

ESCRT COMPLEXES IN MEMBRANE TRAFFICKING

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The **Endosomal Sorting Complex Required for Transport** (ESCRT) complexes are essential for the sorting of transmembrane proteins/receptors into Multi-Vesicular Bodies (MVB). ESCRTs are critical for cell surface receptor down-regulation, budding of HIV, MHC-II antigen presentation and cytokinesis. Consequently, the ESCRT machinery is involved in diverse biological processes and its dysfunction contributes to many diseases ranging from cancer to neuro-degeneration. Monoubiquitination of both biosynthetic and endocytic cargo by the Rsp5 HECT-domain Ub ligase in yeast serves as a critical signal for sorting into MVBs. The yeast Vps27 protein and its mammalian homolog HRS are required for the formation of MVBs. We have identified three distinct protein complexes (ESCRT-I, -II and -III) that function in the recognition and sorting of ubiquitinated transmembrane cargoes. The ESCRT-III subunits Vps20, Snf7, Vps24 and Vps2 only assemble into a complex on endosomes. We have addressed the pathway and the regulation for ESCRT-III assembly. Our findings indicate the ordered assembly of a transient 450kD ESCRT-III complex on endosomes. Despite biochemical and structural similarity, each subunit contributes a specific function. Vps20 nucleates transient oligomerization of Snf7, which appears to sequester MVB cargo. Vps24 terminates Snf7 oligomerization by recruiting Vps2, which subsequently engages the AAA-ATPase Vps4 to dissociate ESCRT-III into the cytoplasm as individual monomers. We propose that the ordered assembly and disassembly of ESCRT-III delineates an MVB sorting domain to sequester cargo and complete the last steps of MVB sorting and viral budding.

The diversity of plasma membrane proteins subject to ESCRT-mediated down-regulation presents a major challenge to achieve cargo-specific regulation of endocytosis. We recently identified a new family of proteins in yeast, ARTs for **Arrestin-Related Trafficking** adaptors, that function by targeting specific PM proteins to the endocytic system. We propose that ARTs provide a cargo-specific pathway that modifies PM proteins and thereby directs their endocytic down-regulation via the ESCRT-mediated MVB sorting pathway.