

The roles of ESCRT proteins in healthy cells and in disease

Jasmina Ilievska, Naomi E Bishop, Sarah J Annesley and Paul R Fisher¹

Department of Microbiology, La Trobe University, Australia.

1 Introduction

Endocytosis is a process that occurs in all eukaryotes and is an essential mechanism for internalizing membrane proteins and controlling intracellular trafficking (Bishop, 2003). Membrane proteins such as active epidermal growth factor receptors (EGFRs) are endocytosed via clathrin-dependent or independent pathways and are typically first delivered to the early endosome (Bishop, 1997; Tarrago-Trani & Storrie, 2007) (Figure 1). The early endosomes (or sorting endosomes) have a crucial role in sorting the endocytosed cargo to three alternative destinations: (i) recycling the cargo back to the plasma membrane (receptor sequestration), (ii) transferring the cargo to the *trans* Golgi network (TGN), (iii) transporting the cargo into intraluminal vesicles (ILVs) of maturing endosomes known as multivesicular bodies (MVBs) (reviewed by Gruenberg & Stenmark, 2004; Russel et al., 2006; Piper & Katzmann, 2007). The ultimate consequence of such sorting is the exposure of the ILVs and their contents to lysosomal hydrolases after fusion of the MVB with lysosomes (receptor down-regulation) (reviewed by Sorkin & von Zastrow, 2009; Wegner et al., 2011). MVBs also play an important role in the traffic of lysosomal enzymes from the TGN, and in the secretion of exosomes from cells (Lakkaraju & Rodriguez-Boulan, 2008; Simons & Raposo, 2009; Thery et al., 2009). MVBs functions extend beyond cargo sorting - they also serve as MHC class II compartments for antigen presentation, T-cell secretory granules and melanosomes in specialised cell types (Raiborg et al., 2003).

Efficient sorting at the early endosome and the MVB compartments typically requires mono- or polyubiquitination of cell surface receptors. The molecular machinery that recognises the ubiquitinated cargo at the early endosome and mediates its sorting into MVBs is a set of interacting protein complexes, the endosomal complexes required for transport (ESCRTs'). The ESCRTs' were first identified in yeast and were initially referred to as class E Vps (vacuolar protein sorting) proteins (Raymond et al., 1992). Characterisation of the 18 class E genes revealed that ten of these encode subunits of the ESCRT system, whereas the others encode ESCRT-related proteins or upstream or downstream interactors (reviewed by Slagsvold et al., 2006) (Table 1).

Extensive genetic, biochemical and structural studies using yeast, *Drosophila* and mammalian model systems have revealed the molecular roles of the ESCRTs'. The ESCRT system consists of four different complexes termed ESCRT-0, -I, -II and -III, and a number of associated proteins such as Vps4 (Babst et al., 2002a, 2002b; Katzmann et al., 2001) (Figure 2). Ubiquitinated endosomal cargo targeted for lysosomal degradation is initially recognised by ESCRT-0. ESCRT-I, -II and -III which are subsequently recruited to the endosomal membrane by protein-protein interactions between the four complexes (reviewed by Roxrud et al., 2010). The ubiquitinated cargo is further concentrated on the endosomal membrane by the action of ESCRT-I and -II, furthermore invaginations that form from the endosomal membrane to become ILVs depend upon ESCRT-III and Vps4 -facilitated membrane abscission (Elia et al., 2011; Babst et al., 2011). The endocytosed contents in the ILVs are ultimately terminated via lysosomal degradation (Figure 1). Following protein sorting into MVBs, the ATPase Vps4 catalyzes the release of the ESCRT machinery from the limiting membrane of the MVB compartment into the cytosol for further rounds of cargo sorting.

The ESCRTs' also have alternative cellular roles beyond lysosomal trafficking. A subset of ESCRTs' have a well-established function in eukaryotic cell abscission (cytokinesis) (Spitzer et al., 2006; Carlton & Martin-Serrano, 2007; Morita et al., 2007), viral budding (Morita & Sundquist, 2004; Fujii et al., 2007) and autophagy (Filimonenko et al., 2007; Lee et al., 2007). Given their importance in fundamental cellular processes, it is not surprising that ESCRT dysfunction is associated with numerous diseases, including neurodegenerative disorders, cancer and infectious diseases. The dynamics and regulation of the ESCRT machinery have been extensively reviewed (Hurley & Emr, 2006; Saksena et al., 2007; Williams & Urbe, 2007; Raiborg & Stanmark, 2009; Hanson et al., 2009; Carlton & Martin-Serrano, 2009; Hurley, 2010; Roxrud et al., 2010; Henne et al., 2011) and will only be mentioned briefly here. This review focuses on understanding the role of the ESCRTs' in disease using model systems, to better understand the mechanisms behind their role in pathogenesis.

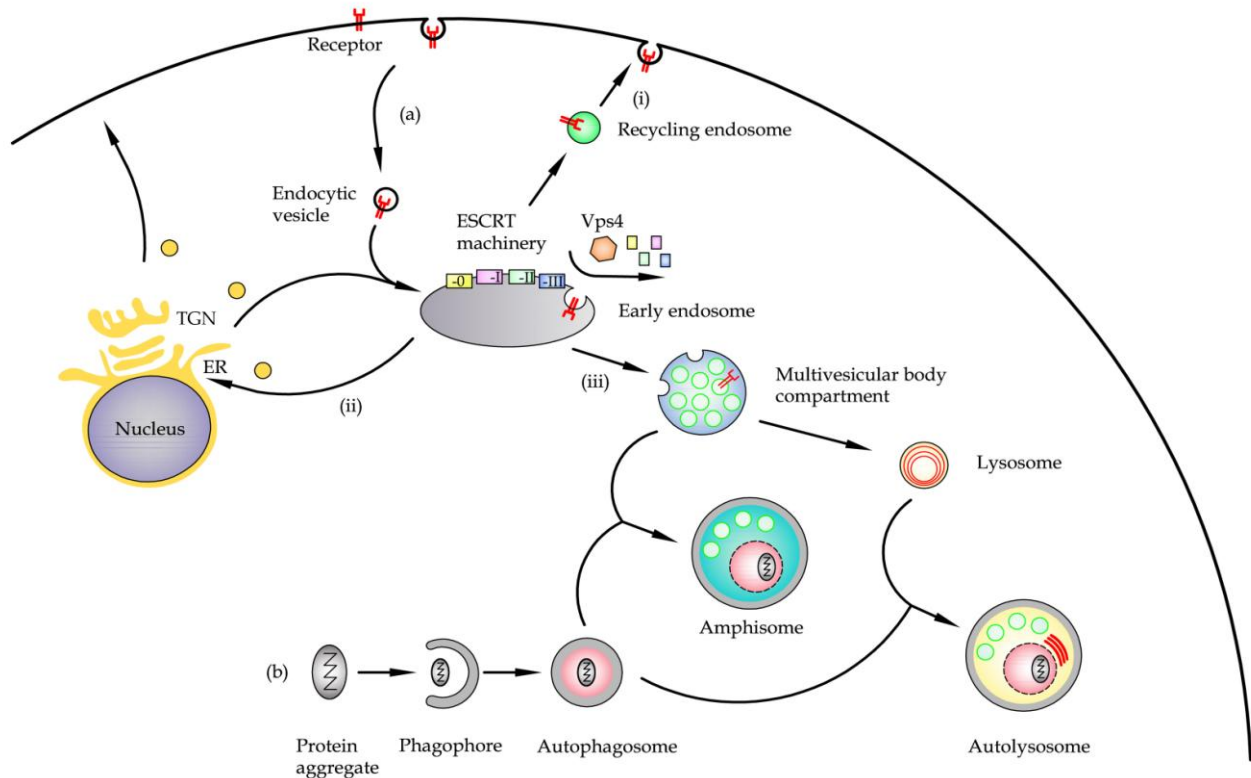


Fig 1. Interrelationships between the endocytic and autophagic pathways.

(a) Receptor-mediated endocytosis involves internalization of plasma membrane cargo into the cell. Endocytosed cargo is first delivered to the early endosome, which also receives cargo from the TGN. From here on, selected cargo can be delivered to three alternative destinations: (i) can be recycled back to the plasma membrane (receptor sequestration), or (ii) sorted into the TGN or (iii) incorporated into ILVs of MVBs. The cargo within the MVB compartment is subsequently transported to the lysosome where the constituents are broken down by lysosomal hydrolases (receptor down-regulation). The MVB biogenesis and the sorting of ubiquitinated cargo is controlled by four ESCRTs', -0, -I, -II -III, and the action of a AAA+ type ATPase Vps4. (b) In contrast to endocytosis, autophagy digests intracellular material by encapsulating damaged organelles or protein aggregates by a phagophore. The resulting autophagosome can fuse directly with the lysosome forming an autolysosome or indirectly via the MVB compartment forming a hybrid organelle, termed an amphisome.

2 Evolutionary conservation of ESCRTs'

Comparative genomic and phylogenetic analysis has revealed in great detail the conservation of the molecular machineries involved in cargo sorting and membrane trafficking. The phylogenetic data has shown that most ESCRT genes emerged early during the evolution of eukaryotes (Slater & Bishop, 2006, Field et al., 2007; Leung et al., 2008, Field & Dacks, 2009). However the ESCRT-III complex and Vps4 have been identified in Archaea, suggesting an even earlier, ancestral function for these components (Lindas et al., 2008; Ghazi-Tabatabai et al., 2009; reviewed by Makarova et al., 2010; Samson et al., 2008, 2011). It has even been suggested a similar mechanism may contribute to bacterial outer membrane vesicle production (Kulp & Kuehn, 2011). All of the other ESCRT complexes with the exception of ESCRT-0, are present across all of the eukaryotic lineages. ESCRT-0 appears to be specific to the opisthokonts (metazoa and fungi) and is absent from *Dictyostelium discoideum*, a member of their sister lineage the Amoebozoa, as well as from plants (Winter & Hauser, 2006; Leung et al., 2008; Field & Dacks, 2009). However *D. discoideum* contains instead a minimal, possibly ancestral ESCRT-0 in which DdTom1 interacts with ubiquitin, clathrin and the ESCRT-1 protein Tsg101 (Blanc et al., 2009). MVBs were also recently identified in the basal amoebozoan *Breviata anathema*, strengthening the conclusion that the ESCRTs' are a common feature of this supergroup (Herman et al., 2011). In mammals and plants several *VpsE* genes such as *Vps37*, *Vps4*, *Vps32*, *Mvb12* and *Bro1* have undergone gene duplications. The domain structure of *VpsE* proteins, especially the domains involved in protein-protein and protein-lipid interactions is well conserved across yeast, metazoa and plants (reviewed by Michelet et al., 2010) (Table 1). Collectively, these data suggests that the fundamental structure and the role of the ESCRTs' is well conserved among many eukaryotic organisms.

ESCRT complex and activity	Yeast Protein names	Metazoan Protein names	Domains/Motifs¹	Biological function
ESCRT-0 <i>Clusters ubiquitinated cargo</i>	Vps27	Hrs	VHS, FYVE, UIM (yeast) DUIM (metazoan), PTAP, GAT, coiled-coil core, clathrin binding	Binds PtdIns3P, ubiquitinated cargo, ESCRT-I and clathrin
	Hse1	STAM1, 2	VHS, UIM, SH3, GAT, coiled-coil core, clathrin binding	Binds ubiquitinated cargo and DUB enzymes
ESCRT-I <i>Membrane deformation and budding</i>	Vps23 Vps28 Vps37 Mvb12	Tsg101 Vps28 Vps37A, B, C, D MVB12A, B	UEV, Pro-rich linker, stalk, headpiece Headpiece, C-terminal Basic helix, head piece Stalk, ubiquitin binding domain	Cargo and ESCRT-0 (Vps27) interaction, contains the viral PTAP motif Binds ESCRT-II (Vps36) Binds membranes Stabilizes ESCRT-I subunits, binds ubiquitin
ESCRT-II <i>Membrane deformation and budding</i>	Vps22 Vps25 Vps36	EAP30, Snf8 EAP20 EAP45	Coiled-coil, WH PPXY, WH GLUE, NZF1, 2 (yeast), WH	Binds membranes Binds ESCRT-III (Vps20), cargo Binds membranes, ubiquitin and ESCRT-I (Vps28)
ESCRT-III <i>Membrane scission</i>	Vps20 Vps32/* (Snf7) Vps24 Vps2/(Did4)	CHMP6 CHMP4A, B, C CHMP3 CHMP2A, B	Charged, coiled-coil, MIM Charged, coiled-coil, MIM Charged, coiled-coil, MIM Charged, coiled-coil, MIM	Initiates membrane scission Membrane scission, binds Bro1 domains Completes membrane scission Recruits Vps4; initiates ESCRT disassembly
Vps4 <i>Disassembly of ESCRTs'</i>	Vps4	Vps4A,B/(SKD1, 2)	AAA+ ATPase, MIT	ESCRT disassembly and recycling
	Vta1	VTA1/LIP5	MIT, VSL	Positively regulates of Vps4
Other	Vps31/(Bro1)	ALIX/AIP1	Bro1, Proline-rich domain	ESCRT-III interaction by recruiting Snf7, Doa4 recruitment, interacts with apoptosis regulators, contains viral YXP domains
	Vps60/(Mos10)	CHMP5	Charged, coiled-coil	ESCRT-III like protein, binds Vta1
	Vps46/(Did2)	CHMP1A, B	Charged, coiled-coil	ESCRT-III like protein, recruits Vps4
	Ist1	IST1	MIM1, MIM2	The tandem ESCRT- III domains bind SNF7B and the DUB UBPY (USP8)
	Doa4	UBPY/USP8	Rhod, UBP	Removes ubiquitin

Table 1: Components of the ESCRT machinery.

