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The Roles of ESCRT Proteins in Healthy Cells and in Disease

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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

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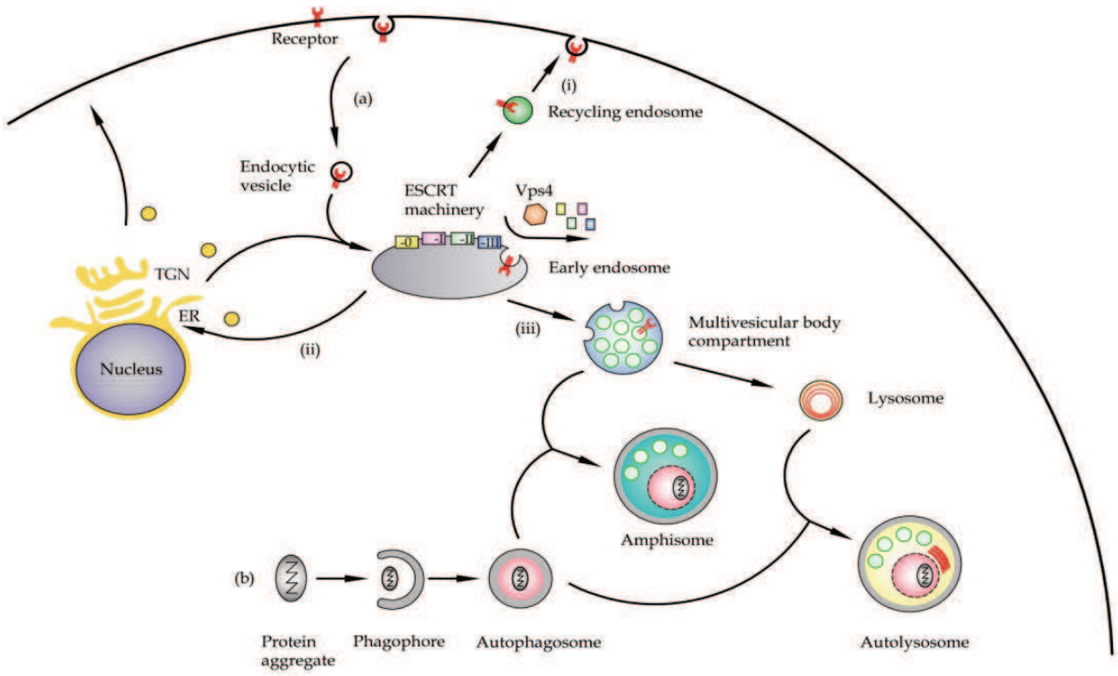

Fig 1. Interrelationships between the endocytic and autophagic pathways.
(a) Receptor-mediated endocytosis involves internalization of plasma membrane cargo into the cell. Endocytosed cargo is first delivered to the early endosome, which also receives cargo from the TGN. From here on, selected cargo 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.

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.

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.

Table 1. Components of the ESCRT machinery. (Table is modified from Hurley & Hanson, 2010, see cited paper for further details on domain/motif structure)

ESCRT complex and activity	Yeast Protein names	Metazoan Protein names	Domains/Motifs[1]	Biological function
ESCRT-0 *Clusters ubiquitinated cargo*	Vps27	Hrs	VHS, FYVE, UIM (yeast) DUIM (metazoan), PTAP, GAT, coiled-coil core, clathrin binding	Binds PtdIns3P, ubiquitinat
	Hse1	STAM1, 2	VHS, UIM, SH3, GAT, coiled-coil core, clathrin binding	Binds ubiquitinated cargo a
ESCRT-I *Membrane deformation and budding*	Vps23	Tsg101	UEV, Pro-rich linker, stalk, headpiece	Cargo and ESCRT-0 (Vps27
	Vps28	Vps28	Headpiece, C-terminal	Binds ESCRT-II (Vps36)
	Vps37	Vps37A, B, C, D	Basic helix, head piece	Binds membranes
	Mvb12	MVB12A, B	Stalk, ubiquitin binding domain	Stabilizes ESCRT-I subunit
ESCRT-II *Membrane deformation and budding*	Vps22	EAP30, Snf8	Coiled-coil, WH	Binds membranes
	Vps25	EAP20	PPXY, WH	Binds ESCRT-III (Vps20), c
	Vps36	EAP45	GLUE, NZF1, 2 (yeast), WH	Binds membranes, ubiquiti
ESCRT-III *Membrane scission*	Vps20	CHMP6	Charged, coiled-coil, MIM	Initiates membrane scissior
	Vps32/* (Snf7)	CHMP4A, B, C	Charged, coiled-coil, MIM	Membrane scission, binds I
	Vps24	CHMP3	Charged, coiled-coil, MIM	Completes membrane sciss
	Vps2/(Did4)	CHMP2A, B	Charged, coiled-coil, MIM	Recruits Vps4; initiates ESC
Vps4 *Disassembly of ESCRTs'*	Vps4	Vps4A,B/(SKD1, 2)	AAA+ ATPase, MIT	ESCRT disassembly and re
	Vta1	VTA1/LIP5	MIT, VSL	Positively regulates of Vps
Other	Vps31/(Bro1)	ALIX/AIP1	Bro1, Proline-rich domain	ESCRT-III interaction by re apoptosis regulators, conta
	Vps60/(Mos10)	CHMP5	Charged, coiled-coil	ESCRT-III like protein, bind
	Vps46/(Did2)	CHMP1A, B	Charged, coiled-coil	ESCRT-III like protein, recr
	Ist1	IST1	MIM1, MIM2	The tandem ESCRT III do
	Doa4	UBPY/USP8	Rhod, UBP	Removes ubiquitin

