Do caveolae regulate signaling pathways? The broad spectrum of signaling pathways sensitive to caveolae or caveolins is remarkable, with impacts on gene expression, cell proliferation, anchorage dependence of cell growth, directional cell migration, extracellular matrix remodeling, and so on. Since caveolins are also found outside of caveolae, some of the functions assigned to caveolin may not be related to caveolae, but it is clear that caveolae directly regulate numerous signaling pathways. Two types of mechanism have been described by which caveolae fine-tune or activate/deactivate signaling cascades. One is the differential lateral plasma membrane distribution of signaling molecules within or outside of caveolae. The second is the movement of caveolae residents between the cell surface and interior due to the translocation of caveolae between the plasma membrane and the endomembrane system, where caveolae presumably lose their characteristic shape. In both cases, the change in localization results in different signaling outputs. Signaling molecules (membrane receptors, non-receptor kinases and adaptors) can be recruited to caveolae through direct binding to caveolins or by caveolin-independent mechanisms.

Is the lack of caveolae associated with human disease? Many oncogenes induce a marked reduction in caveolin-1 expression, resulting in loss of caveolae from transformed cells. This correlates with increased proliferation and anchorage-independent cell growth, but in certain cancers caveolin-1 expression is advantageous for cancer progression and promotes metastasis. Understanding the role of caveolae in cancer progression will require comprehensive knowledge about the role of caveolae and/or caveolin in regulating pathways essential for cell adhesion, proliferation and migration. Mutations in caveolin-1 and cavin-1 have been linked to lipodystrophy in humans, suggesting that the proposed function of caveolae in lipid homeostasis is altered in affected individuals. Similarly, mutations in caveolin-3 have been linked to various muscular disorders, including limb girdle muscular dystrophy and rippling muscle disease. The predominantly cardiovascular phenotypes of caveolin-deficient mice also suggest a potential role in human cardiovascular disorders. Clearly, caveolae are needed for a healthy organism.

What remains to be explored? The central question we cannot yet answer is why it is advantageous for certain cells to contain caveolae. In other words, what is the physiological function of this unique plasma membrane domain? Although caveolae are implicated in many signaling cascades and cellular processes, the reason for the shape of this membrane domain is unclear. The mechanosensory and mechanotransduction capability of caveolae may be an important specific function that differentiates caveolae from other membrane domains. A clearer understanding of how caveolae sense and transmit physical forces will undoubtedly shed light on their physiological role. It is currently unclear whether other functions of caveolae, such as their role in cholesterol homeostasis or specific roles in a given signaling pathway, are related to their role in mechanosensing. Experimental models for exploring the connections between apparently unrelated and diverse caveolae functions will help us to draw a clear picture of the true function of caveolae.

Where can I find out more?

Bastiani, M. and Parton R.G. (2010). Caveolae at a glance. J. Cell Sci. *123*, 3831–3836.
Goetz, J.G., Minguet, S., Navarro-Lérida, I., Lazcano, J.J., Samaniego, R., Calvo, E., Tello, M., Osteso-Ibañéz, T., Pellinen, T., Echarri, A., *et al.* (2011). Biomechanical remodeling of the microenvironment by stromal caveolin-1 favors tumor invasion and metastasis. Cell *146*, 148–**163.**
Hansen, C.G. and Nichols, B.J. (2010). Exploring the caves: cavins, caveolins and caveolae. Trends Cell Biol. *20*, 177–186.
Hill, M.M., Bastiani, M., Luetterforst, R., Kirkham, M., Kirkham, A., Nixon, S.J., Walser, P., Abankwa, D., Oorschot, V.M., Martin, S., *et al.* (2008). PTRF-Cavin, a conserved cytoplasmic protein required for caveola formation and function. Cell *132*, 113–**124.**
Parton, R.G. and Simons, K. (2007). The multiple faces of caveolae. Nat. Rev. Mol. Cell Biol. *8*, 185–194.
Pilch, P.F., and Liu, L. (2011). Fat caves: caveolae, lipid trafficking and lipid metabolism in adipocytes. Trends Endocrinol. Metab. *22*, 318–324.
Sinha B., Köster D., Ruez R., Gonnord P., Bastiani M., Abankwa D., Stan R.V., Butler-Browne G., Vedie B., Johannes L., *et al.* (2011). Cells respond to mechanical stress by rapid disassembly of caveolae. Cell *144*, 402–413.

