IN THE NEWS

Nobel nematodes

Work on programmed cell death, which began on the millimetre-long nematode worm, has earned two UK researchers and a US scientist the 2002 Nobel Prize in Physiology or Medicine.

Sydney Brenner laid the foundation for this year's prize by establishing *Caenhorabditis elegans* as a model system for investigating cell division and organ development, and for linking different genetic mutations to specific effects on organ development; John Sulston showed that programmed cell death was key to shaping the developing worm; and Robert Horvitz "…identified the first bona fide 'death genes'…" (*The New York Times*, 8 October) and discovered that humans also have 'death genes'.

Praising their achievements, the Nobel Assembly said that their work "…had provided a greater understanding of the way cells divide, develop into different body tissues and die when they have served their purpose." (*BBC News*, 7 October). Robert Horvitz told a news conference at the Massachusetts Institute of Technology that "Knowledge of what makes cells die and of what can block the cell-death process may … help identify agents that regulate the cell deaths involved in various human disorders…".

John Sulston told the *New Scientist* (7 October) "It's tremendously exciting for me because once again it reinforces the power of fundamental research." A similar message emerged from last year's Nobel Prize — which was awarded to Paul M. Nurse, Leland H. Hartwell and R. Timothy Hunt for their work on the cell cycle in the simple organism yeast — highlighting the importance of model organisms in research.

Katrin Bussell

MEMBRANE DYNAMICS

From cargo to curves

Many cellular processes — from nutrient uptake to the recycling of synaptic vesicles — rely on clathrin-mediated endocytosis, whereby the cargo is packaged into a clathrin-coated vesicle that buds off from the membrane. Many proteins have been implicated in this process, but a report in *Nature* by Harvey McMahon and colleagues now describes how one of these players — epsin 1 — might act as a crucial link between vesicle formation and the recruitment of cargo.

Epsin 1 has previously been implicated in clathrin-mediated endocytosis as it binds to clathrin, Eps15 (which is localized at the edge of a forming clathrin-coated pit) and the cargo-recruitment complex AP2. Epsin 1 contains a conserved domain known as the epsin N-terminal homology (ENTH) domain, which binds to the membrane lipid phosphatidylinositol-4,5 bisphosphate (PtdIns(4,5)P_2).

McMahon and colleagues first showed that epsin — or even just its ENTH domain — can convert liposomes into tubules. To try and explain this phenomenon, they solved the structure of the epsin ENTH domain crystallized in the presence of inositol-1,4,5-trisphosphate (Ins(1,4,5)P_3). The main difference between this structure and an unliganded crystal form is the presence of a new helix — termed 'helix zero' (α0) — at the amino terminus of the ligand-bound protein. Helix zero folds back across several of the other α-helices in the protein to form a deep binding pocket for the Ins(1,4,5)P_3 ligand. The fact that α0 does not form in the absence of ligand indicates that the binding of Ins(1,4,5)P_3 and the formation of this α-helix are coupled. And further studies showed that epsin binding is specific for certain lipid head groups — the inositol molecule needs to have a phosphate at both positions 4 and 5.

An attractive model to explain these observations is that, when epsin binds to the membrane, the resulting conformational change allows the membrane lipids to bury deep into the epsin groove. This, in turn, could allow epsin to push the head groups apart, reducing the energy needed to curve the membrane into a vesicle, and making it easier for the clathrin cage to then stabilize the curved surface.

But how might such epsin-induced membrane invagination be coupled to the recruitment of cargo and the formation of clathrin-coated vesicles? Cell-expression studies showed that some epsin localizes to distinct puncta in the plasma membrane, and that these puncta could be co-labelled with antibodies against the AP2 complex, clathrin and Eps15. The authors then made a mutant form of epsin that could not bind to membranes containing PtdIns(4,5)P_2 or Ins(1,4,5)P_3, and showed that the puncta no longer appeared with this mutant form. Interestingly, although the distribution of AP2 was disrupted in these mutants, the clathrin retained its punctate distribution. So, say the authors, these results indicate that "targeting of epsin to the plasma membrane by phosphoinositide binding is linked to correct localization of the cargo-recruitment complex AP2".

A final piece of evidence to support this bridging role for epsin came from studies on lipid monolayers containing PtdIns(4,5)P_2. McMahon and co-workers showed that epsin could recruit clathrin to the monolayers, and promote its polymerization to form three-dimensional coated pits. However, neither the α0 epsin mutants nor the mutants defective in phosphoinositide binding were able to do this.

This study paints a tantalizing picture of how membrane invagination and the recruitment of cargo might be linked by epsin. As well as establishing the exact role of epsins in endocytosis, future studies should be able to assess whether — and if so, how — epsin interacts with the various other proteins such as dynamin and endophilin that have previously been implicated in regulating membrane curvature.

Alison Mitchell

References and links

ORIGINAL RESEARCH PAPER Ford, M. G. J. *et al*. Curvature of clathrin-coated pits driven by epsin. *Nature* **419**, 361–366 (2002)

WEB SITE

Harvey McMahon's laboratory: http://www2.mrc-lmb.cam.ac.uk/groups/hmm/