(Table is modified from Hurley & Hanson, 2010, see cited paper for further details on domain/motif structure)

¹**Domain acronyms:** Bro1, Bro1 domain-containing protein 1; CHMP, charged multivesicular body protein; DID, DOA4-independent degradation protein; DUB, deubiquitylating enzyme; DUIM, double-sided ubiquitin-interacting motif; ESCRT, endosomal sorting complex required for transport; GAT; GLUE, GRAM-like ubiquitin-binding in EAP45; Hrs, hepatocyte growth factor-regulated Tyr kinase substrate; Ist1, increased sodium tolerance protein 1; MIM, MIT-interacting motif; MIT, microtubule-interacting and transport; MVB, multivesicular body; NZF, Npl4-type zinc finger; SH3, SRC homology 3; UBPY, ubiquitin isopeptidase Y; UEV, ubiquitin E2 variant; UIM, ubiquitin-interacting motif; VHS, Vps27, Hrs and STAM; Vps, vacuolar protein sorting; VSL and VTA1; WH2, winged helix 2. *Alternative names are provided in brackets.

3 Structure and function of ESCRTs' in normal cells

3.1 Composition of the ESCRT complexes

In order to understand the role of the ESCRTs' in disease, a brief overview of the composition of each complex is provided (Figure 2). ESCRT-0, -I and -II are stable heterotetrameric complexes, while ESCRT-III is formed by polymers formed by four core protein subunits.

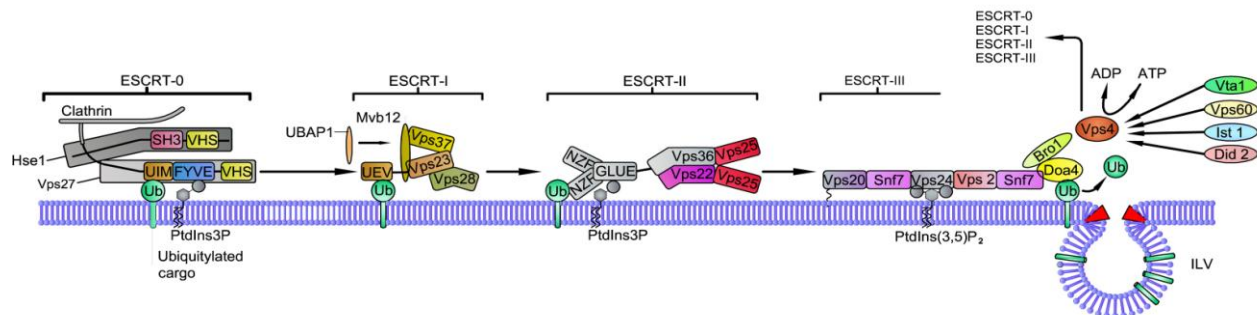


Fig 2. Composition and molecular interactions of the ESCRTs'.

Interactions between the four ESCRTs' are indicated, as are interactions with ubiquitylated cargo, accessory molecules such as phosphatidylinositol 3-phosphate (PtdIns(3)P), deubiquitylating enzymes (DUBs), Bro1 and the ATPase Vps4. Yeast protein names have been used but the figure above is a composite of data obtained from studies of several model systems containing the ESCRTs'.

3.1.1 ESCRT-0

The ESCRT-0 complex has an early role in MVB biogenesis and in the sorting of ubiquitinated proteins into the MVB pathway. ESCRT-0 binds and clusters ubiquitinated cargo destined for delivery into MVBs, and recruits clathrin and deubiquitinating enzymes (Wollert et al., 2010). The ESCRT-0 complex consists of two subunits, Hrs (Vps27 in yeast) and STAM1/2 (Hse1 in yeast). Hrs contains a FYVE zinc finger domain which binds PtdIns(3)P providing membrane recruitment and endosomal specificity for the ESCRT-0 complex (Mao et al., 2000). Hrs and STAM1/2 bind ubiquitin via their UIM and VHS ubiquitin domains respectively, which are essential for efficient sorting of ubiquitinated proteins (Bishop et al., 2002; Mizuno et al., 2003; Bache et al., 2006). Hrs binds directly to the tumour susceptibility gene-101 product (Tsg101) recruiting ESCRT-I to the endosomal membranes (Bishop et al., 2002) (Figure 2).

3.1.2 ESCRT-I

The ESCRT-I complex along with ESCRT-II is required for further concentrating ubiquitinated cargo on the endosomal membrane and initiating the first stages of membrane invagination (Wollert et al., 2010). Mammalian ESCRT-I is composed of four subunits Tsg101 (Vps23 in yeast), Vps28, Vps37 (four isoforms, A-D) and Mvb12 (two isoforms A/B); the yeast ESCRT-I contains single copies of the four subunits (Chu et al., 2006; Curtiss et al., 2007; Kostelansky et al., 2007; Oestreich et al., 2007) (Figure 2). A novel ESCRT-I component was recently identified in mammalian cells, termed UBAP1. UBAP1 contains a region conserved in Mvb12 and binds Bro1 proteins involved in cytokinesis (Stefani et al., 2011). The ESCRT-I structure is organised as a headpiece core with flexibly connected modules that mediate interactions with other partners such as ESCRT-0, ubiquitin, Alix (Bro1 in yeast) and ESCRT-II. The Tsg101 subunit can also directly bind Vps20, an ESCRT-III component, surpassing both ESCRT-I and -II (Katzmann et al., 2003; Bilodeau et al., 2003; Pornillos et al., 2003).

3.1.3 ESCRT-II

The ESCRT-II complex is recruited to the endosomal membrane by the interaction between the ESCRT-I subunit Vps28 and the ESCRT-II subunit Vps36 (Saksena et al., 2009) (Figure 2). The ESCRT-II complex is a heterotetramer with one copy of Vps22 and Vps36 and two copies of Vps25 (Hierro et al., 2004; Im & Hurley, 2008; Teis et al., 2010). Mammalian Vps36 binds PtdIns(3)P and ubiquitin via the GLUE domain and is important for efficient cargo sorting (Teo et al., 2006). The yeast Vps36 contains a GLUE domain with two NZF insertions. NZF1 binds to ESCRT-I (Gill et al., 2007) and NZF2 binds to ubiquitinated cargo (Alam et al., 2004). The C-terminal domain of Vps25 provides a direct link to ESCRT-III by binding to CHMP6 (Vps20).

3.1.4 ESCRT-III

The ESCRT-III complex plays an important role in membrane scission and is responsible for pinching off the neck of the invagination, forming an ILV (Wollert et al., 2009; Wollert & Hurley, 2010) (Figure 2). Mammalian ESCRT-III consists of multiple subunits, CHMP2 (two isoforms A/B.) (in yeast Vps2), CHMP3 (in yeast Vps24), CHMP4 (four isoforms A-D) (in yeast Snf7), and CHMP6 (in yeast Vps20) (Babst et al., 2002a; Bajorek et al., 2009b). The other ESCRT-III subunits

CHMP1 (two isoforms A/B), (in yeast Did2), CHMP5 (in yeast Vps60) and Ist1 are not strictly essential for function and appear to assemble with the rest of the ESCRT-III subunits at a later stage. Did2 and Vps60 recruit and activate Vps4, while Ist1 inhibits Vps4 activity (Nickerson et al., 2006; Dimaano et al., 2008). Vps4 is an AAA-ATPase, which has an important role in catalysing and energizing the dissociation of the ESCRT machinery from the endosomal membrane back to the cytosol, for further rounds of cargo sorting. The ESCRT-III complex does not bind ubiquitin, however it recruits Alix, which plays a key role in the endosomal recruitment of Doa4, a deubiquitinating enzyme (Babst et al., 1997; 1998; Scott et al., 2005; Muziol et al., 2006; Shim et al., 2007; Yu et al., 2008; Teis et al., 2008; Lata et al., 2008; Ghazi-Tabatabai et al., 2009).

3.2 Biological roles of the ESCRTs'

3.2.1 Cytokinesis

In eukaryotes, cytokinesis consists of at least three key steps: (i) assembly of the central spindle, (ii) formation of the cleavage furrow, (iii) and membrane abscission at the midbody (Yang et al., 2008; reviewed by Saksena & Emr, 2009). The membrane scission and the creation of the membrane curvature required in cytokinesis is topologically similar to the curvature needed during MVB sorting and viral budding. Studies have shown that components of ESCRTs' are required for membrane abscission, the final step of cytokinesis. For instance, ESCRT-III is specifically recruited to the midbody to mediate membrane fission and Vps4 is important in the release of ESCRT-III in cytokinesis (Spitzer et al., 2006; Obita et al., 2007; Carlton & Martin-Serrano, 2007). Furthermore, depletion of either Ist1 and Did2 (ESCRT-III and Vps4 human homologues) leads to an arrest in cytokinesis (Agromayor et al., 2009; Bajorek et al., 2009a). Additionally, the ESCRT-I subunit Tsg101 and the ESCRT-III associated protein Alix were found to competitively associate with Cep55 (a multimeric cell division protein essential for late stage cell division) to facilitate recruitment of ESCRT-III and Vps4 for abscission of the two daughter cells (Carlton & Martin-Serrano, 2007; Morita et al., 2007). The role of ESCRT-II in cytokinesis is unclear, although studies conducted by Langelier et al., 2006 indicate that Vps22 of ESCRT-II is located on the centrosomes and is involved in the maturation of these organelles. The mechanisms behind ESCRT mediated scission and their role in microtubule disassembly have been recently reviewed in detail by Henne et al., 2011 and Roxrud et al., 2010 and will not be further discussed in this review.

3.2.2 Autophagy

In the mammalian system there are two pathways that intersect with the lysosome, the MVB pathway as described in the introduction and the autophagy pathway. To date, three autophagy pathways have been described in higher eukaryotes: microautophagy (MA), chaperone-mediated autophagy (CMA) and macroautophagy (Mizushima et al., 2008; Cuervo, 2010). Microautophagy was originally described in yeast, but is not yet well characterised in other eukaryotes (Marzella et al., 1981). In this pathway, the lysosome invaginates and internalizes cytosolic components, which are subsequently degraded in the lumen of the lysosome. Chaperone-mediated autophagy is a more selective autophagy that does not involve vesicle formation but rather a direct translocation of a specific set of proteins across the lysosomal membrane. The cytosolic chaperone hsc70, a major component of the CMA pathway recognises the pentapeptide 'KFERQ' sequence in proteins destined for lysosomal degradation (Sahu et al., 2011). The lysosome-associated protein type 2A (LAMP2A) binds and translocates the KFERQ proteins to the lysosome, through a yet-unclear-mechanism (Orenstein & Cuervo, 2010; reviewed by Shpilka & Elazar, 2011). A recent study has identified a new macroautophagy-like degradation pathway that is distinct from CMA and occurs in lysosomes (Orenstein & Cuervo, 2010). Endosomal microautophagy was shown by Sahu et al., 2011 to occur during MVB formation and requires both ESCRT-I and -III, as well as hsc70 for delivery of KFERQ proteins from the cytosol into MVBs. This study provided fresh insights into the mechanisms of autophagy in mammalian model systems and also extended the role of ESCRTs' to degradation of cytosolic compartments. The role of the ESCRTs' is best characterized in macroautophagy and this will be the focus here.

Macroautophagy (henceforth simply referred to as autophagy) is a bulk degradation pathway responsible for the removal of damaged organelles and for clearance of protein aggregates (reviewed by Mehrpour et al., 2010). The fundamental molecular mechanisms of the autophagy pathway have been extensively studied in yeast, using genetic screening to identify autophagy genes (*atg*) (Klionsky et al., 2003). Subsequent inactivation of *atg* orthologues in higher eukaryotes has shown that the autophagic machinery is highly conserved. The autophagic pathway involves multiple steps: (i) sequestration of cytoplasmic constituents by a double membrane phagophore, resulting in the formation of an autophagosome and (ii) direct fusion of autophagosomes with the lysosome, where the cytoplasmic material is degraded in the resulting autolysosome or alternatively (iii) fusion of the autophagosome with the MVB compartment, forming a hybrid component termed an amphisome, which then fuses with the lysosome (Lawrence & Brown, 1992; Berg et al., 1998; Liou et al., 1997) (Figure 1).

Many age-related neurodegenerative disorders are characterised by an accumulation of ubiquitin-positive aggregates in affected brain regions. Autophagy is necessary for the clearance of these proteins, as aggregates essentially become toxic for postmitotic cells like neurons (reviewed by Eskelinen & Saftig, 2009). Defects in the autophagic pathway are associated with neurodegenerative diseases such as Alzheimer's, Huntington's and Parkinson's diseases. For instance, in Alzheimer's disease (AD) neuronal autophagy is activated in the early stages, however autophagic degradation becomes

impaired as the disease progresses (Boland et al., 2008). Similarly in Huntington's disease (HD), active autophagy helps in the clearance of toxic polyglutamine-containing proteins (Ravikumar et al., 2004). In Parkinson's disease (PD) mutant α -synuclein blocks its own degradation via the chaperone-mediated autophagy pathway resulting in a gain-of-function neurotoxicity (Cuervo et al., 2004).