Integrin Signaling Laboratory, Vascular Biology and Inflammation Department, Centro Nacional de Investigaciones Cardiovasculares (CNIC), Melchor Fernández Almagro, 3, 28029, Madrid, Spain.
*E-mail: madelpozo@cnic.es

The ESCRT machinery

Oliver Schmidt and David Teis*

The endosomal sorting complexes required for transport (ESCRT) assemble into a multisubunit machinery that performs a topologically unique membrane bending and scission reaction away from the cytoplasm. This evolutionarily highly conserved process is required for the multivesicular body (MVB) pathway, cytokinesis and HIV budding. The modular setup of the machinery with five distinct ESCRT complexes (ESCRT-0, -I, -II, -III and the Vps4 complex) that have a clear division of tasks — from interaction with ubiquitinated membrane proteins to membrane deformation and abscission — allows them to be flexibly integrated into these three very different biological processes (Figure 1).

In the first of these processes, the MVB pathway delivers ubiquitinated membrane proteins and lipids into lysosomes for degradation. During MVB sorting the entire ESCRT machinery sequentially assembles on endosomes, where it generates MVB vesicles by budding the limiting endosomal membrane away from the cytoplasm. An ESCRT-mediated membrane scission step finally releases the mature MVB vesicle into the lumen of the organelle. Since this process is required for membrane protein turnover, it is critical for the regulation of cell surface receptor signaling in cells and during development.

In the second process, at the end of cytokinesis, ESCRT complexes coordinate membrane abscission with microtubule disassembly at the midbody to physically separate the two daughter cells.

Finally, in the third process ESCRT complexes are hijacked during HIV budding at the surface of infected host cells where they catalyze the scission of the membrane stalk that connects the budding virus with the host cell.

Despite fundamental differences, all three processes require a topologically equivalent membrane budding and scission reaction — away from the cytoplasm — which is catalyzed by the coordinated action of the ESCRT

complexes (Figure 1). While the MVB pathway requires all five ESCRT complexes, cytokinesis and HIV budding employ only three ESCRT complexes.

The components of the ESCRT machinery were first characterized in yeast as part of the so-called vacuolar protein sorting (*vps*) mutants, which could no longer transport proteins into the vacuole (the yeast equivalent of the lysosome). Out of these 46 *vps* mutants, 13 mutants displayed a similar phenotype, characterized by an exaggerated prevacuolar organelle (aberrant endosomes) called the 'class E compartment'. All 13 'class E' mutants were deficient in MVB biogenesis and blocked the delivery of membrane proteins into the vacuole. Biochemical characterization of these yeast mutants first resulted in the identification of the ESCRT-I complex and subsequently defined the ESCRT-II and ESCRT-III complexes. Earlier the AAA-ATPase Vps4 had been found to be required for pre-vacuolar transport. Now it became clear that Vps4 disassembles the ESCRT complexes from endosomes and recycles them back to the cytoplasm to maintain the function of the MVB pathway. All 13 *vps* 'class E' genes are evolutionarily highly conserved and multiple isoforms exist for many of the ESCRT subunits in many higher organisms. However, individual roles of the respective isoforms are poorly established. Because the function of the ESCRT machinery is best understood in the MVB pathway in yeast, we will predominantly focus on this process and thus apply yeast nomenclature in the figures. In the text, we will refer first to the yeast nomenclature and then additionally to the names and mutant phenotypes of ESCRT genes in higher organisms.

