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MEMBRANE TRAFFICKING

Knowing your ESCRT

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> “...the ESCRT-III–Vps4 association may reflect an ancient function that predates the divergence of eukaryotes and archaea.”

The multiprotein ESCRT (endosomal sorting complex required for transport) complexes are required for membrane fission events, including endosomal intralumenal vesicle formation and viral budding. The VPS4 AAA-family ATPase binds to membrane-bound ESCRT-III complexes and catalyses their disassembly, which may be coupled to membrane fission and vesicle formation. Two reports now provide a structural basis for the interaction between VPS4 and ESCRT-III.

Williams and colleagues showed that the C-terminal region of yeast ESCRT-III protein Vps2 is sufficient for binding the MIT (microtubule-interacting and transport) domain of Vps4. The six Vps2 residues that form the MIT-interacting motif (MIM) are also present in the yeast ESCRT-III subunit Did2 and in the mammalian ESCRT-III subunits CHMP1A and CHMP2A. Mutation of MIM in Vps2 or Did2 caused sorting defects; a protein that normally sorts to the vacuolar lumen accumulated in the vacuolar membrane instead.

In a separate study, Sundquist and co-workers showed that the MIT domains of human proteins VPS4A and VPS4B bind the C termini of human ESCRT-III proteins CHMP1–3, albeit with varying affinity. Both groups determined structures of complexes between the MIT domain of Vps4/VPS4A and the C termini of ESCRT-III proteins (Vps2 and CHMP1A, respectively), and the structures are in good agreement. The MIT domain forms a three-helix bundle of antiparallel helices, whereas the longer MIM-containing region of Vps2 comprises three short helical segments (the shorter CHMP1A construct comprises only the third helix). The third helix of Vps2/CHMP1A binds in the groove between helices 2 and 3 of MIT, but in an opposite orientation to that of a canonical tetratricopeptide-like repeat interaction — thereby creating a unique interaction mode. Distinct hydrophobic pockets along the groove bind three conserved Leu/hydrophobic residues in the MIM of Vps2/CHMP1A and flanking residues make important salt-bridging interactions.

When Williams and colleagues determined the crystal structure of the MIT domain of an archaeal ATPase, they found that it closely resembled that of Vps4. It also interacted with an archaeal ESCRT-III-like protein, even though archaea do not have an endomembrane system. This suggests that the ESCRT-III–Vps4 association may reflect an ancient function that predates the divergence of eukaryotes and archaea.

MIT mutations that inhibit CHMP1A binding caused defective endosomal protein sorting into the vacuolar lumen, blocked VPS4 recruitment to mammalian endosomes and relieved dominant-negative VPS4 inhibition of viral budding. So, the recognition of membrane-associated ESCRT-III by VPS4 ATPase, and subsequent ATP hydrolysis, is crucial for ESCRT-III function. Sundquist and colleagues suggest that membrane association of ESCRT-III may serve to expose the C-terminal regions of CHMP1–3, which promotes the recruitment of oligomeric VPS4. It is not yet clear how ATP hydrolysis leads to the disassembly of the ESCRT-III complex and to vesicle formation.

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ORIGINAL RESEARCH PAPERS Obita, T. *et al.* Structural basis for selective recognition of ESCRT-III by the AAA ATPase Vps4. *Nature* 11 Oct 2007 (doi:10.1038/nature06171) | Stuchell-Brereton, M. D. *et al.* ESCRT-III recognition by VPS4 ATPases. *Nature* 11 Oct 2007 (doi:10.1038/nature06172)
FURTHER READING Williams, R. L. & Urbe, S. The emerging shape of the ESCRT machinery. *Nature Rev. Mol. Cell Biol.* **8**, 355–368 (2007)

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