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UBIQUITYLATION

CUE the beginning

It is well known that polyubiquitin (polyUb) chains promote proteasomal degradation, but what does monoubiquitin (monoUb) do? Recently, monoUb has been shown to function in vesicular trafficking, and now three independent groups have provided new insights by studying Vps9 (vacuolar protein sorting 9) — a yeast guanine nucleotide exchange factor (GEF) that promotes the fusion of plasma-membrane- or Golgi-derived vesicles with a prevacuolar compartment.

In the first paper, which was published in *Current Biology*, the groups of Joazeiro and Supek reported that the CUE domain of Vps9 is a new Ub-binding domain. They showed that it interacts directly with monoUb as well as polyUb, and also highlighted the importance of the former interaction in vesicular trafficking. Using a trans-membrane receptor–monoUb fusion construct, they showed that impairing the interaction between monoUb and Vps9 — by either mutating Ub or deleting *vps9* — resulted in cytoplasmic, rather than vacuolar, accumulation of the construct. Interestingly, though, they found that the trafficking defect caused by mutating Ub could be rescued by deletion of the Vps9 CUE domain. The results indicate that the CUE domain negatively regulates Vps9 until Ub positively regulates Vps9 through interactions with the CUE domain, and that deleting this domain makes Vps9 activation Ub independent.

Hicke and co-workers, reporting in *The EMBO Journal*, also found that the Vps9 CUE domain interacts directly with monoUb and polyUb, and they defined the key interaction surfaces involved. They also proposed that the Vps9 CUE domain negatively regulates Vps9 activity. Furthermore, they showed that the CUE domain of Vps9 is needed to promote Vps9 monoubiquitylation by the Rsp5 *hect* domain ubiquitin ligase, which functions in cell-surface receptor endocytosis. They concluded that the CUE domain is an evolutionarily conserved monoUb-binding domain that mediates intramolecular monoubiquitylation.

The data from Horazdovsky's group, which are published in *The Journal of Biological Chemistry*, concur with the results in the two papers described above and confirm that monoUb is a regulator of Vps9. They

also confirm that Vps9 functions at an intermediate step in the Ub regulation of endocytosis, between internalization and sorting at multivesicular bodies. Horazdovsky's group favour the idea that monoUb binding by the CUE domain functions to localize Vps9, and that CUE-mediated Vps9 monoubiquitylation modulates its GEF activity. However, this is only the beginning of CUE, and the precise roles of this domain and monoUb in Vps9 function remain to be seen.

Rachel Smallridge

References and links

ORIGINAL RESEARCH PAPERS Donaldson, K. M. *et al.* Ubiquitin signals protein trafficking via interaction with a novel ubiquitin binding domain in the membrane fusion regulator, Vps9p. *Curr. Biol.* **13**, 258–262 (2003) | Shih, S. C. *et al.* A ubiquitin-binding motif required for intramolecular monoubiquitylation, the CUE domain. *EMBO J.* **22**, 1273–1281 (2003) | Davies, B. A. *et al.* Vps9p CUE domain ubiquitin binding is required for efficient endocytic protein traffic. *J. Biol. Chem.* 2003 March 24 [epub ahead of print]