in various membrane dynamics and highlight the different recruitment mechanisms employed at specific locations that support the diverse functions of ESCRTs.

Plasma membrane

Viral budding

The plasma membrane is a dynamic structure that can bud towards the cytosol, so-called endocytosis, or bud away from the cytosol to generate membrane-encapsulated vesicles. Membrane budding is a key step in vesicular transport, MVB biogenesis, and enveloped virus release (Thery et al. 2009; Hurley et al. 2010). Recently, the unique mechanism by which ESCRT-III mediates and drives vesicle extrusion and neck closure has become much more evident over the past years. On the plasma membrane of the host cells, some pathogenic viruses, such as human immunodeficiency virus-1 (HIV-1), utilize a subset of host ESCRT-III proteins for budding and propagation to release infectious material from infected cells. CHMP2A and CHMP4B, in cooperation with TSG101 and ALIX, play crucial roles in facilitating viral budding (Figure 2A) (Kieffer et al. 2008; McCullough et al. 2008; Morita et al. 2011). The UEV domain of TSG101 binds to the PTAP motif in the p6 domain of the Gag protein, leading to subsequent recruitment of ESCRT-III, induction of membrane curvature, and viral bud formation (Garrus et al. 2001). Similarly, ALIX binds directly to the viral Gag protein and then recruits downstream ESCRT-III and VPS4 (Ku et al. 2014). A crystallographic study showed that the Bro1 domain of ALIX specifically binds only to the C-terminal amphipathic helices of CHMP4B among the ESCRT-III proteins (McCullough et al. 2008). The interaction between ALIX and CHMP4B is required for HIV-1 budding. Subsequently, CHMP4B binds to CHMP2A, and CHMP2A, in turn, recruits VPS4A. Both interactions are required for HIV-1 budding (Morita et al. 2011). In addition, an interaction between VPS4A and CHMP6 also occurs. Notably, the binding mode between the MIT of VPS4A and the MIM of CHMP6 is distinct from the typical MIT-MIM interaction (Kieffer et al. 2008). This interaction is critical for VPS4A recruitment and constriction of the neck of budding vesicles.

Exocytosis

Exocytosis is a type of active bulk transport by which cells export molecules from the cytosol to the extracellular space (Kita and Shimomura 2022). During exocytosis, membrane-bound secretory vesicles are transported to the plasma membrane, where they transiently fuse. CHMP4A and CHMP4B play a role in the deformation of the plasma membrane and the release of plasma membrane-derived extracellular vesicles called microvesicles (Hanson et al. 2008; Matusek et al. 2014). CHMP4A and CHMP4B assemble into circular membrane-associated polymers capable of deforming the membrane (Hanson et al. 2008). The addition of VPS4B to the CHMP4A-CHMP4B polymer induces membrane bending, leading to the formation of buds and tubules protruding from the cell surface. This mechanism is similar to the aforementioned viral budding mechanism (Christ et al. 2017).

Endolysosomal pathway

MVB biogenesis

ESCRT-III components are essential for recognizing ubiquitinated endocytosed integral membrane proteins and their sorting into ILVs of the MVB and subsequent degradation in lysosomes. ESCRT-mediated protein sorting in endosomes is necessary for endosome maturation, lysosomal function, and regulation of intracellular signaling (Figure 2B). By directly binding to the endosomal lipid phosphatidylinositol 3,5-bisphosphate, ESCRT-III proteins, such as CHMP3, play a key role in the biogenesis of ILVs in MVBs (Whitley et al. 2003; Filimonenko et al. 2007). Following the assembly of the ESCRT-II complex and CHMP6 on the endosomal membrane, proper recruitment of ESCRT-III proteins is necessary to achieve membrane deformation (Henne et al. 2012). CHMP6 nucleates the polymers composed of CHMP2A, CHMP3, and CHMP4B, which mediates ILV sculpting and scission in cooperation with VPS4 (Adell et al. 2014; Chiaruttini et al. 2015; Mierzwa et al. 2017; Schoneberg et al. 2018). Electron microscopy studies have shown that CHMP4B has distinct architectural stages modulated by ESCRT-II to mediate cargo capture and vesicle formation through ordered assembly (Henne et al. 2012). In vivo studies have shown that the constriction of the membrane