Studies conducted using slime moulds, nematodes, flies and mammals as model systems to study neurodegenerative disease have revealed that the ESCRT machinery plays a role in autophagy. Genetic disruption of ESCRT-I, -II and -III in mammalian and *Drosophila* cells leads to an increase in autophagosomes and toxic protein aggregates increase the severity of HD (Lee et al., 2009). Similarly, in rodent cortical neurons, loss of the CHMP2B subunit leads to an accumulation of autophagosomes (Lee et al., 2007). Autophagosome and amphisome accumulation was also observed in HeLa cells when Tsg101 and CHMP3/Vps24 were knocked down or CHMP2B was disrupted (Lee et al., 2007). Consistent with the above data, downregulation of Vps4 in HeLa cells resulted in autophagosome accumulation, impaired degradation of autophagy substrates and impaired delivery of endosomal constituents to autophagosomes (Nara et al., 2002). The observed increase in autophagosomes suggests that there is either an enhanced initiation of autophagy in the cell or a decreased autophagic flux. The ESCRT machinery is therefore predicted to be involved in one or more key stages of the autophagic pathway. The possibilities include: (i) ESCRTs' are involved in signalling pathways that induce autophagy, (ii) ESCRTs' are required for phagophore closure or (iii) ESCRTs' are involved in the fusion of autophagosomes with the lysosome and/or the fusion of the autophagosomes with the MVB (reviewed by Rusten & Stenmark, 2009).

To date, little is known about the underlying mechanisms allowing the ESCRTs' to mediate fusion of autophagosomes with the MVB compartment and lysosomes. It has been shown that tethering of lysosomes to endosomes and autophagosomes is mediated by Rab7 (Bucci et al., 2000; Gutierrez et al., 2004; Jager et al., 2004) and the HOPS complex, which brings the membranes in close proximity (Wurmser et al., 2000; Seals et al., 2000; reviewed by Metcalf & Isaacs, 2010). ESCRT proteins interact directly with the HOPS complex which binds Rab7, as determined by a recent study which revealed that mutant CHMP2B (an ESCRT-III subunit) leads to impaired recruitment of Rab7 (Urwin et al., 2010). This suggests that functional ESCRTs' are required either for recruiting the vesicular fusion machinery to the MVB compartment or for delivery of the fusion machinery to lysosomes or autophagosomes. A number of other proteins are also implicated in autophagosome fusion with endosomes/lysosomes including UVRAG, Rubicon and LAMP-2. It is not yet known whether the ESCRT machinery has an effect on these proteins and processes.

3.2.3 Downregulation of receptor-mediated signaling

Receptor tyrosine kinases (RTKs) are growth factor receptors that play an important regulatory role in controlling cell growth, proliferation, differentiation, survival and metabolism in several tissues and organs (Hunter, 2000; Pawson et al., 2001). Dysfunction of RTKs or mutations in key components of their downstream signaling pathways results in a variety of diseases, such as cancer, diabetes, immune deficiencies and cardiovascular disorders (Blume-Jensen & Hunter, 2001). EGFR is one of the best studied RTKs, and its uncontrolled signaling is associated with the development of a number of human cancers, including mammary carcinomas, squamous carcinomas and glioblastomas (Hunter, 2000; Pawson et al., 2001). The multivesicular body pathway silences RTK signaling via lysosome sequestration and degradation and thus plays an important role in modulating the amplitude and kinetics of amide signaling pathways from activated receptors (Saksena et al., 2007; Hurley & Emr, 2006; Williams & Urbe, 2007). Defects in ESCRT-mediated sorting of these receptors to lysosomal degradation pathways can thus lead to sustained receptor signaling either because of prolonged residence and activity in the endosomal membrane or as a result of increased recycling of the receptors to the plasma membrane.

Drosophila studies have shown that EGFR degradation is impaired and signalling is prolonged by dysfunctional ESCRT-0 (Hrs) (Lloyd et al., 2002), ESCRT-I (Tsg101) (Vaccari & Bilder, 2005) or ESCRT-II (Vps25) (Thompson et al., 2005). In mammals, depleting Tsg101 causes sustained EGFR signaling (Bache et al., 2006), whereas depletion of CHMP3 (ESCRT-III) (Bache et al., 2006) or Eap30 (ESCRT-II) (Malerod et al., 2007) causes delayed EGFR degradation but not sustained signaling (Table 2). Sustained signaling observed in ESCRT-0, -I and -II *Drosophila* mutants and after ESCRT-I depletion in mammals may result from increases in the residence time of receptors in the endosomal membrane and their recycling back to the plasma membrane. Mutations in ESCRT-III subunits do not cause sustained signaling (Bache et al., 2006), possibly because ESCRT-III recruitment occurs after signal termination. This may also explain why ESCRT-III subunits so far have not been implicated in cancer.

The Notch signaling pathway is highly conserved from *Drosophila* to humans and plays a central role in the normal development of many tissues and cell types. It controls various effects on differentiation, survival, and/or proliferation that are highly dependent on signal strength and cellular context. Dysfunction of the Notch signaling pathway leads to many human diseases such as lung and skin cancer (Radtke & Raj, 2003; Allenspach et al., 2002). Studies in *Drosophila* have shown that Notch signaling is terminated via lysosomal degradation suggesting a role for the ESCRT machinery in the regulation of Notch. In *Drosophila*, depletion of Hrs or mutation of Tsg101 or Vps25 leads to an accumulation of the cell-surface receptors Notch, Delta, Thickveins and EGFR (Thompson et al., 2005; Vaccari & Bilder, 2005; Moberg et al., 2005). Notch accumulation stimulates cell proliferation in the eye disc (Chao et al., 2004; Tsai & Sun, 2004) and results in overgrowth phenotypes in surrounding wild-type cells via the JAK/STAT pathway. Furthermore, inactivation of Tsg101

or Vps5 in *Drosophila* results in loss of epithelial cell polarity, which is associated with malignant transformation, suggesting that ESCRT components have a role in organizing the actin and/or microtubule cytoskeleton (Thompson et al., 2005; Vaccari & Bilder, 2005; Moberg et al., 2005; Saksana & Emr, 2009). In summary, there is growing evidence that implicates functional ESCRTs' in suppressing malignant transformation and preventing cancer.

4 The roles of ESCRTs' in disease

4.1 Neurodegenerative diseases

The most direct evidence that ESCRT dysfunction causes neurodegenerative disease comes from the identification of autosomal dominant *CHMP2B* mutations found to cause a rare form of frontotemporal dementia (FTD3) (Skibinski et al., 2005) and amyotrophic lateral sclerosis (ALS) (Parkinson et al., 2006). FTD is the second most common form of early-onset dementia after Alzheimer's disease (Ratnavalli et al., 2002; Harvey et al., 2003) and is characterised by the presence of either tau neurofibrillary tangles or ubiquitin deposits. FTD with the presence of tau or ubiquitin pathology is termed FTL-D-U (frontotemporal lobar degeneration with ubiquitin-immunoreactive inclusions) (Neary et al., 2005). Both FTL-D-U and ALS are characterised by abnormal accumulation of ubiquitin-positive protein deposits (including TDP-43) that contain p62, tau and α -synuclein-negative neuronal cytoplasmic inclusions (Arai et al., 2006; Neumann et al., 2006). The adapter protein p62 is commonly found in protein inclusions associated with neurodegenerative disease (Talbot & Ansoerge, 2006), it binds polyubiquitin (Vadlamudi et al., 1996) and interacts with the autophagic associated protein Atg8/LC3 (Bjorkoy et al., 2005; Pankiv et al., 2007). Collectively, these data implicate p62 as a link between protein accumulation and aggregation with autophagy-mediated clearance (reviewed by Saksena & Emr, 2009). Similarly, ESCRT-depleted cells and cells overexpressing CHMP2 in flies, mice and humans, showed impaired autophagic degradation leading to an accumulation of autophagosomes and protein aggregates containing p62, thereby contributing to the pathogenesis of FTD3. A recent study has shown that deletion of the ESCRT proteins Tsg101 and Vps24 resulted in accumulation of TDP-43, suggesting that impaired MVB function could have a role in TDP-43 aggregate formation in FTL-D-U and ALS (Filimonenko et al., 2007). Furthermore, Vps24 was found to be essential in the clearance of expanded polyglutamine aggregates associated with Huntington's disease (Table 2) (Filimonenko et al., 2007). Collectively, these data suggest that efficient autophagic degradation requires functional ESCRTs' and dysfunction of this machinery is associated with neurodegenerative phenotypes and disorders.

Several indirect links also implicate the ESCRTs' in various neurodegenerative disorders, and several ESCRT-interacting proteins are products of genes that are associated with inherited forms of neurodegeneration (reviewed by Stuffers et al., 2009a). For instance, in mice, a null mutation in Mahoganin, an E3 ubiquitin ligase that ubiquitinates Tsg101, causes spongiform neurodegeneration, a recessively transmitted prion-like disease (Kim, et al., 2007; Jiao et al., 2009). Two putative ESCRT-III interacting proteins, spartin and spastin are mutated in spastic paraplegia, an inherited neurodegenerative disease that paralyzes the lower limbs (Reid et al., 2005). The exact mechanism of CHMP4 contribution to this disease remains unclear and requires further investigation. Finally, Niemann-Pick disease type C is an inherited neurodegenerative disorder characterized by a disruption of lipid trafficking and is caused by a mutation in either of the two genes, *npc1* and *npc2* (reviewed by Eskelinen & Saftig, 2009). A dominant-negative mutant of Vps4 was found to cause an accumulation of ubiquitinated NPC1 (Ohsaki et al., 2006). Together, these data indicate that dysregulation of ESCRT pathways may contribute to a broad spectrum of degenerative diseases.

4.2 Cancer

The first hint that ESCRTs' play a role in cancer came from the identification of *Tsg101* and *Vps37A* as tumour suppressor genes on the basis that they map to chromosomal regions deleted or mutated in cancer (Li & Cohen, 1996; Xu et al., 2003). Genomic deletions and splice variants of *Tsg101* were found in sporadic forms of breast cancer (Li et al., 1997) and other malignancies such as myeloid leukaemia and prostate cancer (Table 2) (Sun et al., 1997; Lin et al., 1998). In addition, *Vps37A* expression in hepatocellular carcinomas was found to be dramatically reduced or undetected suggesting that *Vps37A* may be a potential tumour suppressor (Xu et al., 2003). Similar results were observed with CHMP1A, as overexpression of this protein inhibited cell growth and tumour formation in human pancreatic tumor cells (Li et al., 2009).

Mutations that prevent c-Cbl-mediated ubiquitination of EGFRs and thereby inhibit ESCRT-mediated receptor down-regulation are associated with a number of cancers, particularly acute myeloid leukemia. For example, a mutant EGFR lacking only the direct c-Cbl-binding site transduces stronger mitogenic signals when compared to the wild-type receptor (Waterman et al., 2002; Saksena & Emr, 2009). The c-Met RTK (also known as HGFR) regulates invasive growth and is critical for normal development and wound repair. Its overexpression causes uncontrolled proliferation and growth and consequently is associated with a variety of human cancers (Haddad et al., 2001). In part c-Cbl-mediated ubiquitination controls cellular c-Met levels and therefore ubiquitination and functional ESCRTs' are needed to avoid c-Met-related malignant transformation (Peschard et al., 2001).

Collectively, the foregoing studies indicate that the ESCRTs' have a negative regulatory role in growth receptor signaling, however several independent studies have shown that ESCRTs' also have a positive role in growth factor

signaling. For instance, Tsg101 was recently found to be overexpressed, rather than reduced in breast, thyroid, ovarian and colon cancer (Ma et al., 2008). Furthermore, depletion of Tsg101 prevented tumorigenicity in several cancer lines (Zhu et al., 2004). To further support ESCRTs' positive role in oncogenic signaling, the ESCRT-0 component Hrs was found to be essential for cell proliferation and tumorigenesis in both HeLa and mouse fibroblast cells (Toyoshima et al., 2007).

A positive regulatory role in growth factor signalling for the ESCRTs' has also been observed in *Drosophila melanogaster* (Vaccari et al., 2005; Thompson et al., 2005; Moberg et al., 2005; Vaccari et al., 2009; Herz et al., 2006; Rodahl et al., 2009). For example, *Tsg101* is essential for normal cell growth and cell survival in the fruit fly and clonal loss of this gene in epithelial cells causes hyperplasia of surrounding tissue despite the mutant cells dying via apoptosis (Moberg et al., 2005; reviewed by Stuffers et al., 2009a). Loss of Vps25 causes a similar effect, whereas loss of Hrs is without effect (Vaccari & Bilder, 2005; Thompson et al., 2005). It is important to note that the proapoptotic signaling pathways Hippo, JNK and Hid are activated in the Vps25 *Drosophila* mutants. Expression of the caspase inhibitor p35 in the Vps25 mutant cells restores cell growth and even results in overgrowth, suggesting that mutations in both the ESCRT pathway and the apoptotic pathway are required for overgrowth. Blocking apoptosis by expressing *Ark* (an essential component of the apoptotic pathway) or *Diap1* (*Drosophila* inhibitor of apoptosis protein 1), again results in overgrowth of the Vps25 mutant tissue. Collectively, these results suggest that the ESCRTs' in *Drosophila* do not act as conventional tumor suppressors.

