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Review

ESCRT genes and regulation of developmental signaling

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ABSTRACT

ESCRT (Endosomal Sorting Complex Required for Transport) proteins have been shown to control an increasing number of membrane-associated processes. Some of these, and prominently regulation of receptor trafficking, profoundly shape signal transduction. Evidence in fungi, plants and multiple animal models support the emerging concept that ESCRTs are main actors in coordination of signaling with the changes in cells and tissues occurring during development and homeostasis. Consistent with their pleiotropic function, ESCRTs are regulated in multiple ways to tailor signaling to developmental and homeostatic needs. ESCRT activity is crucial to correct execution of developmental programs, especially at key transitions, allowing eukaryotes to thrive and preventing appearance of congenital defects.

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Abbreviations: ABA, abscisic acid; AUX1, AUXIN-RESISTANT1; CHMP, charged multivesicular body protein; Crb, crumbs; DSL, delta/serrate/lag-2; Dx, Deltex; Dome, domeless; Dpp, decapentaplegic; EGFR, epidermal growth factor receptor; ESCRT, endosomal sorting complex required for transport; FGF, fibroblast growth factor; Hh, Hedgehog; HSP, hereditary spastic paraplegia; ILV, internal lumenal vesicle; IST, increased sodium tolerance 1; Lgd, lethal giant disc; MLIV, mucolipidosis type IV; MVE, multi vesicular endosomes; JNK, c-Jun N-terminal kinase; PIN1, PINFORMED1; Pros, positive regulator of SKD1; RTK, receptor tyrosine kinase; SHH, sonic Hedgehog; Su(Dx), suppressor of Deltex; Tsg101, tumor susceptibility gene 101; Upd, unpaired; Vps, vacuolar protein sorting; Wg, wingless; WT, wild-type.

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1. Introduction

Mutants in ESCRT genes have been initially isolated in yeast in a screen to identify genes that regulated cargo sorting to the vacuole, the yeast lysosome. Some of vacuolar protein sorting (vps) mutants recovered in the screen disrupted the biogenesis of the multi vesicular endosomes (MVEs) inducing the formation an aberrant compartment, named class E vacuole [1,2]. Class E-vps mutants accumulated un-degraded proteins in enlarged, aberrant prevacuolar compartments [3]. The products of class E genes were later found to act in a set of interacting complexes that concentrate ubiquitinated trafficking cargoes and include them in MVEs [4].

The 30 years of research that followed the isolation of the first ESCRT mutations lead to current knowledge that five complexes exist that constitute the ESCRT machinery. These are named ESCRT-0, ESCRT-I, ESCRT-II, ESCRT-III and Vps4 AAA(ATPases Associated with diverse cellular Activities)-ATPase complex. With few exceptions, the genes encoding ESCRT-I, −II, −III and Vps4 components are conserved in all major eukaryotic groups, including plants, stramenopiles, chromealveolates, amoebozoa, and excavates. While ESCRT-III genes are the most ancient, as they are shared with some present-day Archaea, ESCRT-I, −II are apparently early eukaryotic innovations that have subsequently been conserved throughout the evolution and diversification of unicellular and multicellular eukaryotes; ESCRT-0 represents an apparently "recent" innovation, shared only by metazoa and fungi. ESCRTs may have evolved in concert with early eukaryotic endomembrane systems, contributing to increasingly sophisticated intracellular signaling and interactions with the extracellular environment [5,6] (see Table 1 for subunit compositions, evolutionary origin and nomenclature in representative organisms).

A number of biochemical studies have determined the structure of ESCRT complexes and have detailed how ESCRTs act mechanistically in endosomal sorting [reviewed in 7]. ESCRT complexes are cytoplasmic until sequentially recruited to the endosomal membrane. Ubiquitination of cargoes and interaction with phosphatidylinositol 3-phosphate (PI3P) on the endosomal membrane drive initial recruitment of ESCRT-0 to concentrate cargoes in subdomains of the endosomal membrane. ESCRT-0 also summons ESCRT-I, which retains cargoes by ubiquitin binding and hands them to the ESCRT–II complex, which acts as an adapter for the formation of the ESCRT-III complex. The ESCRT-III bends the endosomal membrane away from the cytoplasm to form invaginated buds eventually trapping cargoes in nascent intraluminal vesicles (ILVs) of the MVE. Finally, the deubiquitinating enzyme Doa4, and the Vps4 ATPase remove ubiquitin and unfold the ESCRT-III complex favoring pinching off the ILV neck, the final step of MVB biogenesis [8–13].