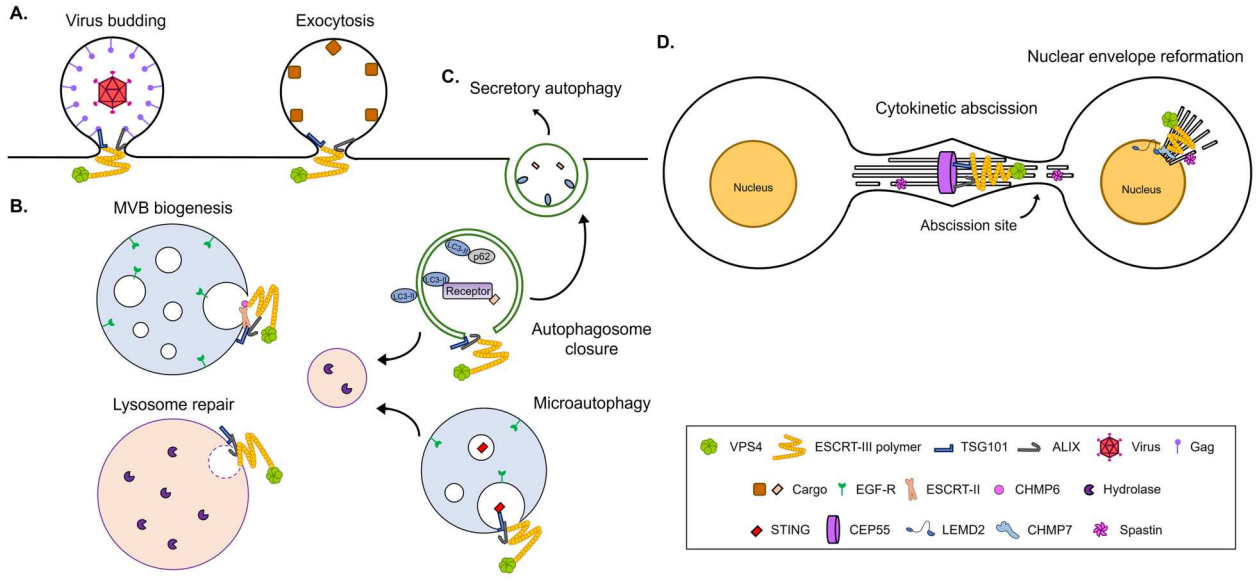

Figure 2. The involvement of ESCRT-III proteins in various membrane dynamics. (A) The pathogenic virus utilizes the host ESCRT-III complex for its budding and propagation from infected cells at the plasma membrane. Similar to virus budding, the addition of VPS4 into the ESCRT-III polymer induces membrane bending, leading to the formation of buds and tubules protruding from the cell surface for exocytosis. (B) Along with the ESCRT-II complex and CHMP6 on endosomal membranes, the ESCRT-III complex regulates the biogenesis of ILVs within MVBs derived from early endosomes containing EGF-R trafficked through endocytosis. ESCRT-III proteins mediate the repair of damaged lysosomal membranes upon the recruitment of TSG101 and ALIX. (C) The ESCRT-III complex plays crucial roles in phagophore sealing during degradative and secretory autophagosome formation. For termination of the STING signaling, the degradation of STING is regulated by TSG101 and ESCRT-III-mediated microautophagy. (D) At the end of cytokinesis, ESCRT complex and adaptor proteins are sequentially recruited to the constriction zones in intercellular bridges, resulting in the formation of spiral-like ESCRT-III polymers at the abscission site. Then, VPS4, spastin, and MITD1 induce constriction of the abscission site, which eventually drives a membrane cut. On the other hand, the ESCRT-III complex is transiently recruited to the reassembling site of the nuclear envelope during the anaphase. The inner nuclear membrane protein LEMD2 recruits CHMP7, which promotes nuclear membrane sealing.