ESCRT-0

The ESCRT-0 complex initiates the MVB pathway. It is the first complex of the ESCRT machinery that localizes to endosomes and does so via an interaction with an endosome-enriched phospholipid, phosphatidylinositol-3-phosphate (PI3P) (Figure 2). On endosomes, ESCRT-0 binds to ubiquitin moieties that are attached to membrane proteins destined for degradation, and thus executes the first sorting step in the MVB pathway. ESCRT-0 is a 1:1 heterodimer of Vps27/HRS (HGF-regulated tyrosine
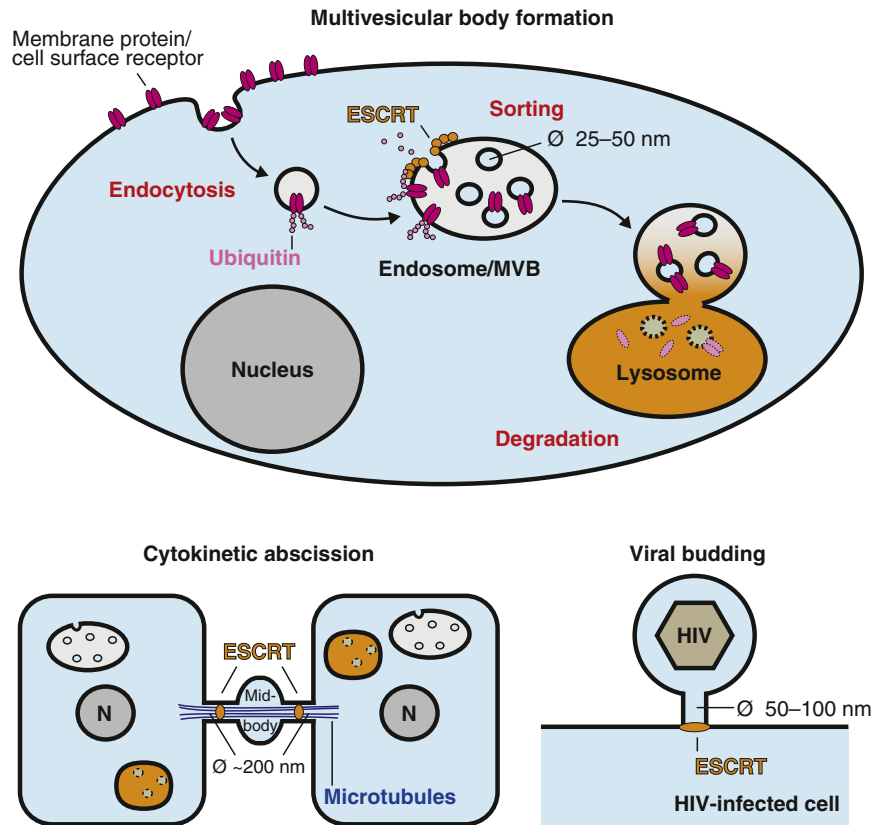

Figure 1. ESCRT-dependent processes.
ESCRT complexes catalyze a topologically distinct membrane-remodelling event: budding and scission of membranes away from the cytosol. During multivesicular body (MVB) sorting the ESCRT machinery generates intraluminal vesicles (diameter of ~25 nm in yeast and ~50 nm in human cells) of MVBs to deliver ubiquitinated membrane proteins into lysosomes for degradation. During cytokinesis ESCRT complexes catalyze the final membrane abscission at the midbody. Additionally, the ESCRT machinery is required for the release of certain enveloped viruses (i.e. human immunodeficiency virus, HIV) from the surface of infected cells.

kinase substrate) and Hse1/STAM (signal transducing adaptor molecule). Vps27/HRS and Hse1/STAM interact via long coiled-coil GAT domains. The FYVE zinc finger domain of Vps27/HRS binds PI3P, which directs the entire ESCRT-0 complex to endosomes. The ESCRT-0 complex contains multiple ubiquitin-binding domains: Hse1/STAM contains one VHS domain and one ubiquitin interaction motif (UIM). Vps27/HRS contains a VHS domain plus one double-sided UIM (HRS) or two separated UIMs (Vps27). Hence, a single ESCRT-0 complex can bind up to five different ubiquitinated membrane proteins or multiple ubiquitin moieties of poly-ubiquitinated cargo. Both possibilities are not mutually exclusive and such multivalent binding may help to concentrate ubiquitinated membrane proteins at the initial step of the MVB pathway. Cargo concentration on

early endosomes might additionally be supported by the formation of flat clathrin lattices that co-localize with HRS and may be recruited by its carboxy-terminal clathrin box.