Overall, the ESCRTs' have been implicated in both positive and negative roles in growth factor receptor signaling and cancer, suggesting that the exact role of the ESCRTs' in tumorigenesis may be cell-type and context-dependent. Alternatively, ESCRT-mediated actions in controlling cell proliferation may reflect diverse endosomal sorting roles on a broad range of molecular targets with many different roles in cellular homeostasis (reviewed by Lobert & Stenmark, 2011). Further research needs to be conducted using different model systems to better understand the complex roles of the ESCRTs' in signaling and cell proliferation. More specifically, future studies need to address whether ESCRTs' act as genuine tumour suppressors in mammals, since at this stage this is still unclear.

4.3 Infectious diseases

4.3.1 Microbial infections

The endocytic and autophagic pathways play an important role in innate immunity. Multiple studies have now shown that these host cell pathways can be manipulated by viruses and microorganisms in order to facilitate infection (von Schwedler et al., 2003; Vieira et al., 2004; Philips et al., 2008; Morita & Sundquist, 2004; Martin-Serrano & Marsh, 2007; McCullough et al., 2008). ESCRTs' play an important role in degenerative endosomal trafficking, so it is not surprising that they are involved in killing many microorganisms. For example, functional ESCRTs' have been shown to restrict mycobacterial growth and infection (Philips et al., 2008). Mycobacteria may invade macrophages and are able to survive and replicate intracellularly due to their ability to prevent fusion of bacteria-containing phagosomes with lysosomes. In both the *Drosophila* model system, and in mammalian macrophages, mutation of ESCRTs' renders cells susceptible to mycobacterial infections. Similarly, overexpression of Vps4 in the host cell results in deficient differentiation and virulence of the intracellular protozoal pathogen *Leishmania major* (Table 2) (Vieira et al., 2004; Philips et al., 2008). Furthermore, autophagosome accumulation was also observed, and both functional endosomal and autophagic pathways are required for optimal *L. major* virulence and infection (Besteiro et al., 2006). The mechanisms by which ESCRTs' mediate resistance to microbial infection have not been defined. It is possible that ESCRTs' are required for the delivery of the pathogen to the lysosome, more specifically having a role in phagosome maturation and fusion between the phagosome and lysosome. Like the involvement of the ESCRTs' in the autophagic pathway these results suggest that the ESCRTs' affect multiple cellular trafficking events. The finding that ESCRT components restrict the growth of intracellular microbial pathogens means that they can now be considered as therapeutic targets for treatment of these infections which cause millions of deaths every year.

In the case of eukaryotic pathogens, the ESCRTs' of the pathogen may also play important roles in virulence. *Candida albicans* causes opportunistic fungal infections and its ESCRT proteins have multiple roles in pathogenesis. The fungal ESCRT components are suggested to contribute to diverse fungal functions including cell signaling, nutrient acquisition and possibly cell wall architecture (Cornet et al., 2005; Wolf et al., 2010). However the role of ESCRTs' in candidiasis is not yet fully understood.

Complex	Component	Dysfunction/disease	Pathogenesis	Model systems
Cancer				
ESCRT-0	Hrs (Vps27)	Tumourigenesis and metastatic potential	Hrs depletion is associated with the upregulation of E-cadherin and reduced β -catenin signalling ¹	Human cancer cells, MEF, mice
ESCRT-0 associated	Hrs (Vps27)	Benign brain tumours (e.g. Schwannomas, meningiomas, ependymomas)	Interaction with neurofibromatosis 2 tumour suppressor protein schwannomin/merlin, regulating STAT signalling ^{13, 14}	Human cancer cells, rat cells
ESCRT-I	Vps37A	Hepatocellular ca. (HCC) and metastasis	Growth inhibitory protein, suppressing proliferation, transformation and invasion; strongly reduced levels in HCC ²	Human tissue and cancer cells
	Tsg101 (Vps23)	Ovarian cancer	Up regulation of Tsg101: suppression of p21 expression and posttranslational regulation through MAPK signalling ^{3, 4}	Human tissue and cancer cells
	Tsg101 (Vps23)	Mammary cancer	Overexpression of Tsg101: increased signalling through MAPK ⁵	Human tissue, transgenic mice
	Tsg101 (Vps23)	Papillary thyroid cancer, gastrointestinal stromal tumours	Overexpression of Tsg101 (consequences not known) ^{6, 7}	Human tissue
ESCRT-I/II	Erupted Tsg101/Vps25	Neoplastic transformation (ovary and imaginal discs), over-proliferation of adjacent WT cells	Enhanced Notch and growth factor signalling in mutant cells ^{8, 9, 10}	<i>Drosophila</i>
ESCRT-III	CHMP3 (Vps24)	Prostate cancer	CHMP3 induces neuroendocrine cell differentiation ¹¹	Human cells
	CHMP3 (Vps24)	Non-small cell lung cancer	CHMP3 has a functional role in neuroendocrine cell differentiation ¹²	Human cancer cells
ESCRT-III associated	CHMP1A	Ductal pancreatic cancer	Tumour suppressor, regulating tumour growth potentially through p53 signalling pathway ¹⁵	Human cells, mice
Neurodegenerative diseases				
ESCRT-I/III	Tsg101 (Vps23) / CHMP3 (Vps24) / CHMP2B	Neurodegeneration (FTLD-U, ALS, Huntington's disease (HD))	Reduced autophagic degradation, accumulation of Ub-protein aggregates containing TDP-43; reduced clearance of Huntington-positive inclusions ¹⁸	Human cells, mouse cells
ESCRT-I associated	Tsg101 (Vps23)	Spongiform neurodegeneration (hallmark of prion disease)	E3 ubiquitin-protein ligase Mahogunin ubiquitinates Tsg101; depletion of Mahogunin disrupts endosomal trafficking ²¹	Human cells, rat tissue
ESCRT-I associated	Tsg101 (Vps23)	Charcot-Marie-Tooth disease (CMT1C)	Interaction with SIMPLE; SIMPLE plays a role in the lysosomal sorting of plasma membrane proteins ²²	
ESCRT-III	CHMP2B (Vps2)	FTLD-U and ALS	Disruption of endosomal trafficking, protein accumulation ^{16, 17}	Human cells
	CHMP4B (Snf7-2) / CHMP2B	Neurodegeneration (FTLD-U, ALS)	Accumulation of autophagosomes; failure of mutant CHMP2B to dissociate properly leading to	<i>Drosophila</i> , mice

			dysfunctional ESCRT-III on late endosomes ²⁰	
ESCRT-III associated	CHMP1B	Hereditary spastic paraplegia	Interaction with spastin; spastin mutation results in disruption of endosomal trafficking ²³	Monkey cells
Infection				
ESCRT-0	Hrs (Vps27)	<i>Mycobacterium marinum</i>	Inability to recruit Hrs contributes to the arrest of phagosomal maturation induced by pathogenic mycobacteria Hrs ²⁴	Mouse cells, monkey cells
ESCRT-0/I/III and associated	Vps27/Vps28/Vps32, Vps4, Bro1, Doa4	<i>Candida albicans</i>	ESCRT depletion reduces virulence of <i>C. albicans</i> ^{25, 26}	Various model systems
ESCRT-I/III and associated	Tsg101, Vps25/Vps36, Vps24/Vps20, Vps4	<i>Mycobacterium tuberculosis</i>	The ESCRT machinery directly acts on the bacterial phagosome ²⁷	<i>Drosophila</i> , macrophages
ESCRT-I/III, associated	Tsg101, CHMPs, AIP1/Alix	RNA virus infections (e.g. HIV-1, Ebola, EIAV, Rabies, Lassa)	Hijacking the ESCRT machinery via L-domain motifs, virus budding via MVE pathway ²⁸	Human cells
ESCRT-III associated	Vps4	<i>Leishmania major</i>	Dominant-negative of Vps4 results in deficient differentiation and virulence of <i>Leishmania major</i> ²⁹	Parasites
Other				
ESCRT-III	CHMP4B (Snf7-2)	Autosomal dominant cataract	Gain-of-function defects CHMP4B triggers loss in lens transparency ³⁰	Human cells

Table 2. ESCRT-associated diseases in various model systems

(Modified from Stuffers et al., 2009a)

References: ¹Toyoshima et al., 2007; ²Xu et al., 2003; ³Young et al., 2007; ⁴Young et al., 2007; ⁵Oh et al., 2007; ⁶Liu et al., 2002; ⁷Koon et al., 2004; ⁸Moberg et al., 2005; ⁹Vaccari & Bilder et al., 2005; ¹⁰Thompson et al., 2005; ¹¹Wilson et al., 2001; ¹²Walker et al., 2006; ¹³Gutmann et al., 2001; ¹⁴Scoles et al., 2002; ¹⁵Li et al., 2008; ¹⁶Parkinson et al., 2006; ¹⁷Skibinski et al., 2005; ¹⁸Filimonenko et al., 2007; ¹⁹Rusten et al., 2007; ²⁰Lee et al., 2007; ²¹Kim et al., 2007; ²²Shirk et al., 2005; ²³Reid et al., 2005; ²⁴Vieira et al., 2004; ²⁵Cornet et al., 2005; ²⁶Wolf et al., 2011; ²⁷Babst et al., 1998; ²⁸Spitzer et al., 2006; ²⁹Besteiro et al., 2006; ³⁰Shiels et al., 2007.

4.3.2 Viral infections

The beneficial role of ESCRTs' in protecting against intracellular bacteria is reversed in viral infections. Many membrane-enveloped viruses hijack the ESCRT machinery to bud out of host cells. Retroviruses (HIV-1), filoviruses (Ebola virus), rhabdoviruses and arenaviruses encode short sequence motifs termed L-domains (late domains) within their structural (Gag) polyproteins that are essential for the release of assembled viruses from the host cells (reviewed by Carlton & Martin-Serrano, 2009; Stuffers et al., 2009b). The P(S/T)AP motif found on the HIV-1 Gag protein for example binds directly to the UEV domain of Tsg101 of ESCRT-I. Even though HIV-1 budding is normally ESCRT-I dependent, if Tsg101 is unavailable, the virus alternatively binds to Alix via the YPxL domain and buds (Stark et al., 2003). Both ESCRT-I and Alix can independently recruit ESCRT-III, which together with Vps4 are required for efficient virus budding. Recent studies have shown that ESCRT-III and Vps4 can be recruited independently of either Tsg101 or Alix by the herpes simplex virus type-1 (Pawliczek & Crump et al., 2009) and the hepatitis C virus (Corless et al., 2010). ESCRT-II was found not to be essential for HIV- budding (Langelier et al., 2006), however ESCRT-II was discovered recently to be essential for release of the avian sarcoma virus (Pincetic et al., 2008). Other viruses such as the rabies virus can indirectly recruit the ESCRTs' by using the PPxY motif to specifically recruit WW-domain-containing E3 ubiquitin ligases of the Nedd4 family (Kikonyogo et al., 2001). Disruption of ESCRT function by RNA interference or dominant-negative Vps4 arrests viral release at the plasma membrane (Garrus et al., 2001; Martin-Serrano & Neil, 2011; Demirov et al., 2002; Strack et al., 2003; reviewed by Carlton & Martin-Serrano, 2009). Collectively, this data confirms that different enveloped viruses require specific proteins for budding and that the ESCRT machinery regulates viral release from the plasma membrane.

5 Conclusions

The ESCRT machinery is ubiquitous in eukaryotes and has been highly conserved in evolution due to its vital functions including endocytosis, cytokinesis and autophagy. Our understanding of the ESCRTs' roles in endocytosis, receptor downregulation, membrane deformation and scission has made great progress over the past few years and the study of various model systems has contributed significantly to this. We know that the ESCRTs', in particular ESCRT-III and Vps4 have an intrinsic budding and scission activity that is focused on the neck of the ILVs and that they are important regulators of cytokinesis (Spitzer et al., 2006; Obita et al., 2007; Carlton & Martin-Serrano, 2007). Model systems have implicated the ESCRTs' in autophagic fusion events and in endosome-lysosome degradation. Impaired function of these pathways causes various neurodegenerative disorders, cancers and is implicated in microbial infections. Genetic disruption of ESCRT-I, -II and -III in mammalian and *Drosophila* systems has been shown to result in an accumulation of autophagosomes and toxic aggregates which accelerates neurodegeneration (Lee et al., 2007). Mutations in the ESCRT-III subunit CHMP2B, have been shown to cause FTD3 (Skibinski et al., 2005) and ALS (Parkinson et al., 2006). Furthermore, the ESCRTs' and their associated proteins are also indirectly implicated in causing spongiform neurodegeneration (Kim, et al., 2007; Jiao et al., 2009), spastic paraplegia (Reid et al., 2005) and Niemann-Pick type C neurodegeneration (Ohsaki et al., 2006). Sustained receptor signaling is a key event in carcinogenesis, and Tsg101 (Li et al., 1997, Sun et al., 1997; Lin et al., 1998), Vps37A (Xu et al., 2003) and CHMP1A (Li et al., 2009) have been identified as potential tumor suppressors. However several other subsequent studies found Tsg101 to play a role in cell cycle control, a conclusion that is in contradiction to the tumor suppressor properties of Tsg101 (Zhu et al., 2004). In *Drosophila* ESCRT-I and -II were found to behave as tumor suppressors (Li & Cohen, 1996; Xu et al., 2003; Li et al., 2008). Tissues expressing mutant ESCRT-I or -II were found to form tumors that are largely attributable to the cell non-autonomous stimulation of proliferation caused by excessive cytokine production by the mutant cells. This is triggered by overactive Notch signaling from endosomes, signifying that the ESCRT machinery is crucial for silencing Notch signaling and thereby for tumor suppression in flies. It has not yet been clarified whether this is the case in mammals. The ESCRTs' were found to have a beneficial role in innate immunity by restricting microbial growth and infection (von Schwedler et al., 2003; Vieira et al., 2004; Philips et al., 2008; Morita & Sundquist, 2004; Martin-Serrano & Marsh, 2007; McCullough et al., 2008). The ESCRTs' however, are turned against the host in viral infections. Several viruses, such as HIV-1 use the ESCRT components to bud out cells and cause infection (reviewed by Carlton & Martin-Serrano, 2009; Stuffers et al., 2009b). Further dissection of the roles of the ESCRTs' in these events will shed light on the basic mechanism of vesicular traffic and provide new insights into disease pathogenesis and preventative and therapeutic strategies.