neck during ILV formation is linked to the binding of VPS4 to ESCRT-III (Adell et al. 2014). This process is coordinated through interactions of VPS4 with CHMP2A and CHMP4B (Chiaruttini et al. 2015). These findings demonstrate that VPS4 cooperates with ESCRT-III to facilitate distinct membrane-remodeling steps, ultimately leading to efficient membrane scission at the end of ILV biogenesis (Mierzwa et al. 2017). Notably, a recent study confirmed that ESCRT-III proteins, such as CHMP2A and CHMP4B, along with VPS4, can generate ATP-dependent forces within a narrow membrane tube (Schoneberg et al. 2018). This study also demonstrated that forces contribute to membrane constriction and are associated with reverse-topology membrane scission. Indeed, the depletion of ESCRT-III in mammalian cells led to the formation of MVBs with aberrant morphology and impaired degradation of proteins, such as EGF-R, which is trafficked through the endocytic pathway (Slagsvold et al. 2006).

Lysosome repair

Lysosomes are membrane-bound acidic organelles that mediate intracellular digestion and recycling processes, such as autophagic pathways. Therefore, lysosomes are essential organelles for maintaining cellular homeostasis (Lawrence and Zoncu 2019). They contain high concentrations of acid hydrolases and protons that maintain a low pH, allowing these enzymes to remain active. Lysosomal membrane rupture due to damage leads to the release of lysosomal contents into the cytosol, which can be hazardous to cells. Therefore, cells struggle to repair damaged lysosomal membranes or remove damaged lysosomes through lysophagy, a selective macroautophagy that targets lysosomes for degradation (Maejima et al. 2013; Papadopoulos and Meyer 2017). Some studies have suggested the role of the ESCRT machinery in endolysosomal organelles during lysosomal repair (Figure 2B). Live-cell imaging study of fluorescently tagged ESCRT proteins together with probes to monitor compartmental integrity has shown that ESCRT-III proteins, such as CHMP4A and CHMP2B, were rapidly recruited to the damaged endolysosomes after acute membrane damage (Skowyra et al. 2018). Recruitment of ESCRT-III proteins was dependent on TSG101, ALIX, and calcium. Depleting ESCRT-III components impaired the reacidification and functional recovery of transiently injured organelles. These results indicate that ESCRT-III

proteins can act as first responders to repair limited membrane damage, thereby restoring compartmental integrity and function. Other studies have also reported that CHMP4B mediates the repair of the damaged lysosomal membranes after the recruitment of both TSG101 and ALIX to damaged lysosomes (Radulovic et al. 2018; Skowyra et al. 2018). Interestingly, both studies revealed that ESCRT-III-mediated lysosomal membrane repair is independent of lysophagy, or at least precedes lysophagy.

Autophagy

Autophagosome closure

Autophagy is a significant intracellular degradation process essential for maintaining cellular homeostasis and quality control (Mizushima and Komatsu 2011; Boya et al. 2013; Pohl and Dikic 2019). It is induced by various stress stimuli such as starvation, endoplasmic reticulum (ER) stress, hypoxia, mitochondrial dysfunction, and lysosomal damage (Filomeni et al. 2015; Radulovic et al. 2018; Park et al. 2021; Lee et al. 2022). Autophagy is initiated by the formation and expansion of a double-membrane structure, termed the phagophore, which engulfs and sequesters cargoes to be degraded as it closes to form an autophagosome (Antonioli et al. 2017). A recent study demonstrated that phagophore closure is mediated by CHMP2A and VPS4A (Takahashi et al. 2018). Depletion of CHMP2A resulted in the accumulation of unclosed autophagosomal membranes. Upon nutrient starvation, CHMP2A was translocated to the phagophore and induced the separation of the inner and outer autophagosomal membranes. Overexpression of ATPase-deficient mutant of VPS4A inhibited completion of phagophore closure. These results indicate a direct role for the ESCRT machinery in phagophore sealing during autophagy. ESCRT-mediated phagophore sealing also occurs during mitophagy. Depletion of CHMP2A and CHMP4B inhibited parkin-dependent and parkin-independent mitophagy (Takahashi et al. 2018; Zhen et al. 2020). In yeast, Vps21/Rab5 has been demonstrated to be required for the recruitment of Atg17/FIP200 to the nascent autophagosome and facilitate interactions between Atg17/FIP200 and Snf7/CHMP4B (Zhou et al. 2019). Subsequently, ESCRT-mediated autophagosome closure is facilitated.