It seems that Vps27/HRS is key to the initiation of the MVB pathway, not only by binding to ubiquitinated cargo and PI3P, but also because it recruits the ESCRT-I complex. Vps27/HRS binds directly to the amino terminus of the Vps23/TSG101 subunit of ESCRT-I via its carboxy-terminal P(T/S)AP motif (Figure 2). Interestingly ESCRT-0 is only found in fungi and animals. Protists and plants lack ESCRT-0 and yet still employ the ESCRT-dependent MVB pathway for membrane protein degradation. Probably a different, as yet unknown adaptor complex is used to recruit ESCRT-I to endosomes in these organisms.
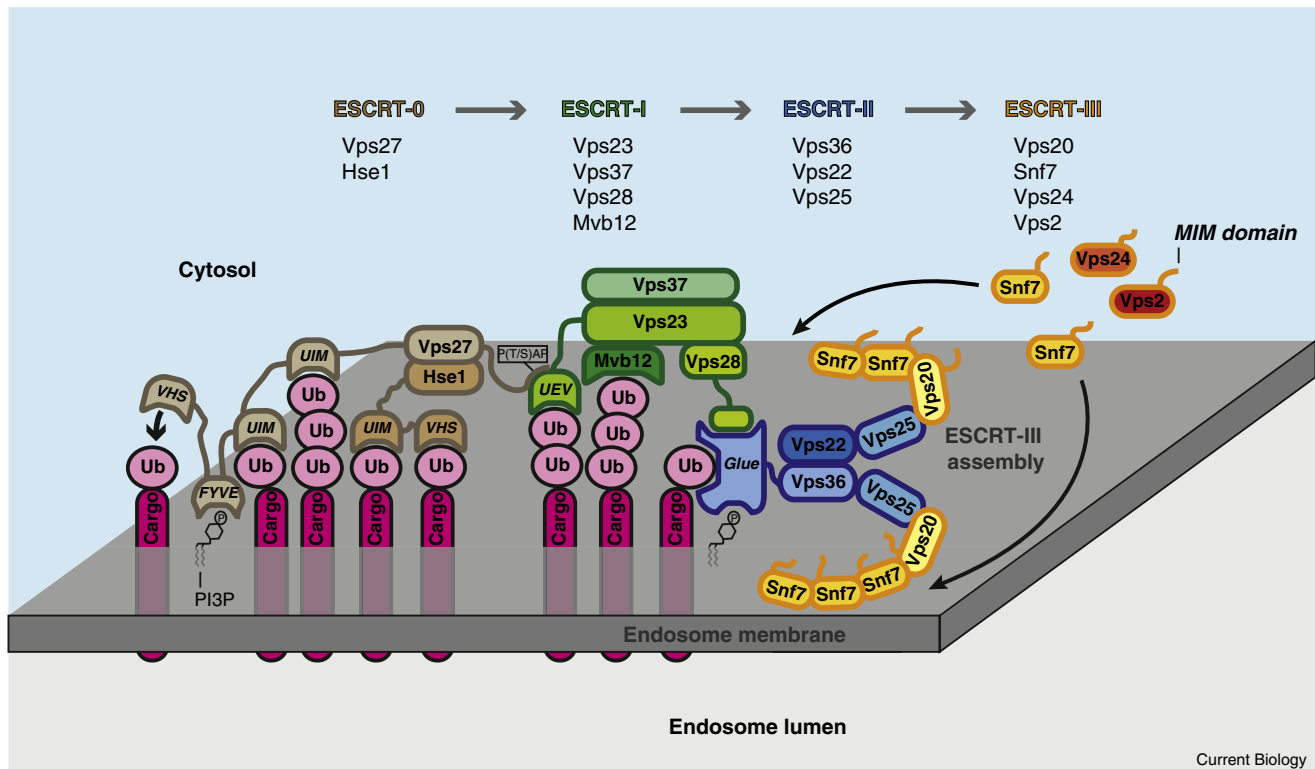
Figure 2. Model for cargo clustering and sequential assembly of the ESCRT complexes.
ESCRT-0 (brown) initiates the MVB pathway. ESCRT-0 binds to PI3P and clusters ubiquitinated membrane proteins via multiple ubiquitin-binding domains. ESCRT-I (green) is recruited by ESCRT-0 (Vps27) and also binds to ubiquitinated cargo. ESCRT-II (blue) interacts via the Glue domain of Vps36 with ESCRT-I, PI3P and cargo. The ESCRT-II subunit Vps25 serves as a nucleation point for stepwise assembly of the filamentous ESCRT-III complex (yellow–orange), which sequesters cargo and drives inward budding of the vesicle.

ESCRT-I

ESCRT-I is a soluble hetero-tetramer consisting of Vps23/TSG101, Vps28, Vps37(A–D) and Mvb12(A,B) or ubiquitin-associated protein 1 (UBAP1) (Figure 2). Its efficient recruitment from the cytoplasm to endosomes requires protein–protein interactions with the ESCRT-0 complex. UBAP1-containing ESCRT-I appears to be more specific for MVB sorting, whereas Mvb12A/B-containing ESCRT-I also functions during HIV budding.

