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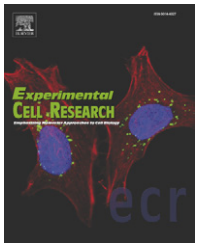

Review

ESCRT proteins in physiology and disease

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ABSTRACT

As a mechanism of signal attenuation, receptors for growth factors, peptide hormones and cytokines are internalized in response to ligand binding, followed by degradation in lysosomes. Receptor ubiquitination is a key signal for such downregulation, and four protein complexes known as endosomal sorting complex required for transport (ESCRT)-0, -I, -II and -III have been identified as the machinery required for degradative endosomal sorting of ubiquitinated membrane proteins in yeast and metazoans. Three of these complexes contain ubiquitin-binding domains whereas ESCRT-III instead recruits deubiquitinating enzymes. The concerted action of the ESCRTs not only serves to sort ubiquitinated cargo but is also thought to cause inward vesiculation of endosomal membranes, thereby mediating biogenesis of multivesicular endosomes (MVEs). Because ligand-mediated receptor downregulation plays an important role in signal attenuation, it is not surprising that dysfunction of ESCRT components is associated with disease. In this review we discuss the possible roles of ESCRTs in protection against cancer, neurodegenerative diseases and bacterial infections, and we highlight the fact that many RNA viruses exploit the ESCRT machinery for the final abscission step of their budding from cells. We also review the additional functions of ESCRT proteins in cytokinesis and discuss how these may be related to ESCRT-associated pathologies.

Contents

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Introduction

Transmembrane proteins such as transporters and receptors are not permanently located at the plasma membrane but are internalized at rates that differ greatly between different proteins [1]. Nutrient receptors (e.g. transferrin receptors and lipoprotein receptors) are constitutively endocytosed at high rates whereas most receptors for hormones, growth factors and cytokines have low endocytosis rates in the absence of ligands and highly accelerated internalization rates in response to ligand binding. Likewise, after delivery to early (sorting) endosomes, different cargoes behave differently. Whereas nutrient receptors typically recycle back to the plasma membrane for re-use in multiple rounds of ligand internalization, hormone, growth factor and cytokine receptors often are internalized into intraluminal vesicles (ILVs) of multivesicular endosomes (MVEs) and get degraded when the latter fuse with lysosomes [2]. The signal for such degradative trafficking is provided by ubiquitin, the small protein tag that is conjugated to lysine residues of substrate proteins. At least in mammalian cells, multiple ubiquitins are thought to be required for efficient lysosomal targeting of membrane proteins, either in the form of multiple mono-ubiquitin moieties, or in the form of polyubiquitin chains formed through linkages of the lysine-63 residues of ubiquitin [3,4].

Studies of yeast vacuolar protein sorting mutants have yielded a subgroup of mutants, class E *vps* mutants, which are defective in MVE biogenesis and degradative protein sorting [5]. Genetic and biochemical characterization of class E *vps* mutants have unveiled a machinery responsible for these processes (Fig. 1). This machinery consists of two ubiquitin binding complexes, endosomal sorting complex required for transport (ESCRT)-I and -II, and one complex that instead recruits deubiquitinating enzymes, ESCRT-III [6–8]. In addition, parallel studies in yeast, *Drosophila* and mammalian cells have led to the identification of a fourth complex that functions upstream of ESCRT-I [9–13]. Consequently, this complex has been dubbed ESCRT-0 [14].

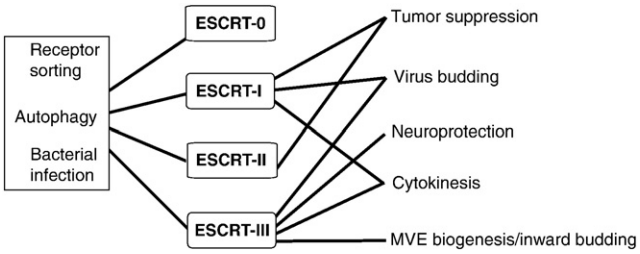

Fig. 2 – Cell biological and (patho)physiological processes controlled by the ESCRT machinery.