Microautophagy

Microautophagy is an autophagic pathway in which lysosomes directly engulf cytoplasmic cargo. In mammalian cells, there are two types of microautophagy, endosomal microautophagy and lysosomal microautophagy. ESCRT-III plays critical roles in both types of microautophagy (Kuchitsu and Taguchi 2023). Silencing CHMP4B prevented the capture of cytosolic proteins by the inward budding of the endolysosomal membrane, suggesting that CHMP4B is a crucial regulator of endosomal microautophagy (Mejlvang et al. 2018). Depletion of VPS4 or CHMP4B inhibited starvation-induced endosomal microautophagy, resulting in the accumulation of autophagy receptors such as NBR1, TAX1BP1, and p62 (Liu et al. 2015; Mejlvang et al. 2018; Kuchitsu and Taguchi 2023). Growing evidence suggests that ESCRT-III proteins are involved in the lysosomal microautophagy-mediated degradation of various substrates, including glycolytic enzymes, lipid droplets, ER domains containing misfolded collagen, translocon complex, and transmembrane proteins on the limiting membrane of lysosomes (Luzio et al. 2007; Loi et al. 2019; Schuck 2020). Interestingly, CHMP4B and VPS4A mediate micro-ER-phagy, a critical catabolic pathway activated for remodeling the mammalian ER upon recovery from ER stress (Loi et al. 2019; Kwon et al. 2023). A recent study showed that STING vesicles originating from recycling endosomes are directly encapsulated in lysosomes in an ESCRT-dependent manner (Kuchitsu et al. 2023). Degradation of STING vesicles is mediated by K63-linked polyubiquitination, which is known as a degradation signal for lysosomal microautophagy. Ubiquitinated STING interacts with the UEV domain of Tsg101, which may lead to the recruitment of other ESCRT proteins for lysosomal microautophagy-mediated degradation of STING and termination of STING signaling.

Secretory autophagy

Proteins without a leader sequence reach the extracellular space or the plasma membrane in a Golgi-independent manner, a process known as unconventional protein secretion (Nickel and Rabouille 2009; Bruns et al. 2011). Interleukin-1beta (IL-1β), a typical leaderless protein, is secreted through an unconventional protein secretion pathway mediated by an autophagosome (Dupont et al. 2011). The autophagosome then fuses directly with either the plasma membrane or an MVB to generate an amphisome that later fuses with the plasma membrane to release soluble IL-1β (Figure 2C). The role of ESCRTs in unconventional secretion was first identified in yeasts (Bruns et al. 2011). Previous studies in yeasts demonstrated that Snf7/CHMP4B binds to the compartment for unconventional protein secretion (CUPS) during maturation and is required for

maintaining stable CUPS, which contains a leaderless cargo such as acyl-CoA binding protein 1 (Acb1), for secretory autophagosome formation (Bruns et al. 2011; Curwin et al. 2016). It has also been reported that CHMP2B and CHMP4B play critical roles in the stress-induced unconventional secretion of the cystic fibrosis transmembrane conductance regulator (CFTR) through early autophagosome formation and the ESCRT/MVB pathway (Noh et al. 2018).

Mitosis

Cytokinesis

Cell division, the fundamental process of replacing damaged, aged, or destroyed cells, involves a series of intricate steps that eventually result in the production of genetically identical daughter cells. Cell division can be categorized into mitosis and meiosis. Mitosis is conventionally divided into five stages: prophase, prometaphase, metaphase, anaphase, telophase, followed by cytokinesis (McIntosh 2016). During division, the cell membrane undergoes dramatic and complex rearrangement and constriction (Carlton et al. 2020). The ESCRT-III complex significantly contributes to membrane dynamics in two fundamental processes: cytokinetic abscission and nuclear envelope sealing during mitotic exit (Stoten and Carlton 2018).