A string of investigations in the past 15 years have revealed that the ancestral membrane-bending activity of ESCRT-III is deployed not only at endosomes but rather at cytoplasmic side of most membranes in the cell requiring bending for multiples purposes, including cytokinesis, exovesicle formation, viral budding and membrane repair [14–16,17–20]. We also know that the ESCRT system couples the ESCRT-III complex activity with the targeting activity of the ESCRT-I complex, which in some cases is substituted or integrated by ALIX/Bro1 or other specialized factors. In addition, it appears that the ESCRT-II complex is not the only complex connecting ESCRT-I functions with ESCRT-III. Indeed, a set of adapters alternative to ESCRT-II are used in specific ESCRT-dependent processes. This is also the case of ESCRT-0, whose activity in cargo sorting is often dispensable or substituted by alternative complexes, most notably the TOM1 complex in plants [21] [for an extensive review of the diversity of ESCRT mechanisms of action please see 21].

In this chapter, we will focus on recent advances on how ESCRTs regulate signal transduction during development in fungi, plants and animals. We will also discuss the association of ESCRTs with congenital and early onset disorders, which are directly linked to failures of signaling regulation during development. We will not cover the role of ESCRTs in the formation of exovesicles – which might carry developmentally important signals, or control secretion in specialized cellular system or in autophagy and cytokinesis, as these are covered elsewhere in this issue. Likewise, we refer readers interested in their involvement in cancer, neurodegeneration and pathogenic diseases to [22].

2. ESCRT-dependent development and homeostasis in fungi

2.1. The PacC/Rim101 system

In the fungi *Saccharomyces cerevisiae, Aspergillus nidulans, Candida albicans, Criptococcus neoformans, Neurospora crassa* and Ustilago *maydis,* ESCRTs are required for the processing and maturation of the transcription factor Rim101 (also called PacC; Fig. 1). The Rim/Pal system includes the transmembrane sensor Rim21/PalH, which is associated with the arrestin-like factor Rim8/PalF (Fig. 1A). Upon ubiquitination by the Nedd4-like ubiquitin ligase Rsp5, the Rim8 complex is internalized in endosomes by ESCRT-mediated sorting and cleavage and activation of Rim101 by the calpain-like protease Rim13 occurs (Fig. 1B) [23]. Surprisingly, a recent study indicated that while ESCRTs and ubiquitination are required for Rim101 processing, at least in yeast, endocytic internalization is dispensable and ESCRT recruitment initiates at the plasma membrane [24]. These data suggest that activation of the Rim101 and down regulation of Rim8 complex could be two distinct events. Given that plasma membrane association of ESCRT is observed during formation of exovesicles [16,25], it remains to be determined whether signaling involves exovesicle formation or a novel form ESCRT-dependent signaling activation at the plasma membrane.

2.2. Environment cues are controlled by ESCRTs

A major use of the PacC/Rim101 system that depends on ESCRT-I, −II and −III but not ESCRT-0 is response to extracellular pH [26]. In Aspergillus nidulans, changes induced by extracellular alkalization and transduced by Rim101 signaling lead to the switch from yeast-like growth to pseudohyphal growth that generates filaments of cells for dispersal towards new substrates (Fig. 1A) [23]. Similarly, the ESCRT-III regulator Vps60 (also called MOS10) is required for the late stages of pseudohyphal growth in Saccharomyces cerevisiae, while disruption of other ESCRT-III components results in different, early-growth phenotypes – indicating a specific function of Vps60 in the process. While signaling alterations associated with this phenotype have not been reported, pseudohyphal growth is controlled by nutrients and the signal is transduced by Cyclic AMP and MAP Kinase cascades, suggesting that signaling cascades other than Rim101 are regulated by ESCRT-mediated trafficking in yeast [27].