ESCRT-I forms a rigid 25 nm long rod-shaped complex. On one end, the UEV domain of Vps23/TSG101 interacts with ESCRT-0 and ubiquitinated membrane proteins. Since UBAP1 and yeast Mvb12 bind ubiquitin, ESCRT-I could bind two ubiquitin moieties on endosomes. At the opposite end of the ESCRT-I rod, Vps28 binds to the GLUE domain of the ESCRT-II protein Vps36/Eap45 and thereby interacts with the ESCRT-II complex. In addition to cargo sorting, ESCRT-I together with ESCRT-II is capable of budding membranes into the lumen of giant unilamellar vesicles. The rigid architecture and size of ESCRT-I and ESCRT-II (see below) may help to stabilize the bud neck of a growing vesicle.

ESCRT-II

ESCRT-II is a hetero-tetrameric protein complex. It consists of Vps36/Eap45 and Vps22/Eap22 and two Vps25/Eap20 molecules. While Vps36/Eap45 and Vps22/Eap22 tightly interact with each other, one Vps25/Eap20 molecule binds to Vps36/Eap45 and the other one to Vps22/Eap22, thus generating the two arms of the characteristic Y-shaped structure of the ESCRT-II complex (Figure 2). The GLUE domain of Vps36/Eap45 is attached to the base of the Y and functions as a hub that connects to Vps28 of ESCRT-I and can bind simultaneously to PI3P and ubiquitin.

Thus, each of the three early ESCRT complexes (ESCRT-0, -I, and -II) can interact with ubiquitinated cargo, and it seems likely that they cooperate in some way to sort ubiquitinated membrane proteins into the MVB pathway. Cargo molecules might be transferred from one ESCRT complex to another, like on a conveyor belt. Alternatively ESCRT-0, -I and -II could interact simultaneously with different membrane proteins and thereby generate a sorting domain on the surface of endosomes that matures into a site of MVB formation (Figures 2 and 3). While cargo is collected, ESCRT-I together with ESCRT-II could initiate the budding process of the endosomal membrane. At the same time, both arms of ESCRT-II (Vps25/Eap20) could already interact with one copy of the first ESCRT-III subunit, Vps20/CHMP6 (charged multi-vesicular body protein 6), and convert it into an active nucleator for ESCRT-III assembly on endosomes.
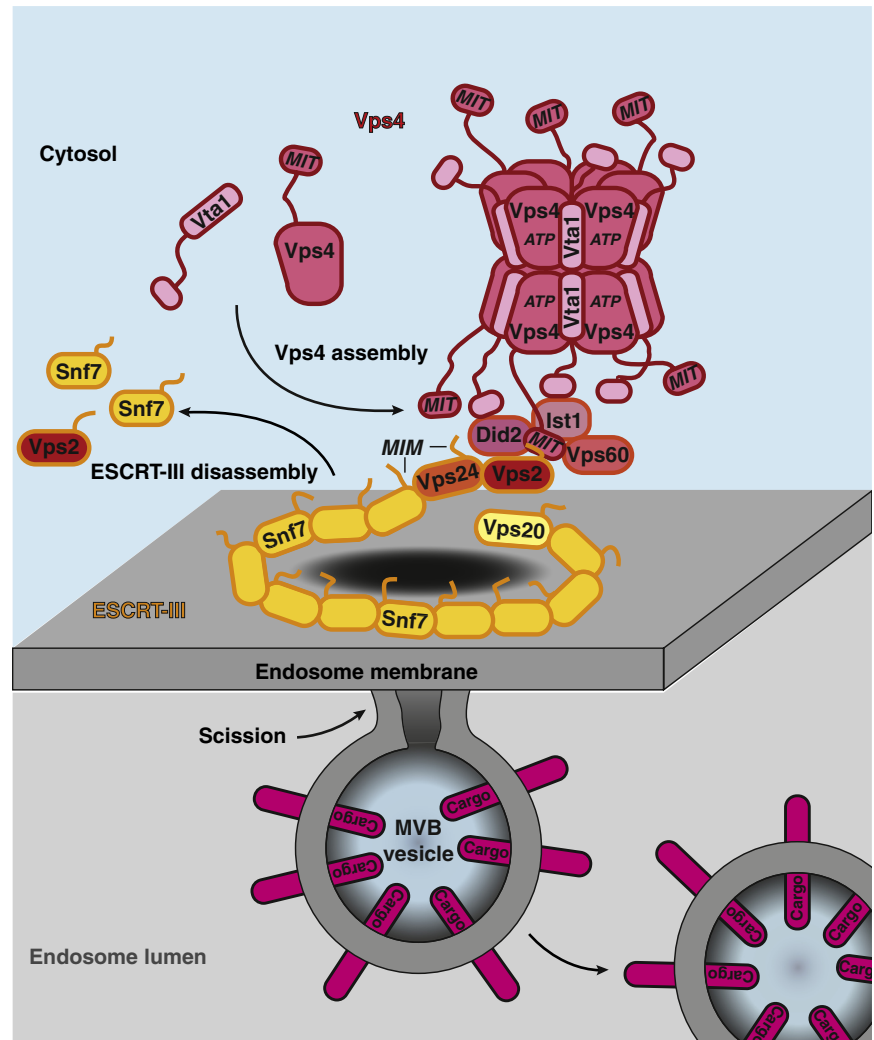
ESCRT-III