In the final stage of cell division, cells undergo cytoplasmic separation, known as cytokinesis. In the final stages of cytokinesis, an intercellular bridge is formed between two daughter cells. The midbody, which is the central region of the microtubule-rich intercellular bridge, is severed by membrane separation during cytokinetic abscission (Stoten and Carlton 2018). The ESCRT-III complex plays a pivotal role in modulating cytokinesis (Figure 2D). The ESCRT-III complex and VPS4 are assembled into 17 nm-diameter filaments with constriction zones in intercellular bridges (Carlton and Martin-Serrano 2007; Guizetti et al. 2011). Furthermore, the depletion of ESCRT-III subunits, such as CHMP2A, CHMP1A, or CHMP1B, blocked cytokinetic abscission (Bajorek et al. 2009; Guizetti et al. 2011). During cytokinesis, ESCRT-III proteins are recruited to the midbody through interactions with ESCRT-II components and adaptor proteins, such as VPS36, EAP30, ALIX, TSG101, and CEP55 (Fabbro et al. 2005; Morita et al. 2007; Carlton et al. 2008; Goliand et al. 2014; Christ et al. 2016; Sun et al. 2016). ALIX accumulation in the midbody results in the formation of spiral-like structures at the abscission site that recruit CHMP4B to the midbody (Pust et al. 2023). CHMP4B and CHMP6 initially localize adjacent to the midbody and later constrict themselves to split the plasma membrane (Morita et al. 2007; Guizetti et al. 2011; Mierzwa et al. 2017). Subsequently, CHMP2B, CHMP3, and CHMP4B form a series of cortical rings to construct ESCRT filaments (Elia et al. 2011; Guizetti et al. 2011; Christ et al. 2016; Mierzwa et al. 2017). In addition, CHMP8 plays a crucial role in abscission (Agromayor et al. 2009; Bajorek et al. 2009). The assembly of CHMPs and CHMP-like proteins promotes the recruitment of interactors to construct multiprotein complexes required for efficient cytokinetic abscission (Yang et al. 2008; Lee et al. 2012; Wenzel et al. 2022). MIT domain containing 1 (MITD1) interacts with CHMP1B, CHMP2A, and CHMP8, and this interaction is important for ESCRT filament remodeling (Lee et al. 2012). Another interactor, spastin, which interacts with CHMP1B and CHMP8, facilitates constriction of the abscission site by cleaving microtubules (Yang et al. 2008). Thus, ESCRT-III and its interacting proteins collaborate to induce membrane remodeling events and complete cell division.

Nuclear envelope reformation

The nuclear envelope disassembles at the beginning of mitosis and is reformed into individual daughter cells at the end of mitosis. After chromatid separation, individual daughter nuclei are regenerated during the anaphase and telophase. Daughter nuclei are enveloped by cellular membranes, forming two juxtaposed membranes, termed the inner and outer nuclear membranes. These membranes, which may be derived from the ER, are sealed by the ESCRT complex to fill annular holes (Stauffer et al. 2001; Guttinger et al. 2009; Olmos et al. 2015). The ESCRT-III machinery is transiently localized to the reassembly site of the nuclear envelope during late anaphase and polymerizes into filaments lining the inside of the membrane (Henne et al. 2013; Olmos et al. 2015; Vietri et al. 2015). Conversely, depletion of CHMP2A resulted in reduced partitioning of nucleo-cytoplasm with the persistence of unsealed holes in the post-mitotic nuclear envelope (Olmos et al. 2015). Unlike MVB biogenesis, viral budding, and cytokinetic abscission, adaptor proteins of the ESCRT-III complex such as CEP55, HRS, TSG101, and ALIX are not concentrated at the sites of nuclear envelope reformation. Moreover, these adaptor proteins do not influence the recruitment of CHMP4B to the reformation sites (Vietri et al. 2015). In contrast, depletion of CHMP7 hindered the localization of CHMP4B to the nuclear envelope, while not affecting its localization to the midbody (Vietri et al. 2015). Mechanistically, CHMP7 binds to the nuclear envelope through its N-terminal domain, enabling CHMP7 to provide a platform for the recruitment of ESCRT-III components to the

nuclear envelope during mitotic exit (Olmos et al. 2016; Webster et al. 2016). CHMP8 directly recruits the AAA ATPase spastin to sever microtubules, facilitating membrane reformation at nuclear envelope formation sites (Vietri et al. 2015). In addition to CHMP7 and CHMP8, the p97-associated factor, ubiquitin fusion degradation-1-like (UFD1L), contributes to the assembly of the ESCRT-III complex for nuclear membrane sealing (Olmos et al. 2015). Consequently, the assembly of the ESCRT-III complex at the nuclear envelope reforming sites is necessary for proper post-mitotic nucleo-cytoplasmic compartmentalization (Figure 2D) (Olmos et al. 2015; Vietri et al. 2015; Gu et al. 2017).