The biochemistry of the ESCRTs has been extensively reviewed in recent reviews [14,15] and will only be briefly summarized here. ESCRT-0 consists of Vps27p and Hse1p in yeast, corresponding to hepatocyte growth factor regulated tyrosine kinase substrate (Hrs) and signal-transducing adaptor molecule (STAM) in mammalian cells [9,12]. Both these subunits contain ubiquitin-interacting motifs (UIMs), and mammalian ESCRT-0 contains an additional UIM-containing protein, Eps15b [16]. ESCRT-0 recruits ESCRT-I to endosomal membranes [10,11,13], a heterotetrameric complex consisting of Vps23p (Tsg101 in mammals), Vps28p, Vps37p and Mvb12p [17]. Humans express 4 isoforms of Vps37 and two isoforms of Mvb12. The Vps28p subunit of ESCRT-I interacts with Vps36p in ESCRT-II, presumably facilitating the recruitment of the latter complex to endosomal membranes. The Vps36p subunit not only binds Vps28p but also ubiquitin, a binding that is mediated by an NZF zinc finger in yeast Vps36p and a phosphoinositide-interacting GLUE domain in mammalian Vps36 [18,19]. In addition to one subunit of Vps36p, ESCRT-II contains one subunit of Vps22p and two subunits of Vps25p [20,21]. The latter subunits interact with Vps20p in ESCRT-III, thus probably contributing to recruitment of this complex. The core components of ESCRT-III consist of Vps20p, Snf7p, Vps24p and Vps2p [7] and form polymeric filaments on the endosomal membrane. In spite of the structural insight into the organization of the ESCRTs, it is

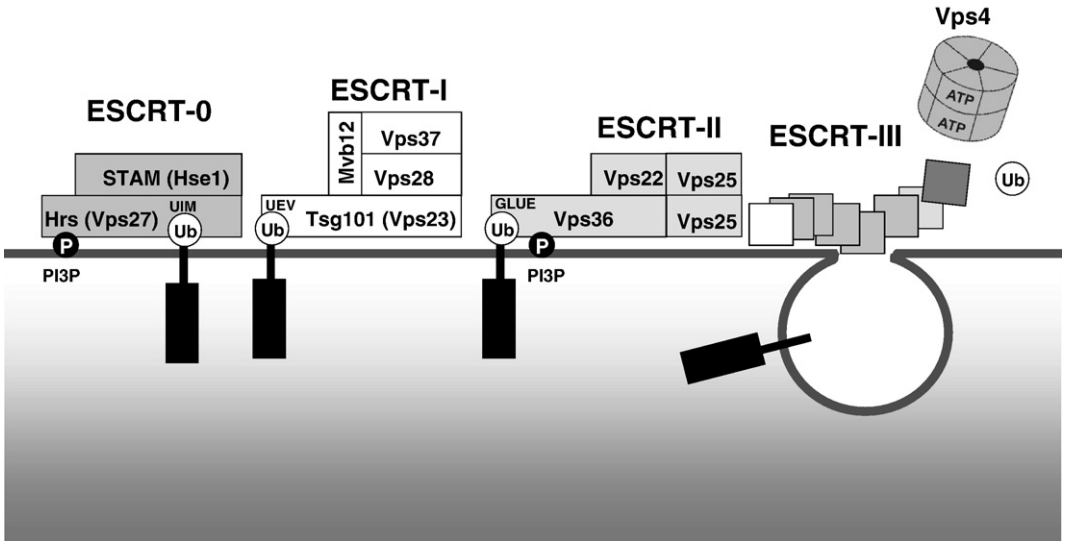

Fig. 1 – The ESCRTs in MVE biogenesis. ESCRT-0 -I and -II contain ubiquitin-binding domains that interact with ubiquitinated cargo. ESCRT-III recruits deubiquitinating enzymes that remove the ubiquitin tag. Polymeric filaments formed by ESCRT-III are thought to mediate membrane invagination and ILV abscission. The ATPase Vps4 is recruited by ESCRT-III and mediates disassembly of polymers. In cases where subunits have different names in yeast and mammals, the yeast names are in parentheses.