In contrast to the early ESCRT complexes (ESCRT-0, -I and -II), which form stable protein complexes in the cytoplasm, the ESCRT-III complex only transiently assembles on endosomes. The ESCRT-III complex consists of four core subunits, Vps20/CHMP6, Snf7/CHMP4(A–C), Vps24/CHMP3 and Vps2/CHMP2(A,B) (Figures 2 and 3), and three accessory components, Did2/CHMP1(A,B), Vps60/CHMP5 and Ist1 (Figure 3). The core subunits are relatively small, 221–241 amino-acid

proteins with similar biochemical properties and probably adopt a common molecular architecture. Their amino-terminal region consists of two helices (α1, α2) that form a 7 nm hairpin structure important for membrane binding and homo- or hetero-dimerization. In the cytoplasm, the negatively charged carboxy-terminal region (α5 and α6) folds back on the positively charged amino-terminal hairpin, which confers an autoinhibitory mechanism that stabilizes the inactive monomers. The carboxyl terminus also harbors the so-called MIT (microtubule-interacting and transport)-interacting motifs (MIMs) for interaction with the AAA-ATPase Vps4.

Despite their structural similarity, each ESCRT-III subunit has a specific function. The ordered assembly into the active filament begins when ESCRT-II converts Vps20 into an active nucleator, which triggers the stepwise homo-oligomerization of Snf7 (Figure 2). This oligomerization is capped by binding of Vps24 to the last Snf7 protomer. In turn, Vps24 recruits Vps2, which completes the assembly of the ESCRT-III filament (Figure 3). While the precise stoichiometry of ESCRT-III has not been determined, the Snf7 homo-oligomer appears to be its major component. The activation of ESCRT-III molecules requires a series of conformational changes that relieve autoinhibition, stabilize membrane binding, enable interaction with other ESCRT-III molecules and expose the MIM domain. The growing ESCRT-III complex recruits deubiquitinases, which mediate cargo deubiquitination and thus ubiquitin recycling prior to vesicle formation. These include AMSH (associated molecule with the SH3 domain of STAM), USP8/UBPY (ubiquitin-specific protease 8) and in yeast Doa4 (which binds via Bro1 to Snf7). It is possible that at this stage of the MVB pathway the cargo proteins have been encircled by a ring-shaped ESCRT-III filament that can be observed upon overexpression of CHMP4 *in vivo* and *in vitro*. Now deubiquitination can safely take place without the risk of cargo evading lysosomal degradation. Although it has not been demonstrated, cargo deubiquitination may help to release the early, ubiquitin-binding ESCRT complexes into the cytoplasm.

In vivo and *in vitro* data suggest a key role for the ESCRT-III complex in all ESCRT-mediated membrane remodeling (budding and scission)

Current Biology

Figure 3. Membrane scission and ESCRT-III disassembly by Vps4.
The ESCRT-III subunits Vps24 and Vps2 terminate assembly of the ESCRT-III filament (orange) on the endosome surface. Vps2 together with Did2, Ist1 and Vps60 build a recruitment complex for the AAA-ATPase Vps4 and its cofactor Vta1. Once assembled, the Vps4 complex (pink) catalyzes disassembly of the ESCRT-III filament in an ATP-driven reaction. ESCRT-III disassembly terminates each round of the MVB pathway, which results in the generation of a cargo-laden 25 nm MVB vesicle (50 nm in human cells).

reactions, although the mechanism is not understood. Hence, ESCRT-III filaments may have a dual role during MVB sorting: cargo sequestration within the site of MVB vesicle formation and membrane budding/scission.