Roles of ESCRT-III in neurodegenerative diseases

CHMP2B in frontotemporal dementia and hereditary spastic paraplegias

Mutations in CHMP2B, which plays a crucial role in the early assembly of ESCRT-III, have been linked to various neurodegenerative diseases. Frontotemporal dementia linked to chromosome 3 (FTD-3) is a significant genetic disorder associated with CHMP2B mutations (van der Zee et al. 2008). Patients with FTD-3 typically exhibit early-onset dementia and may manifest symptoms related to motor neuron damage (Pasquier and Petit 1997; Spillantini et al. 2000). Patients with FTD-3 carry a truncated form of the *CHMP2B* gene due to a G-to-C transition at the acceptor splice site of exon 6 (Skibinski et al. 2005). In the brains of affected individuals, a nonsense mutation in Intron5 ($CHMP2B^{Intron5}$) and a frameshift mutation resulting in Δ10 ($CHMP2B^{\Delta 10}$) are observed. Both mutations lead to the loss of the C-terminal acidic amino acid region and MIM domain. These truncated forms are incapable of interacting with the VPS4 complex, thereby impairing the proper assembly and disassembly of ESCRT-III polymers (Ugbode and West 2021). Notably, $CHMP2B^{Intron5}$ proteins are constitutively active, self-aggregate, and exhibit cytotoxicity. In the postmortem brain of patients with FTD-3, ubiquitin inclusion bodies are often observed, which are p62-positive but TAR DNA binding protein-43 (TDP-43)-negative (Holm et al. 2007). These characteristics are distinct from those of the ubiquitin inclusion bodies frequently observed in neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease (PD), or Huntington's disease (Anuppalle et al. 2013). Cells with the $CHMP2B^{Intron5}$ mutation showed an accumulation of autophagosomes and abnormal late endosomes (Lee et al. 2007). Since abnormal late endosomes may arise from dysfunction of the ESCRT complex, further research is needed to elucidate the mechanisms underlying autophagy defects.

The $CHMP2B^{Intron5}$ mutation has also been reported to be associated with hereditary spastic paraplegia (HSP). HSP is another neurodegenerative disorder characterized by progressive stiffness and contraction of the lower extremities (McDermott et al. 2000). Interestingly, spastin, an MIT-domain-harboring ATPase, is most commonly mutated in autosomal dominant HSP (Chen et al. 2022). Spastin exhibited a strong affinity for $CHMP2B^{Intron5}$ proteins in p62-positive aggregates. Defects in endosomal tubule fission and lysosomal enzyme trafficking were observed in skin fibroblasts bearing spastin mutations (Allison et al. 2017; Chen et al. 2022). These studies suggest that CHMP2B mutations significantly contribute to the pathogenesis of neurodegenerative diseases, emphasizing the close association between FTD-3 and HSP.

CHMP3 in PD

PD is a progressive neurological disorder characterized by movement difficulties such as tremors, muscle stiffness, and slow movement. The risk of developing this disease increases with age and primarily affects older individuals. PD is pathophysiologically characterized by the death of dopaminergic neurons in the substantia nigra of the midbrain. However, the cause of cell death remains poorly understood (Dauer and Przedborski 2003; Gómez-Benito et al. 2020; Bloem et al. 2021). Recent studies suggest that α-synuclein aggregates may play a key role in the pathology of PD and dementia with Lewy bodies (DLB), a type of dementia characterized by difficulties in sleep, cognition, and movement (Spillantini et al. 1997; Kim et al. 2014; Colom-Cadena et al. 2017; Henderson et al. 2019). In patients with PD or DLB, the accumulation of Lewy bodies containing α-synuclein aggregates is typically observed. This accumulation inhibits cellular functions and leads to apoptosis; hence, these diseases are referred to as synucleinopathies. In patients with PD, it occurs explicitly in the neurons responsible for dopamine production, and a decrease in dopamine levels is associated with decreased motor function, a typical symptom of PD. Recently, CHMP3 was reported to be involved in the degradation of α-synuclein through lysosomes (Spencer et al. 2016). CHMP3 protein levels in the membrane fraction were lower in the brains of DLB patients than in those of normal subjects. In addition, the levels of α-synuclein were increased when CHMP3 was knocked down and lysosome degradation was inhibited (Zenko et al. 2023). Notably, this process was independent of autophagy. These results suggest that CHMP3 is critical in α-synuclein degradation through the endolysosomal pathway. Therefore, elucidating the detailed mechanism by which CHMP3