6 Acknowledgments

Due to the vast body of primary research that has contributed to our understanding of endocytosis, autophagy and ESCRTs', we have been unable to cite many research papers in the field and we apologise to those authors whose articles are not directly cited. J. Ilievska was the recipient of an Australian postgraduate award scholarship (APA). This work was supported by grants from the Australian Research Council and the Thyne Reid Memorial Trusts. The authors are grateful to F. Nesci for assistance with preparing the Figures and S. Aracic for proofreading the work.

7 References

- Agromayor, M., Carlton, J. G., Phelan, J. P., Matthews, D. R., Carlin, L. M., Ameer-Beg, S., Bowers, K. & Martin-Serrano, J.; (2009). Essential role of hIST1 in cytokinesis. *Mol Biol Cell*, **20**, 5, (Mar, 2009), 1374-1387.
- Alam, S. L., Sun, J., Payne, M., Welch, B. D., Blake, B. K., Davis, D. R., Meyer, H. H., Emr, S. D. & Sundquist, W. I.; (2004). Ubiquitin interactions of NZF zinc fingers. *EMBO J*, **23**, 7, (Apr, 2004), 1411-1421.
- Allenspach, E. J., Maillard, I., Aster, J. C. & Pear, W. S.; (2002). Notch signaling in cancer. *Cancer Biol Ther*, **1**, 5, (Sep, 2002), 466-476.
- Arai, T., Hasegawa, M., Akiyama, H., Ikeda, K., Nonaka, T., Mori, H., Mann, D., Tsuchiya, K., Yoshida, M., Hashizume, Y. & Oda, T.; (2006). TDP-43 is a component of ubiquitin-positive tau-negative inclusions in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. *Biochem Biophys Res Commun*, **351**, 3, (Dec, 2006), 602-611.
- Babst, M., Davies, B. A. & Katzmam, D. J.; (2011). Regulation of Vps4 during MVB sorting and cytokinesis. *Traffic*, **12**, 10, (Oct, 2011), 1298-1305.
- Babst, M., Sato, T. K., Banta, L. M. & Emr, S. D.; (1997). Endosomal transport function in yeast requires a novel AAA-type ATPase, Vps4. *EMBO J*, **16**, 8, (Apr, 1997), 1820-1831.
- Babst, M., Wendland, B., Estepa, E. J. & Emr, S. D.; (1998). The Vps4 AAA ATPase regulates membrane association of a Vps protein complex required for normal endosome function. *EMBO J*, **17**, 11, (Jun, 1998), 2982-2993.
- Babst, M., Katzmam, D. J., Estepa-Sabal, E. J., Meerloo, T. & Emr, S. D.; (2002a). ESCRT-III: an endosome-associated heterooligomeric protein complex required for MVB sorting. *Dev Cell*, **3**, 2, (Aug, 2002), 271-282.
- Babst, M., Katzmam, D. J., Snyder, W. B., Wendland, B. & Emr, S. D.; (2002b). Endosome-associated complex, ESCRT-II, recruits transport machinery for protein sorting at the multivesicular body. *Dev Cell*, **3**, 2, (Aug, 2002), 283-289.
- Bache, K. G., Stuffers, S., Malerod, L., Slagsvold, T., Raiborg, C., Lechardeur, D., Walchli, S., Lukacs, G. L., Brech, A. & Stenmark, H.; (2006). The ESCRT-III subunit hVps24 is required for degradation but not silencing of the epidermal growth factor receptor. *Mol Biol Cell*, **17**, 6, (Jun, 2006), 2513-2523.
- Bajorek, M., Morita, E., Skalicky, J. J., Morham, S. G., Babst, M. & Sundquist, W. I.; (2009a). Biochemical analyses of human IST1 and its function in cytokinesis. *Mol Biol Cell*, **20**, 5, (Mar, 2009), 1360-1373.
- Bajorek, M., Schubert, H. L., McCullough, J., Langelier, C., Eckert, D. M., Stubblefield, W. M., Uter, N. T., Myszk, D. G., Hill, C. P. & Sundquist, W. I.; (2009b). Structural basis for ESCRT-III protein autoinhibition. *Nat Struct Mol Biol*, **16**, 7, (Jul, 2009), 754-762.
- Berg, T. O., Fengsrud, M., Stromhaug, P. E., Berg, T. & Seglen, P. O.; (1998). Isolation and characterization of rat liver amphisomes. Evidence for fusion of autophagosomes with both early and late endosomes. *J Biol Chem*, **273**, 34, (Aug, 1998), 21883-21892.
- Besteiro, S., Williams, R. A., Morrison, L. S., Coombs, G. H. & Mottram, J. C.; (2006). Endosome sorting and autophagy are essential for differentiation and virulence of *Leishmania major*. *J Biol Chem*, **281**, 16, (Apr, 2006), 11384-11396.
- Bilodeau, P. S., Winistorfer, S. C., Kearney, W. R., Robertson, A. D. & Piper, R. C.; (2003). Vps27-Hse1 and ESCRT-I complexes cooperate to increase efficiency of sorting ubiquitinated proteins at the endosome. *J Cell Biol*, **163**, 2, (Oct, 2003), 237-243.
- Bishop, N., Horman, A. & Woodman, P.; (2002). Mammalian class E vps proteins recognize ubiquitin and act in the removal of endosomal protein-ubiquitin conjugates. *J Cell Biol*, **157**, 1, (Apr, 2002), 91-101.
- Bishop, N. E.; (1997). An update on non-clathrin-coated endocytosis. *Rev Med Virol*, **7**, 4, (Dec, 1997), 199-209.
- Bishop, N. E.; (2003). Dynamics of endosomal sorting. *Int Rev Cytol*, **232**, 1-57.
- Bjorkoy, G., Lamark, T., Brech, A., Outzen, H., Perander, M., Overvatn, A., Stenmark, H. & Johansen, T.; (2005). p62/SQSTM1 forms protein aggregates degraded by autophagy and has a protective effect on huntingtin-induced cell death. *J Cell Biol*, **171**, 4, (Nov, 2005), 603-614.
- Blanc, C., Charette, S. J., Mattei, S., Aubry, L., Smith, E. W., Cosson, P. & Letourneur, F.; (2009). *Dictyostelium* Tom1 participates to an ancestral ESCRT-0 complex. *Traffic*, **10**, 2, (Feb, 2009), 161-171.
- Blume-Jensen, P. & Hunter, T.; (2001). Oncogenic kinase signalling. *Nature*, **411**, 6835, (May, 2001), 355-365.
- Boland, B., Kumar, A., Lee, S., Platt, F. M., Wegiel, J., Yu, W. H. & Nixon, R. A.; (2008). Autophagy induction and autophagosome clearance in neurons: relationship to autophagic pathology in Alzheimer's disease. *J Neurosci*, **28**, 27, (Jul, 2008), 6926-6937.
- Bucci, C., Thomsen, P., Nicoziani, P., McCarthy, J. & van Deurs, B.; (2000). Rab7: a key to lysosome biogenesis. *Mol Biol Cell*, **11**, 2, (Feb, 2000), 467-480.
- Carlton, J. G. & Martin-Serrano, J.; (2007). Parallels between cytokinesis and retroviral budding: a role for the ESCRT machinery. *Science*, **316**, 5833, (Jun, 2007), 1908-1912.
- Carlton, J. G. & Martin-Serrano, J.; (2009). The ESCRT machinery: new functions in viral and cellular biology. *Biochem Soc Trans*, **37**, 1, (Feb, 2009), 195-199.
- Chao, J. L., Tsai, Y. C., Chiu, S. J. & Sun, Y. H.; (2004). Localized Notch signal acts through eyg and upd to promote global growth in *Drosophila* eye. *Development*, **131**, 16, (Aug, 2004), 3839-3847.
- Chu, T., Sun, J., Saksena, S. & Emr, S. D.; (2006). New component of ESCRT-I regulates endosomal sorting complex assembly. *J Cell Biol*, **175**, 5, (Dec, 2006), 815-823.
- Corless, L., Crump, C. M., Griffin, S. D. & Harris, M.; (2010). Vps4 and the ESCRT-III complex are required for the release of infectious hepatitis C virus particles. *J Gen Virol*, **91**, 2, (Feb, 2010), 362-372.

- Cornet, M., Bidard, F., Schwarz, P., Da Costa, G., Blanchin-Roland, S., Dromer, F. & Gaillardin, C.; (2005). Deletions of endocytic components VPS28 and VPS32 affect growth at alkaline pH and virulence through both RIM101-dependent and RIM101-independent pathways in *Candida albicans*. *Infect Immun*, **73**, 12, (Dec, 2005), 7977-7987.
- Cuervo, A. M.; (2004). Autophagy: many paths to the same end. *Mol Cell Biochem*, **263**, 1-2, (Aug, 2004), 55-72.
- Cuervo, A. M.; (2010). Chaperone-mediated autophagy: selectivity pays off. *Trends Endocrinol Metab*, **21**, 3, (Mar, 2010), 142-150.
- Curtiss, M., Jones, C. & Babst, M.; (2007). Efficient cargo sorting by ESCRT-I and the subsequent release of ESCRT-I from multivesicular bodies requires the subunit Mvb12. *Mol Biol Cell*, **18**, 2, (Feb, 2007), 636-645.
- Demirov, D. G., Orenstein, J. M. & Freed, E. O.; (2002). The late domain of human immunodeficiency virus type 1 p6 promotes virus release in a cell type-dependent manner. *J Virol*, **76**, 1, (Jan, 2002), 105-117.
- Dimaano, C., Jones, C. B., Hanono, A., Curtiss, M. & Babst, M.; (2008). Ist1 regulates Vps4 localization and assembly. *Mol Biol Cell*, **19**, 2, (Feb, 2008), 465-474.
- Elia, N., Sougrat, R., Spurlin, T. A., Hurley, J. H. & Lippincott-Schwartz, J.; (2011). Dynamics of endosomal sorting complex required for transport (ESCRT) machinery during cytokinesis and its role in abscission. *Proc Natl Acad Sci U S A*, **108**, 12, (Mar, 2011), 4846-4851.
- Eskelinen, E. L. & Saftig, P.; (2009). Autophagy: a lysosomal degradation pathway with a central role in health and disease. *Biochim Biophys Acta*, **1793**, 4, (Apr, 2009), 664-673.
- Field, M. C. & Dacks, J. B.; (2009). First and last ancestors: reconstructing evolution of the endomembrane system with ESCRTs', vesicle coat proteins, and nuclear pore complexes. *Curr Opin Cell Biol*, **21**, 1, (Feb, 2009), 4-13.
- Field, M. C., Gabernet-Castello, C. & Dacks, J. B.; (2007). Reconstructing the evolution of the endocytic system: insights from genomics and molecular cell biology. *Adv Exp Med Biol*, **607**, 84-96.
- Filimonenko, M., Stuffers, S., Raiborg, C., Yamamoto, A., Malerod, L., Fisher, E. M., Isaacs, A., Brech, A., Stenmark, H. & Simonsen, A.; (2007). Functional multivesicular bodies are required for autophagic clearance of protein aggregates associated with neurodegenerative disease. *J Cell Biol*, **179**, 3, (Nov, 2007), 485-500.
- Fujii, K., Hurley, J. H. & Freed, E. O.; (2007). Beyond Tsg101: the role of Alix in 'ESCRTing' HIV-1. *Nat Rev Microbiol*, **5**, 12, (Dec, 2007), 912-916.
- Garrus, J. E., von Schwedler, U. K., Pornillos, O. W., Morham, S. G., Zavitz, K. H., Wang, H. E., Wettstein, D. A., Stray, K. M., Cote, M., Rich, R. L., Myszka, D. G. & Sundquist, W. I.; (2001). Tsg101 and the vacuolar protein sorting pathway are essential for HIV-1 budding. *Cell*, **107**, 1, (Oct, 2001), 55-65.
- Ghazi-Tabatabai, S., Obita, T., Pobbati, A. V., Perisic, O., Samson, R. Y., Bell, S. D. & Williams, R. L.; (2009). Evolution and assembly of ESCRTs'. *Biochem Soc Trans*, **37**, 1, (Feb, 2009), 151-155.
- Gill, D. J., Teo, H., Sun, J., Perisic, O., Veprintsev, D. B., Emr, S. D. & Williams, R. L.; (2007). Structural insight into the ESCRT-I/-II link and its role in MVB trafficking. *EMBO J*, **26**, 2, (Jan, 2007), 600-612.
- Gruenberg, J. & Stenmark, H.; (2004). The biogenesis of multivesicular endosomes. *Nat Rev Mol Cell Biol*, **5**, 4, (Apr, 2004), 317-323.
- Gutierrez, M. G., Munafo, D. B., Beron, W. & Colombo, M. I.; (2004). Rab7 is required for the normal progression of the autophagic pathway in mammalian cells. *J Cell Sci*, **117**, 13, (Jun, 2004), 2687-2697.
- Gutmann, D. H., Haipek, C. A., Burke, S. P., Sun, C. X., Scoles, D. R. & Pulst, S. M.; (2001). The NF2 interactor, hepatocyte growth factor-regulated tyrosine kinase substrate (HRS), associates with merlin in the "open" conformation and suppresses cell growth and motility. *Hum Mol Genet*, **10**, 8, (Apr, 2001), 825-834.
- Haddad, R., Lipson, K. E. & Webb, C. P.; (2001). Hepatocyte growth factor expression in human cancer and therapy with specific inhibitors. *Anticancer Res*, **21**, 6B, (Dec, 2001), 4243-4252.
- Hanson, P. I., Shim, S. & Merrill, S. A.; (2009). Cell biology of the ESCRT machinery. *Curr Opin Cell Biol*, **21**, 4, (Aug, 2009), 568-574.
- Harvey, R. J., Skelton-Robinson, M. & Rossor, M. N.; (2003). The prevalence and causes of dementia in people under the age of 65 years. *J Neurol Neurosurg Psychiatry*, **74**, 9, (Sep, 2003), 1206-1209.
- Henne, W. M., Buchkovich, N. J. & Emr, S. D.; (2011). The ESCRT pathway. *Dev Cell*, **21**, 1, (Jul, 2011), 77-91.
- Herman, E. K., Walker, G., van der Giezen, M. & Dacks, J. B.; (2011). Multivesicular bodies in the enigmatic amoeboid flagellate *Breviata anathema* and the evolution of ESCRT 0. *J Cell Sci*, **124**, 4, (Feb, 2011), 613-621.
- Herz, H. M., Chen, Z., Scherr, H., Lackey, M., Bolduc, C. & Bergmann, A.; (2006). Vps25 mosaics display non-autonomous cell survival and overgrowth, and autonomous apoptosis. *Development*, **133**, 10, (May, 2006), 1871-1880.
- Hierro, A., Sun, J., Rusnak, A. S., Kim, J., Prag, G., Emr, S. D. & Hurley, J. H.; (2004). Structure of the ESCRT-II endosomal trafficking complex. *Nature*, **431**, 7005, (Sep, 2004), 221-225.
- Hong, L., Ning, X., Shi, Y., Shen, H., Zhang, Y., Lan, M., Liang, S., Wang, J. & Fan, D.; (2004). Reversal of multidrug resistance of gastric cancer cells by down-regulation of ZNRD1 with ZNRD1 siRNA. *Br J Biomed Sci*, **61**, 4, 206-210.
- Hunter, T.; (2000). Signaling-2000 and beyond. *Cell*, **100**, 1, (Jan, 2000), 113-127.
- Hurley, J. H. & Emr, S. D.; (2006). The ESCRT complexes: structure and mechanism of a membrane-trafficking network. *Annu Rev Biophys Biomol Struct*, **35**, (Nov, 2006) 277-298.
- Hurley, J. H., Boura, E., Carlson, L. A. & Rozycki, B.; (2010). Membrane budding. *Cell*, **143**, 6, (Dec, 2010), 875-887.