Vps4 complex
ESCRT-III and the Vps4 complex are the most conserved building blocks of the ESCRT machinery. Homologues of Vps4 and ESCRT-III subunits are found in all eukaryotic species and in certain prokaryotic organisms: Crenarcheota of the genus *Sulfolobus*. The Vps4 complex consists of the type I AAA-ATPase Vps4 and its co-factor Vta1. In the cytoplasm, Vps4 is an

inactive protomer (monomer or dimer). A recruitment complex regulates the assembly of Vps4 onto ESCRT-III (Figure 3). Its central component is the ESCRT-III subunit Vps2/CHMP2, which functions together with Did2/CHMP1, Ist1 and Vps60/CHMP5. Since Vps2 also completes ESCRT-III assembly, it provides an intrinsic timer for ESCRT-III disassembly. Vps4 contains an amino-terminal MIT domain that probably binds first to the carboxy-terminal MIM domain of Vps2. Once recruited to the ESCRT-III complex, Vps4 assembles into a dodecamer, consisting of two stacked hexameric rings with a central pore. The binding of Vta1 results in an active Vps4–Vta1 complex

with enhanced ATPase activity. Like other AAA-ATPases, Vps4 is a mechanoenzyme. It invests the energy from ATP hydrolysis into mechanical power to disassemble the membrane-bound ESCRT-III filament and thereby recycles its individual subunits back to the cytoplasm. After completion of ESCRT-III disassembly, the Vps4 complex also dissociates into its inactive protomers. As such, the Vps4 complex terminates each round of MVB cargo sorting and vesicle formation.

ESCRT mutant phenotypes associated with defects in the MVB pathway
Several mutations of ESCRT components exist in higher eukaryotes, including humans, mouse, *Drosophila melanogaster* and *Caenorhabditis elegans*. The predominant phenotype of yeast ESCRT mutants — a defect in the MVB pathway with an aberrant endosomal compartment — is phenocopied in the mutant cells of these organisms. As a consequence, ESCRT mutant cells fail to downregulate and degrade cell-surface signaling receptors (Notch, EGFR and many others), which frequently results in sustained receptor signaling and hyperproliferation in tissues. Yet, hyperproliferation may be counterbalanced by increased apoptosis and cell-cycle defects displayed by certain ESCRT mutants. Additionally, adverse effects may contribute to the complexity of ESCRT mutant phenotypes observed during the development of higher eukaryotes. For example, Wingless/Wnt signaling appears to require a functional MVB pathway. Moreover, a wide range of ESCRT mutants in human, fly and worm cells are defective in autophagosome fusion with lysosomes, although the role of ESCRTs in this process is elusive. Also, autophagy defects in ESCRT mutants have been associated with reduced clearance of protein aggregates typical for neurodegenerative diseases, and mutations in Vps2/CHMP2B were described in patients with hereditary forms of amyotropic lateral sclerosis and fronto-temporal dementia.

The complexity of ESCRT mutant phenotypes during tissue development is maybe best demonstrated in *Drosophila* epithelia, where most ESCRT mutant cells lose cell polarity, which causes neoplastic transformation and non-cell-autonomous hyperproliferation of the neighboring

wild-type cells. The ESCRT mutant cells themselves could only hyperproliferate once cell death was blocked.

Mice deficient in HRS, CHMP5 or STAM1/2 die during embryonic development at day 11 (E11), with severe morphogenesis defects. CHMP4B/mSnf7-2 and TSG101 knockout mice die at days E8 and E6, respectively. Thus, a prominent and complex role for the ESCRT machinery during development, cancer and neurodegeneration is emerging.

The ESCRT machinery during cytokinesis
In higher eukaryotes and certain archaea, but not in budding yeast, the ESCRT machinery also executes cell abscission, the final membrane scission step that terminates cytokinesis (Figure 1). ESCRT-0 and ESCRT-II are not required for this process. The centrosomal protein CEP55 recruits TSG101 and the Bro-domain-containing protein Alix into two cortical rings at the midbody. Alix binds to and may activate Snf7/CHMP4. Somehow, ESCRT-I and Alix trigger ESCRT-III assembly into long helical filaments that extend from the midbody to the site of abscission. Interestingly, the ESCRT-III subunit Did2/CHMP1B recruits the AAA-ATPase spastin, which severs the thick microtubule bundles at the midbody prior to membrane abscission. Thus, during cytokinesis ESCRT-III filaments coordinate membrane scission with spastin-mediated microtubule disintegration. Importantly, Crenarchaeota, which lack other protofilaments such as FtsZ/tubulin or MreB/actin for cell division, use the ESCRT-III–Vps4 system instead.