degrades α-synuclein would provide crucial insights into the pathogenesis of PD and DLB.

Conclusion

Since their initial discovery in 2001, research on ESCRT proteins has progressed remarkably, utilizing various organisms from yeast to mammals. Recent methodological advances, including high-resolution imaging and in vitro membrane model systems, have significantly contributed to elucidating the intricate details of the assembly and disassembly processes of ESCRT complexes. Although progress has been made in ESCRT research, the field still has numerous open questions that need to be addressed.

Two primary models currently represent how ESCRT-III proteins facilitate membrane scission: the 'ESCRT-III only' model and the 'ESCRT-III-VPS4' model (Adell and Teis 2011). In the 'ESCRT-III only' model, the assembly of ESCRT-III subunits is sufficient to constrict membrane necks below a critical threshold, leading to scission without direct involvement of VPS4. The role of VPS4 in this model is to recycle ESCRT-III subunits for subsequent rounds. Conversely, the 'ESCRT-III-VPS4' model suggests that the VPS4-mediated disassembly of ESCRT-III filaments is actively involved in membrane remodeling and scission, potentially through mechanisms like the 'purse string' model or by causing a sudden relaxation of membrane strain. Both models acknowledge the critical role of ESCRT-III in the formation of filaments or dome-like structures that narrow membrane necks; however, they differ in the role and timing of VPS4 activity in relation to scission events. Further research is needed to determine whether only one of these two models is correct, or whether the mechanisms of membrane scission vary depending on the biological context in which it participates.

The ESCRT system is a conserved and pervasive cellular machinery that orchestrates membrane budding and fission events. A hallmark of ESCRT-driven processes, such as HIV-1 particle release, is their ability to drive membrane deformation and scission away from the cytosol, termed 'reverse topology.' However, ESCRTs exhibit notable versatility, as they can also facilitate scission events directed toward the cytosol, known as 'normal topology.' This bidirectional capability sets ESCRTs apart from other membrane remodeling proteins, which typically operate with a unidirectional bias. The unique adaptability of ESCRT to mediate scission in both topological orientations underscores its exceptional nature within the context of membrane dynamics. However, the factors that determine the ability of ESCRTs to mediate these two distinct topological orientations remain unknown. Further research is required to elucidate the mechanisms underlying this dual function.

Considering the multifaceted roles of ESCRT proteins, relatively few genetic disorders have been linked to ESCRT dysfunction. Pathologies associated with ESCRT abnormalities broadly fall into three categories: cancer, infections, and neurodegenerative diseases (Stuffers et al. 2009). Among these, ESCRT-III is strongly associated with neurodegenerative diseases. The pathogenesis of neurodegenerative diseases is characterized by the accumulation of neurotoxic proteins that are primarily degraded by autophagy. As previously discussed, ESCRT-III mediates membrane remodeling at various stages of autophagy. Consequently, any perturbation in ESCRT-III function would disturb autophagic processes, potentially contributing to the build-up of toxic proteins and subsequent neurodegeneration. Despite this close association, studies on the specific role of ESCRT-III in neurodegenerative disorders are relatively limited. Moreover, it is necessary to investigate whether ESCRT-III is involved in additional steps of autophagy beyond those already identified. These investigations may deepen our understanding of the contribution of ESCRT-III to cellular homeostasis, in addition to revealing its potential implications in neuropathology.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This work was supported by grants from the National Research Foundation of Korea (NRF) funded by the Ministry of Science and ICT (NRF-2021R1A5A2031612).

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