- Hurley, J. H & Hanson, P. I (2010). Membrane budding & scission by the ESCRT machinery : its all in the neck. *Nat Rev Mol Cell Biol*, **11**, 8, 556-566.
- Im, Y. J. & Hurley, J. H.; (2008). Integrated structural model and membrane targeting mechanism of the human ESCRT-II complex. *Dev Cell*, **14**, 6, (Jun, 2008), 902-913.
- Jager, S., Bucci, C., Tanida, I., Ueno, T., Kominami, E., Saftig, P. & Eskelinen, E. L.; (2004). Role for Rab7 in maturation of late autophagic vacuoles. *J Cell Sci*, **117**, 20, (Sep, 2004), 4837-4848.
- Jiao, J., Sun, K., Walker, W. P., Bagher, P., Cota, C. D. & Gunn, T. M.; (2009). Abnormal regulation of TSG101 in mice with spongiform neurodegeneration. *Biochim Biophys Acta*, **1792**, 10, (Oct, 2009), 1027-1035.
- Katzmann, D. J., Babst, M. & 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**, 2, (Jul, 2001), 145-155.
- Katzmann, D. J., Stefan, C. J., Babst, M. & Emr, S. D.; (2003). Vps27 recruits ESCRT machinery to endosomes during MVB sorting. *J Cell Biol*, **162**, 3, (Aug, 2003), 413-423.
- Kikonyogo, A., Bouamr, F., Vana, M. L., Xiang, Y., Aiyar, A., Carter, C. & Leis, J.; (2001). Proteins related to the Nedd4 family of ubiquitin protein ligases interact with the L domain of Rous sarcoma virus and are required for gag budding from cells. *Proc Natl Acad Sci U S A*, **98**, 20, (Sep, 2001), 11199-11204.
- Kim, B. Y., Olzmann, J. A., Barsh, G. S., Chin, L. S. & Li, L.; (2007). Spongiform neurodegeneration-associated E3 ligase Mahogunin ubiquitylates TSG101 and regulates endosomal trafficking. *Mol Biol Cell*, **18**, 4, (Apr, 2007), 1129-1142.
- Klionsky, D. J., Cregg, J. M., Dunn, W. A., Jr., Emr, S. D., Sakai, Y., Sandoval, I. V., Sibirny, A., Subramani, S., Thumm, M., Veenhuis, M. & Ohsumi, Y.; (2003). A unified nomenclature for yeast autophagy-related genes. *Dev Cell*, **5**, 4, (Oct, 2003), 539-545.
- Koon, N., Schneider-Stock, R., Sarlomo-Rikala, M., Lasota, J., Smolkin, M., Petroni, G., Zaika, A., Boltze, C., Meyer, F., Andersson, L., Knuutila, S., Miettinen, M. & El-Rifai, W.; (2004). Molecular targets for tumour progression in gastrointestinal stromal tumours. *Gut*, **53**, 2, (Feb, 2004), 235-240.
- Kostelansky, M. S., Schluter, C., Tam, Y. Y., Lee, S., Ghirlando, R., Beach, B., Conibear, E. & Hurley, J. H.; (2007). Molecular architecture and functional model of the complete yeast ESCRT-I heterotetramer. *Cell*, **129**, 3, (May, 2007), 485-498.
- Kulp, A. & Kuehn, M. J.; (2011). The recognition of {beta}-strand motifs by RseB is required for {sigma}E activity in *Escherichia coli*. *J Bacteriol*, **193**, 22, (Sep, 2011), 6179-6186.
- Lakkaraju, A. & Rodriguez-Boulan, E.; (2008). Itinerant exosomes: emerging roles in cell and tissue polarity. *Trends Cell Biol*, **18**, 5, (May, 2008), 199-209.
- Langelier, C., von Schwedler, U. K., Fisher, R. D., De Domenico, I., White, P. L., Hill, C. P., Kaplan, J., Ward, D. & Sundquist, W. I.; (2006). Human ESCRT-II complex and its role in human immunodeficiency virus type 1 release. *J Virol*, **80**, 19, (Oct, 2006), 9465-9480.
- Lata, S., Schoehn, G., Jain, A., Pires, R., Piehler, J., Gottlinger, H. G. & Weissenhorn, W.; (2008). Helical structures of ESCRT-III are disassembled by VPS4. *Science*, **321**, 5894, (Sep, 2008), 1354-1357.
- Lawrence, B. P. & Brown, W. J.; (1992). Autophagic vacuoles rapidly fuse with pre-existing lysosomes in cultured hepatocytes. *J Cell Sci*, **102**, 3, (Jul, 1992), 515-526.
- Lee, J. A., Liu, L. & Gao, F. B.; (2009). Autophagy defects contribute to neurodegeneration induced by dysfunctional ESCRT-III. *Autophagy*, **5**, 7, (Oct, 2009), 1070-1072.
- Lee, J. A., Beigneux, A., Ahmad, S. T., Young, S. G. & Gao, F. B.; (2007). ESCRT-III dysfunction causes autophagosome accumulation and neurodegeneration. *Curr Biol*, **17**, 18, (Sep, 2007), 1561-1567.
- Leung, K. F., Dacks, J. B. & Field, M. C.; (2008). Evolution of the multivesicular body ESCRT machinery; retention across the eukaryotic lineage. *Traffic*, **9**, 10, (Sep, 2008), 1698-1716.
- Li, J., Belogortseva, N., Porter, D. & Park, M.; (2008). Chmp1A functions as a novel tumor suppressor gene in human embryonic kidney and ductal pancreatic tumor cells. *Cell Cycle*, **7**, 18, (Sep, 2008), 2886-2893.
- Li, J., Orr, B., White, K., Belogortseva, N., Niles, R., Boskovic, G., Nguyen, H., Dykes, A. & Park, M.; (2009). Chmp 1A is a mediator of the anti-proliferative effects of all-trans retinoic acid in human pancreatic cancer cells. *Mol Cancer*, **8**, 7, (Sept, 2008), 2886-2893.
- Li, L. & Cohen, S. N.; (1996). Tsg101: a novel tumor susceptibility gene isolated by controlled homozygous functional knockout of allelic loci in mammalian cells. *Cell*, **85**, 3, (May, 1996), 319-329.
- Li, L., Li, X., Francke, U. & Cohen, S. N.; (1997). The TSG101 tumor susceptibility gene is located in chromosome 11 band p15 and is mutated in human breast cancer. *Cell*, **88**, 1, (Jan, 1997), 143-154.
- Lin, P. M., Liu, T. C., Chang, J. G., Chen, T. P. & Lin, S. F.; (1998). Aberrant TSG101 transcripts in acute myeloid leukaemia. *Br J Haematol*, **102**, 3, (Aug, 1998), 753-758.
- Lindas, A. C., Karlsson, E. A., Lindgren, M. T., Ettema, T. J. & Bernander, R.; (2008). A unique cell division machinery in the Archaea. *Proc Natl Acad Sci U S A*, **105**, 48, (Dec, 2008), 18942-18946.
- Liou, W., Geuze, H. J., Geelen, M. J. & Slot, J. W.; (1997). The autophagic and endocytic pathways converge at the nascent autophagic vacuoles. *J Cell Biol*, **136**, 1, (Jan, 1997), 61-70.