Loss or reduction of ESCRT function in human cells, *Arabidopsis thaliana* and *Sulfolobus acidocaldarius* frequently results in multinucleated cells, caused by a failure of cytokinetic abscission and probably subsequent cleavage furrow regression upon prolonged cytokinesis arrest.

The ESCRT machinery during HIV budding
HIV and other retroviruses, such as Ebola and human T-lymphotropic virus, exploit certain components of the ESCRT machinery to bud out of infected host cells (Figure 1). ESCRT-0 and ESCRT-II are dispensable for HIV budding, whereas Alix is required. Of the ESCRT-III subunits only CHMP4 and CHMP2 appear to be essential. The

HIV Gag protein hijacks ESCRT-I at the plasma membrane. PTAP motifs in the Gag protein mimic the P(T/S)AP motif of HRS and thus recruit TSG101 to the cell surface. The successive recruitment of Alix, ESCRT-III and Vps4 is then required to sever the neck of the maturing virus. Loss of ESCRT function inhibits viral release with arrested buds accumulating on the surface of infected cells.

Outlook
While it is now clear that ESCRTs function as a protein sorting and membrane sculpting/scission machinery, there are still major open questions. Among the most pressing questions are the molecular mechanism underlying ESCRT-mediated membrane deformation and scission, and its different kinetics and energy requirements in the MVB pathway, cytokinesis and HIV budding. More work must be invested before we truly understand these processes.

Further reading
Babst, M., Katzmann, D.J., Estepa-Sabal, E.J., Meerloo, T., and Emr, S.D. (2002). Escrt-III: an endosome-associated heterooligomeric protein complex required for mvb sorting. Dev. Cell *3*, 271–282.
Babst, M., Katzmann, D.J., Snyder, W.B., Wendland, B., and Emr, S.D. (2002). Endosome-associated complex, ESCRT-II, recruits transport machinery for protein sorting at the multivesicular body. Dev. Cell *3*, 283–289.
Bilodeau, P.S., Urbanowski, J.L., Winistorfer, S.C., and Piper, R.C. (2002). The Vps27p Hse1p complex binds ubiquitin and mediates endosomal protein sorting. Nat. Cell Biol. *4*, 534–539.
Carlton, J.G., and Martin-Serrano, J. (2007). Parallels between cytokinesis and retroviral budding: a role for the ESCRT machinery. Science *316*, 1908–1912.
Hanson, P.I., Roth, R., Lin, Y., and Heuser, J.E. (2008). Plasma membrane deformation by circular arrays of ESCRT-III protein filaments. J. Cell Biol. *180*, 389–402.
Katzmann, D.J., Babst, M., and Emr, S.D. (2001). Ubiquitin-dependent sorting into the multivesicular body pathway requires the function of a conserved endosomal protein sorting complex, ESCRT-I. Cell *106*, 145–155.
Kostelansky, M.S., Schluter, C., Tam, Y.Y., Lee, S., Ghirlando, R., Beach, B., Conibear, E., and Hurley, J.H. (2007). Molecular architecture and functional model of the complete yeast ESCRT-I heterotetramer. Cell *129*, 485–498.
Raymond, C.K., Howald-Stevenson, I., Vater, C.A., and Stevens, T.H. (1992). Morphological classification of the yeast vacuolar protein sorting mutants: evidence for a prevacuolar compartment in class E vps mutants. Mol. Biol. Cell *3*, 1389–1402.
von Schwedler, U.K., Stuchell, M., Muller, B., Ward, D.M., Chung, H.Y., Morita, E., Wang, H.E., Davis, T., He, G.P., Cimbora, D.M., *et al*. (2003). The protein network of HIV budding. Cell *114*, 701–713.
Wollert, T., Wunder, C., Lippincott-Schwartz, J., and Hurley, J.H. (2009). Membrane scission by the ESCRT-III complex. Nature *458*, 172–177.

Biocenter, Division of Cell Biology, Innsbruck Medical University, Innsbruck, Austria.
*E-mail: david.teis@i-med.ac.at