[1]**Domain acronyms:** Bro1, Bro1 domain-containing protein 1; CHMP, charged multivesicular body protein; DID, DO protein; DUB, deubiquitylating enzyme; DUIM, double-sided ubiquitin-interacting motif; ESCRT, endosomal sorting GAT; GLUE, GRAM-like ubiquitin-binding in EAP45; Hrs, hepatocyte growth factor-regulated Tyr kinase substrate; protein 1; MIM, MIT-interacting motif; MIT, microtubule-interacting and transport; MVB, multivesicular body; NZF homology 3; UBPY, ubiquitin isopeptidase Y; UEV, ubiquitin E2 variant; UIM, ubiquitin-interacting motif; VHS, Vps 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.

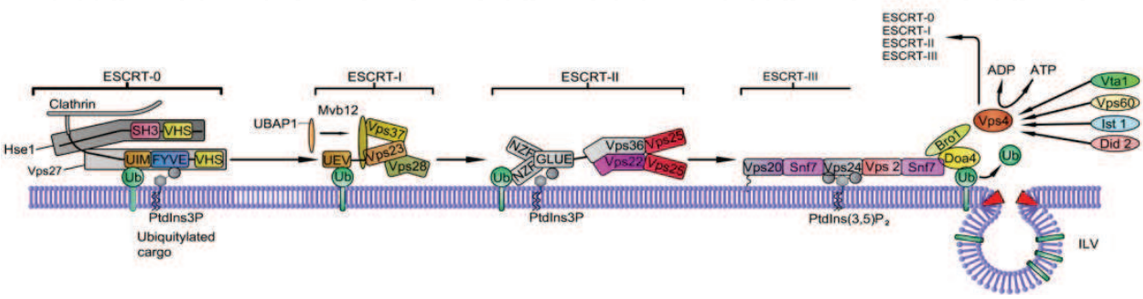

Fig. 2. Composition and molecular interactions of the ESCRTs'.

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 form 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 a important regulatory roles 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 el 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 el 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 FTLD-U (frontotemporal lobar degeneration with ubiquitin-immunoreactive inclusions) (Neary et al., 2005). Both FTLD-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 & Ansorge, 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 FTLD-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 then 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 tumourigenesis 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]	*Drosophila*
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 dysfunctional ESCRT-III on late endosomes[20]	*Drosophila*, mice
ESCRT-III associated	CHMP1B	Hereditary spastic	Interaction with spastin; spastin	Monkey cells

Table 2. ESCRT-associated diseases in various model systems
(Modified from Stuffers et al., 2009a)

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

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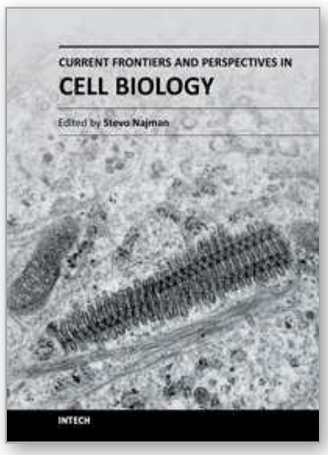

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