- Liu, R. T., Huang, C. C., You, H. L., Chou, F. F., Hu, C. C., Chao, F. P., Chen, C. M. & Cheng, J. T.; (2002). Overexpression of tumor susceptibility gene TSG101 in human papillary thyroid carcinomas. *Oncogene*, **21**, 31, (Jul, 2002), 4830-4837.
- Lloyd, T. E., Atkinson, R., Wu, M. N., Zhou, Y., Pennetta, G. & Bellen, H. J.; (2002) Hrs regulates endosome membrane invagination and tyrosine kinase receptor signaling in *Drosophila*. *Cell* **108**, 2, (Jan, 2002), 261-269.
- Lobert, V. H. & Stenmark, H.; (2011). Cell polarity and migration: emerging role for the endosomal sorting machinery. *Physiology*, **26**, 3, (Jun, 2011), 171-180.
- Ma, X. R., Edmund Sim, U. H., Pauline, B., Patricia, L. & Rahman, J.; (2008). Overexpression of WNT2 and TSG101 genes in colorectal carcinoma. *Trop Biomed*, **25**, 1, (Apr, 2008), 46-57.
- Makarova, K. S., Yutin, N., Bell, S. D. & Koonin, E. V.; (2010). Evolution of diverse cell division and vesicle formation systems in Archaea. *Nat Rev Microbiol*, **8**, 10, (Oct, 2010), 731-741.
- Malerod, L., Stuffers, S., Brech, A. & Stenmark, H.; (2007). Vps22/EAP30 in ESCRT-II mediates endosomal sorting of growth factor and chemokine receptors destined for lysosomal degradation. *Traffic* **8**, 11, (Nov, 2007) 1617-1629.
- Mao, Y., Nickitenko, A., Duan, X., Lloyd, T. E., Wu, M. N., Bellen, H. & Quioco, F. A.; (2000). Crystal structure of the VHS and FYVE tandem domains of Hrs, a protein involved in membrane trafficking and signal transduction. *Cell*, **100**, 4, (Feb, 2000), 447-456.
- Martin-Serrano, J. & Marsh, M.; (2007). ALIX catches HIV. *Cell Host Microbe*, **1**, 1, (Mar, 2007), 5-7.
- Martin-Serrano, J. & Neil, S. J.; (2011). Host factors involved in retroviral budding and release. *Nat Rev Microbiol*, **9**, 7, (Jul, 2011), 519-531.
- Marzella, L., Ahlberg, J. & Glaumann, H.; (1981). Autophagy, heterophagy, microautophagy and crinophagy as the means for intracellular degradation. *Virchows Arch B Cell Pathol Incl Mol Pathol*, **36**, 2-3, 219-234.
- McCullough, J., Fisher, R. D., Whitby, F. G., Sundquist, W. I. & Hill, C. P.; (2008). ALIX-CHMP4 interactions in the human ESCRT pathway. *Proc Natl Acad Sci U S A*, **105**, 22, (Jun, 2008), 7687-7691.
- Mehrpour, M., Esclatine, A., Beau, I. & Codogno, P.; (2010). Overview of macroautophagy regulation in mammalian cells. *Cell Res*, **20**, 7, (Jul, 2010), 748-762.
- Metcalfe, D. & Isaacs, A. M.; (2010). The role of ESCRT proteins in fusion events involving lysosomes, endosomes and autophagosomes. *Biochem Soc Trans*, **38**, 6, (Dec, 2010), 1469-1473.
- Michelet, X., Djeddi, A. & Legouis, R.; (2010). Developmental and cellular functions of the ESCRT machinery in pluricellular organisms. *Biol Cell*, **102**, 3, (Mar, 2010), 191-202.
- Mizuno, E., Kawahata, K., Kato, M., Kitamura, N. & Komada, M.; (2003). STAM proteins bind ubiquitinated proteins on the early endosome via the VHS domain and ubiquitin-interacting motif. *Mol Biol Cell*, **14**, 9, (Sep, 2003), 3675-3689.
- Mizushima, N., Levine, B., Cuervo, A. M. & Klionsky, D. J.; (2008). Autophagy fights disease through cellular self-digestion. *Nature*, **451**, 7182, (Feb, 2008), 1069-1075.
- Moberg, K. H., Schelble, S., Burdick, S. K. & Hariharan, I. K.; (2005). Mutations in erupted, the *Drosophila* ortholog of mammalian tumor susceptibility gene 101, elicit non-cell-autonomous overgrowth. *Dev Cell*, **9**, 5, (Nov, 2005), 699-710.
- Morita, E. & Sundquist, W. I.; (2004). Retrovirus budding. *Annu Rev Cell Dev Biol*, **20**, (Jun, 2004), 395-425.
- Morita, E., Sandrin, V., Chung, H. Y., Morham, S. G., Gygi, S. P., Rodesch, C. K. & Sundquist, W. I.; (2007). Human ESCRT and ALIX proteins interact with proteins of the midbody and function in cytokinesis. *EMBO J*, **26**, 19, (Oct, 2007), 4215-4227.
- Muziol, T., Pineda-Molina, E., Ravelli, R. B., Zamborlini, A., Usami, Y., Gottlinger, H. & Weissenhorn, W.; (2006). Structural basis for budding by the ESCRT-III factor CHMP3. *Dev Cell*, **10**, 6, (Jun, 2006), 821-830.
- Nara, A., Mizushima, N., Yamamoto, A., Kabeya, Y., Ohsumi, Y. & Yoshimori, T.; (2002). SKD1 AAA ATPase-dependent endosomal transport is involved in autolysosome formation. *Cell Struct Funct*, **27**, 1, (Feb, 2002), 29-37.
- Neary, D., Snowden, J. & Mann, D.; (2005). Frontotemporal dementia. *Lancet Neurol*, **4**, 11, (Nov, 2005), 771-780.
- Neumann, M., Sampathu, D. M., Kwong, L. K., Truax, A. C., Micsenyi, M. C., Chou, T. T., Bruce, J., Schuck, T., Grossman, M., Clark, C. M., McCluskey, L. F., Miller, B. L., Masliah, E., Mackenzie, I. R., Feldman, H., Feiden, W., Kretzschmar, H. A., Trojanowski, J. Q. & Lee, V. M.; (2006). Ubiquitinated TDP-43 in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. *Science*, **314**, 5796, (Oct, 2006), 130-133.
- Nickerson, D. P., West, M. & Odorizzi, G.; (2006). Did2 coordinates Vps4-mediated dissociation of ESCRT-III from endosomes. *J Cell Biol*, **175**, 5, (Dec, 2006), 715-720.
- Obita, T., Saksena, S., Ghazi-Tabatabai, S., Gill, D. J., Perisic, O., Emr, S. D. & Williams, R. L.; (2007). Structural basis for selective recognition of ESCRT-III by the AAA ATPase Vps4. *Nature*, **449**, 7163, (Oct, 2007), 735-739.
- Oestreich, A. J., Davies, B. A., Payne, J. A. & Katzmann, D. J.; (2007). Mvb12 is a novel member of ESCRT-I involved in cargo selection by the multivesicular body pathway. *Mol Biol Cell*, **18**, 2, (Feb, 2007), 646-657.
- Oh, K. B., Stanton, M. J., West, W. W., Todd, G. L. & Wagner, K. U.; (2007). Tsg101 is upregulated in a subset of invasive human breast cancers and its targeted overexpression in transgenic mice reveals weak oncogenic properties for mammary cancer initiation. *Oncogene*, **26**, 40, (Aug, 2007), 5950-5959.

- Ohsaki, Y., Sugimoto, Y., Suzuki, M., Hosokawa, H., Yoshimori, T., Davies, J. P., Ioannou, Y. A., Vanier, M. T., Ohno, K. & Ninomiya, H.; (2006). Cholesterol depletion facilitates ubiquitylation of NPC1 and its association with SKD1/Vps4. *J Cell Sci*, **119**, 3, (Jul, 2006), 2643-2653.
- Orenstein, S. J. & Cuervo, A. M.; (2010). Chaperone-mediated autophagy: molecular mechanisms and physiological relevance. *Semin Cell Dev Biol*, **21**, 7, (Sep, 2010), 719-726.
- Pankiv, S., Clausen, T. H., Lamark, T., Brech, A., Bruun, J. A., Outzen, H., Overvatn, A., Bjorkoy, G. & Johansen, T.; (2007). p62/SQSTM1 binds directly to Atg8/LC3 to facilitate degradation of ubiquitinated protein aggregates by autophagy. *J Biol Chem*, **282**, 33, (Aug, 2007), 24131-24145.
- Parkinson, N., Ince, P. G., Smith, M. O., Highley, R., Skibinski, G., Andersen, P. M., Morrison, K. E., Pall, H. S., Hardiman, O., Collinge, J., Shaw, P. J. & Fisher, E. M.; (2006). ALS phenotypes with mutations in CHMP2B (charged multivesicular body protein 2B). *Neurology*, **67**, 6, (Sep, 2006), 1074-1077.
- Pawliczek, T. & Crump, C. M.; (2009). Herpes simplex virus type 1 production requires a functional ESCRT-III complex but is independent of TSG101 and ALIX expression. *J Virol*, **83**, 21, (Nov, 2009), 11254-11264.
- Pawson, T., Gish, G. D. & Nash, P.; (2001). SH2 domains, interaction modules and cellular wiring. *Trends Cell Biol*, **11**, 12, (Dec, 2001), 504-511.
- Peschard, P., Fournier, T. M., Lamorte, L., Naujokas, M. A., Band, H., Langdon, W. Y. & Park, M.; (2001). Mutation of the c-Cbl TKB domain binding site on the Met receptor tyrosine kinase converts it into a transforming protein. *Mol Cell*, **8**, 5, (Nov, 2001), 995-1004.
- Philips, J. A., Porto, M. C., Wang, H., Rubin, E. J. & Perrimon, N.; (2008). ESCRT factors restrict mycobacterial growth. *Proc Natl Acad Sci U S A*, **105**, 8, (Feb, 2008), 3070-3075.
- Pincetic, A., Medina, G., Carter, C. & Leis, J.; (2008). Avian sarcoma virus and human immunodeficiency virus, type 1 use different subsets of ESCRT proteins to facilitate the budding process. *J Biol Chem*, **283**, 44, (Oct, 2008), 29822-29830.
- Piper, R. C. & Katzmann, D. J.; (2007). Biogenesis and function of multivesicular bodies. *Annu Rev Cell Dev Biol*, **23**, 519-547.
- Pornillos, O., Higginson, D. S., Stray, K. M., Fisher, R. D., Garrus, J. E., Payne, M., He, G. P., Wang, H. E., Morham, S. G. & Sundquist, W. I.; (2003). HIV Gag mimics the Tsg101-recruiting activity of the human Hrs protein. *J Cell Biol*, **162**, 3, (Aug, 2003), 425-434.
- Radtke, F. & Raj, K.; (2003) The role of Notch in tumorigenesis: oncogene or tumour suppressor? *Nat Rev Cancer*, **3**, 10, (Oct, 2003), 756-767.
- Raiborg, C. & Stenmark, H.; (2009). The ESCRT machinery in endosomal sorting of ubiquitylated membrane proteins. *Nature*, **458**, 7237, (Mar, 2009), 445-452.
- Raiborg, C., Rusten, T. E. & Stenmark, H.; (2003). Protein sorting into multivesicular endosomes. *Curr Opin Cell Biol*, **15**, 4, (Aug, 2003), 446-455.
- Ratnavalli, E., Brayne, C., Dawson, K. & Hodges, J. R.; (2002). The prevalence of frontotemporal dementia. *Neurology*, **58**, 11, (Jun, 2002), 1615-1621.
- Ravikumar, B., Vacher, C., Berger, Z., Davies, J. E., Luo, S., Oroz, L. G., Scaravilli, F., Easton, D. F., Duden, R., O'Kane, C. J. & Rubinsztein, D. C.; (2004). Inhibition of mTOR induces autophagy and reduces toxicity of polyglutamine expansions in fly and mouse models of Huntington disease. *Nat Genet*, **36**, 6, (Jun, 2004), 585-595.
- Raymond, C. K., Howald-Stevenson, I., Vater, C. A. & 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**, 12, (Dec, 1992), 1389-1402.
- Reid, E., Connell, J., Edwards, T. L., Duley, S., Brown, S. E. & Sanderson, C. M.; (2005). The hereditary spastic paraplegia protein spastin interacts with the ESCRT-III complex-associated endosomal protein CHMP1B. *Hum Mol Genet*, **14**, 1, (Jan, 2005), 19-38.
- Rodahl, L. M., Haglund, K., Sem-Jacobsen, C., Wendler, F., Vincent, J. P., Lindmo, K., Rusten, T. E. & Stenmark, H.; (2009). Disruption of Vps4 and JNK function in *Drosophila* causes tumour growth. *PLoS One*, **4**, 2, (2009).
- Roxrud, I., Stenmark, H. & Malerod, L.; (2010). ESCRT & Co. *Biol Cell*, **102**, 5, (May, 2010), 293-318.
- Russell, M. R., Nickerson, D. P. & Odorizzi, G.; (2006). Molecular mechanisms of late endosome morphology, identity and sorting. *Curr Opin Cell Biol*, **18**, 4, (Aug, 2006), 422-428.
- Rusten, T. E. & Stenmark, H.; (2009). How do ESCRT proteins control autophagy? *J Cell Sci*, **122**, 13, (Jul, 2009), 2179-2183.
- Rusten, T. E., Vaccari, T., Lindmo, K., Rodahl, L. M., Nezis, I. P., Sem-Jacobsen, C., Wendler, F., Vincent, J. P., Brech, A., Bilder, D. & Stenmark, H.; (2007). ESCRTs' and Fab1 regulate distinct steps of autophagy. *Curr Biol*, **17**, 20, (Oct, 2007), 1817-1825.
- Sahu, R., Kaushik, S., Clement, C. C., Cannizzo, E. S., Scharf, B., Follenzi, A., Potolicchio, I., Nieves, E., Cuervo, A. M. & Santambrogio, L.; (2011). Microautophagy of cytosolic proteins by late endosomes. *Dev Cell*, **20**, 1, (Jan, 2011), 131-139.
- Saksena, S. & Emr, S. D.; (2009). ESCRTs' and human disease. *Biochem Soc Trans*, **37**, 1, (Feb, 2009), 167-172.
- Saksena, S., Sun, J., Chu, T. & Emr, S. D.; (2007). ESCRTing proteins in the endocytic pathway. *Trends Biochem Sci*, **32**, 12, (Dec, 2007), 561-573.

- Saksena, S., Wahlman, J., Teis, D., Johnson, A. E. & Emr, S. D.; (2009). Functional reconstitution of ESCRT-III assembly and disassembly. *Cell*, **136**, 1, (Jan, 2009), 97-109.
- Samson, R. Y., Obita, T., Freund, S. M., Williams, R. L. & Bell, S. D.; (2008). A role for the ESCRT system in cell division in archaea. *Science*, **322**, 5908, (Dec, 2008), 1710-1713.
- Samson, R. Y., Obita, T., Hodgson, B., Shaw, M. K., Chong, P. L., Williams, R. L. & Bell, S. D.; (2011). Molecular and structural basis of ESCRT-III recruitment to membranes during archaeal cell division. *Mol Cell*, **41**, 2, (Jan, 2011), 186-196.
- Scoles, D. R., Nguyen, V. D., Qin, Y., Sun, C. X., Morrison, H., Gutmann, D. H. & Pulst, S. M.; (2002). Neurofibromatosis 2 (NF2) tumor suppressor schwannomin and its interacting protein HRS regulate STAT signaling. *Hum Mol Genet*, **11**, 25, (Dec, 2002), 3179-3189.
- Scott, A., Chung, H. Y., Gonciarz-Swiatek, M., Hill, G. C., Whitby, F. G., Gaspar, J., Holton, J. M., Viswanathan, R., Ghaffarian, S., Hill, C. P. & Sundquist, W. I.; (2005). Structural and mechanistic studies of VPS4 proteins. *EMBO J*, **24**, 20, (Oct, 2005), 3658-3669.
- Seals, D. F., Eitzen, G., Margolis, N., Wickner, W. T. & Price, A.; (2000). A Ypt/Rab effector complex containing the Sec1 homolog Vps33p is required for homotypic vacuole fusion. *Proc Natl Acad Sci U S A*, **97**, 17, (Aug, 2000), 9402-9407.
- Shiels, A., Bennett, T. M., Knopf, H. L., Yamada, K., Yoshiura, K., Niikawa, N., Shim, S. & Hanson, P. I.; (2007). CHMP4B, a novel gene for autosomal dominant cataracts linked to chromosome 20q. *Am J Hum Genet*, **81**, 3, (Sep, 2007), 596-606.
- Shim, S., Kimpler, L. A. & Hanson, P. I.; (2007). Structure/function analysis of four core ESCRT-III proteins reveals common regulatory role for extreme C-terminal domain. *Traffic*, **8**, 8, (Aug, 2007), 1068-1079.
- Shirk, A. J., Anderson, S. K., Hashemi, S. H., Chance, P. F. & Bennett, C. L.; (2005). SIMPLE interacts with NEDD4 and TSG101: evidence for a role in lysosomal sorting and implications for Charcot-Marie-Tooth disease. *J Neurosci Res*, **82**, 1, (Oct, 2005), 43-50.
- Shpilka, T. & Elazar, Z.; (2011). Shedding light on mammalian microautophagy. *Dev Cell*, **20**, 1, (Jan, 2011), 1-2.
- Simons, M. & Raposo, G.; (2009). Exosomes-vesicular carriers for intercellular communication. *Curr Opin Cell Biol*, **21**, 4, (Aug, 2009), 575-581.
- Skibinski, G., Parkinson, N. J., Brown, J. M., Chakrabarti, L., Lloyd, S. L., Hummerich, H., Nielsen, J. E., Hodges, J. R., Spillantini, M. G., Thusgaard, T., Brandner, S., Brun, A., Rossor, M. N., Gade, A., Johannsen, P., Sorensen, S. A., Gydesen, S., Fisher, E. M. & Collinge, J.; (2005). Mutations in the endosomal ESCRT-III complex subunit CHMP2B in frontotemporal dementia. *Nat Genet*, **37**, 8, (Aug, 2005), 806-808.
- Slagsvold, T., Pattni, K., Malerod, L. & Stenmark, H.; (2006). Endosomal and non-endosomal functions of ESCRT proteins. *Trends Cell Biol*, **16**, 6, (Jun, 2006), 317-326.
- Slater, R. & Bishop, N. E.; (2006). Genetic structure and evolution of the Vps25 family, a yeast ESCRT-II component. *BMC Evol Biol*, **6**, (Aug, 2006), 59.
- Sorkin, A. & von Zastrow, M.; (2009). Endocytosis and signalling: intertwining molecular networks. *Nat Rev Mol Cell Biol*, **10**, 9, (Sep, 2009), 609-622.
- Spitzer, C., Schellmann, S., Sabovljevic, A., Shahriari, M., Keshavaiah, C., Bechtold, N., Herzog, M., Muller, S., Hanisch, F. G. & Hulskamp, M.; (2006). The *Arabidopsis* elch mutant reveals functions of an ESCRT component in cytokinesis. *Development*, **133**, 23, (Dec, 2006), 4679-4689.
- Stark, P., Bodemer, W., Hannig, H., Luboshitz, J., Shaklai, M. & Shohat, B.; (2003). Human T lymphotropic virus type 1 in a seronegative B chronic lymphocytic leukemia patient. *Med Microbiol Immunol*, **192**, 4, (Nov, 2003), 205-209.
- Stefani, F., Zhang, L., Taylor, S., Donovan, J., Rollinson, S., Doyotte, A., Brownhill, K., Bennion, J., Pickering-Brown, S. & Woodman, P.; (2011). UBAP1 is a component of an endosome-specific ESCRT-I complex that is essential for MVB sorting. *Curr Biol*, **21**, 14, (Jul, 2011), 1245-1250.
- Strack, B., Calistri, A., Craig, S., Popova, E. & Gottlinger, H. G.; (2003). AIP1/ALIX is a binding partner for HIV-1 p6 and EIAV p9 functioning in virus budding. *Cell*, **114**, 6, (Sep, 2003), 689-699.
- Stuffers, S., Brech, A. & Stenmark, H.; (2009a). ESCRT proteins in physiology and disease. *Exp Cell Res*, **315**, 9, (May, 2009), 1619-1626.
- Stuffers, S., Sem Wegner, C., Stenmark, H. & Brech, A.; (2009b). Multivesicular endosome biogenesis in the absence of ESCRTs'. *Traffic*, **10**, 7, (Jul, 2009), 925-937.
- Sun, Z., Pan, J., Bublely, G. & Balk, S. P.; (1997). Frequent abnormalities of TSG101 transcripts in human prostate cancer. *Oncogene*, **15**, 25, (Dec, 1997), 3121-3125.
- Talbot, K. & Ansorge, O.; (2006). Recent advances in the genetics of amyotrophic lateral sclerosis and frontotemporal dementia: common pathways in neurodegenerative disease. *Hum Mol Genet*, **15**, 2, (Oct, 2006), 182-187.
- Tarrago-Trani, M. T. & Storrie, B.; (2007). Alternate routes for drug delivery to the cell interior: pathways to the Golgi apparatus and endoplasmic reticulum. *Adv Drug Deliv Rev*, **59**, 8, (Aug, 2007), 782-797.
- Teis, D., Saksena, S. & Emr, S. D.; (2008). Ordered assembly of the ESCRT-III complex on endosomes is required to sequester cargo during MVB formation. *Dev Cell*, **15**, 4, (Oct, 2008), 578-589.
- Teis, D., Saksena, S., Judson, B. L. & Emr, S. D.; (2010). ESCRT-II coordinates the assembly of ESCRT-III filaments for cargo sorting and multivesicular body vesicle formation. *EMBO J*, **29**, 5, (Mar, 2010), 871-883.

- Teo, H., Gill, D. J., Sun, J., Perisic, O., Veprintsev, D. B., Vallis, Y., Emr, S. D. & Williams, R. L.; (2006). ESCRT-I core and ESCRT-II GLUE domain structures reveal role for GLUE in linking to ESCRT-I and membranes. *Cell*, **125**, 1, (Apr, 2006), 99-111.
- Thery, C., Ostrowski, M. & Segura, E.; (2009). Membrane vesicles as conveyors of immune responses. *Nat Rev Immunol*, **9**, 8, (Aug, 2009), 581-593.
- Thompson, B. J., Mathieu, J., Sung, H. H., Loeser, E., Rorth, P. & Cohen, S. M.; (2005). Tumor suppressor properties of the ESCRT-II complex component Vps25 in *Drosophila*. *Dev Cell*, **9**, 5, (Nov, 2005), 711-720.
- Toyoshima, M., Tanaka, N., Aoki, J., Tanaka, Y., Murata, K., Kyuuma, M., Kobayashi, H., Ishii, N., Yaegashi, N. & Sugamura, K.; (2007). Inhibition of tumor growth and metastasis by depletion of vesicular sorting protein Hrs: its regulatory role on E-cadherin and beta-catenin. *Cancer Res*, **67**, 11, (Jun, 2007), 5162-5171.
- Tsai, Y. C. & Sun, Y. H.; (2004). Long-range effect of upd, a ligand for JAK/STAT pathway, on cell cycle in *Drosophila* eye development. *Genesis*, **39**, 2, (Jun, 2004), 141-153.
- Urwin, H., Authier, A., Nielsen, J. E., Metcalf, D., Powell, C., Froud, K., Malcolm, D. S., Holm, I., Johannsen, P., Brown, J., Fisher, E. M., van der Zee, J., Bruyland, M., Van Broeckhoven, C., Collinge, J., Brandner, S., Fütter, C. & Isaacs, A. M.; (2010). Disruption of endocytic trafficking in frontotemporal dementia with CHMP2B mutations. *Hum Mol Genet*, **19**, 11, (Jun, 2010), 2228-2238.
- Vaccari, T. & Bilder, D.; (2005). The *Drosophila* tumor suppressor Vps25 prevents nonautonomous overproliferation by regulating notch trafficking. *Dev Cell*, **9**, 5, (Nov, 2005), 687-698.
- Vaccari, T., Rusten, T. E., Menut, L., Nezis, I. P., Brech, A., Stenmark, H. & Bilder, D.; (2009). Comparative analysis of ESCRT-I, ESCRT-II and ESCRT-III function in *Drosophila* by efficient isolation of ESCRT mutants. *J Cell Sci*, **122**, 14, (Jul, 2009), 2413-2423.
- Vadlamudi, R. K., Joung, I., Strominger, J. L. & Shin, J.; (1996). p62, a phosphotyrosine-independent ligand of the SH2 domain of p56lck, belongs to a new class of ubiquitin-binding proteins. *J Biol Chem*, **271**, 34, (Aug, 1996), 20235-20237.
- Vieira, O. V., Harrison, R. E., Scott, C. C., Stenmark, H., Alexander, D., Liu, J., Gruenberg, J., Schreiber, A. D. & Grinstein, S.; (2004). Acquisition of Hrs, an essential component of phagosomal maturation, is impaired by mycobacteria. *Mol Cell Biol*, **24**, 10, (May, 2004), 4593-4604.
- 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., Scott, A., Krausslich, H. G., Kaplan, J., Morham, S. G. & Sundquist, W. I.; (2003). The protein network of HIV budding. *Cell*, **114**, 6, (Sep, 2003), 701-713.
- Walker, G. E., Antoniono, R. J., Ross, H. J., Paisley, T. E. & Oh, Y.; (2006). Neuroendocrine-like differentiation of non-small cell lung carcinoma cells: regulation by cAMP and the interaction of mac25/IGFBP-rP1 and 25.1. *Oncogene*, **25**, 13, (Mar, 2006), 1943-1954.
- Waterman, H., Katz, M., Rubin, C., Shtiegman, K., Lavi, S., Elson, A., Jovin, T. & Yarden, Y.; (2002). A mutant EGF-receptor defective in ubiquitylation and endocytosis unveils a role for Grb2 in negative signaling. *EMBO J*, **21**, 3, (Feb, 2002), 303-313.
- Wegner, C. S., Rodahl, L. M. & Stenmark, H.; (2011). ESCRT proteins and cell signalling. *Traffic*, **12**, 10, (Oct, 2011), 1291-1297.
- Williams, R. L. & Urbe, S.; (2007). The emerging shape of the ESCRT machinery. *Nat Rev Mol Cell Biol*, **8**, 5, (May, 2007), 355-368.
- Wilson, E. M., Oh, Y., Hwa, V. & Rosenfeld, R. G.; (2001). Interaction of IGF-binding protein-related protein 1 with a novel protein, neuroendocrine differentiation factor, results in neuroendocrine differentiation of prostate cancer cells. *J Clin Endocrinol Metab*, **86**, 9, (Sep, 2001), 4504-4511.
- Winter, V. & Hauser, M. T.; (2006). Exploring the ESCRTing machinery in eukaryotes. *Trends Plant Sci*, **11**, 3, (Mar, 2006), 115-123.
- Wolf, J. M., Johnson, D. J., Chmielewski, D. & Davis, D. A.; (2010). The *Candida albicans* ESCRT pathway makes Rim101-dependent and -independent contributes to pathogenesis. *Eukaryot Cell*, **9**, 8, (Jun, 2010), 1203-1215.
- Wollert, T. & Hurley, J. H.; (2010). Molecular mechanism of multivesicular body biogenesis by ESCRT complexes. *Nature*, **464**, 7290, (Apr, 2010), 864-869.
- Wollert, T., Wunder, C., Lippincott-Schwartz, J. & Hurley, J. H.; (2009). Membrane scission by the ESCRT-III complex. *Nature*, **458**, 7235, (Mar, 2009), 172-177.
- Wurmser, A. E., Sato, T. K. & Emr, S. D.; (2000). New component of the vacuolar class C-Vps complex couples nucleotide exchange on the Ypt7 GTPase to SNARE-dependent docking and fusion. *J Cell Biol*, **151**, 3, (Oct, 2000), 551-562.
- Xu, Z., Liang, L., Wang, H., Li, T. & Zhao, M.; (2003). HCRP1, a novel gene that is downregulated in hepatocellular carcinoma, encodes a growth-inhibitory protein. *Biochem Biophys Res Commun*, **311**, 4, (Nov, 2003), 1057-1066.
- Yang, D., Rismanchi, N., Renvoise, B., Lippincott-Schwartz, J., Blackstone, C. & Hurley, J. H.; (2008). Structural basis for midbody targeting of spastin by the ESCRT-III protein CHMP1B. *Nat Struct Mol Biol*, **15**, 12, (Dec, 2008), 1278-1286.
- Young, T. W., Mei, F. C., Rosen, D. G., Yang, G., Li, N., Liu, J. & Cheng, X.; (2007a). Up-regulation of tumor susceptibility gene 101 protein in ovarian carcinomas revealed by proteomics analyses. *Mol Cell Proteomics*, **6**, 2, (Feb, 2007), 294-304.

- Young, T. W., Rosen, D. G., Mei, F. C., Li, N., Liu, J., Wang, X. F. & Cheng, X.; (2007b). Up-regulation of tumor susceptibility gene 101 conveys poor prognosis through suppression of p21 expression in ovarian cancer. *Clin Cancer Res*, **13**, 13, (Jul, 2007), 3848-3854.
- Yu, Z., Gonciarz, M. D., Sundquist, W. I., Hill, C. P. & Jensen, G. J.; (2008). Cryo-EM structure of dodecameric Vps4p and its 2:1 complex with Vta1p. *J Mol Biol*, **377**, 2, (Mar, 2008), 364-377.
- Zhu, G., Gilchrist, R., Borley, N., Chng, H. W., Morgan, M., Marshall, J. F., Camplejohn, R. S., Muir, G. H. & Hart, I. R.; (2004). Reduction of TSG101 protein has a negative impact on tumor cell growth. *Int J Cancer*, **109**, 4, (Apr, 2004), 541-547.