In This Issue

Clean up or go crazy

Autophagy is needed to clear up dementia-inducing proteins from the cell, report Filimonenko et al.

During autophagy, the cell gobbles up its own internal components into membranous structures called autophagosomes, which fuse with multivesicular bodies (MVBs) before delivery to lysosomes, where the sequestered material is degraded. Autophagy is particularly important at times of cell stress and energy depletion, when the cell must recycle old organelles and cytoplasmic proteins to provide a source of amino acids. Even unstressed cells, however, probably clean house regularly using a low level of autophagy.

Those autophagy vesicles—the MVBs—were recently linked to a form of dementia. A family with frontotemporal dementia (FTD) was found to have mutations in an MVB-associated protein called CHMP2B. CHMP2B is a subunit of the ESCRT complexes, which sort ubiquitinated endocytosed proteins into MVBs for degradation in the lysosome. CHMP2B mutations have also been found in patients with amyotrophic lateral sclerosis (ALS). FTD and ALS are neurodegenerative diseases characterized by abnormal ubiquitin-positive protein deposits in affected neurons.

To investigate the molecular basis of disease in patients with CHMP2B mutations, Filimonenko and colleagues knocked down different ESCRT subunits or overexpressed CHMP2B mutants in cultured cells. Tracking the progress of autophagosomes in these cells revealed that fusion of MVBs with lysosomes was impaired. The resulting lack of lysosomal degradation caused ubiquitinated proteins to build up in the autophagic pathway and in the cytosol.

The autophagy-deficient cells seemed to be trying to compensate by ramping up a second protein-degradation pathway, headed by the proteasome. This was insufficient to compensate for the autophagy deficiency, however.

The authors also found that ESCRT depletion inhibited degradation of the expanded polyglutamine aggregates that are associated with Huntington’s disease, indicating that MVBs are generally needed for both autophagic housekeeping duties and healthy neuronal function.

Reference: Filimonenko, M., et al. 2007. J. Cell Biol. 179:485–500.

Putting ER in its place

The importance of ER positioning is very clear in budding yeast, report Loewen et al. Get it wrong, and the cells pause division.

The positioning of particular organelles can often be important for cell function. How a cell senses organelle positioning, however, is unknown. The budding yeast is a useful model organism for getting to the bottom of this question, as its organelles move into the bud in a highly ordered manner. The ER, for example, travels along actin cables into the bud, and then attaches to the bud tip and spreads around the cortex.

Sites of contact between the ER and the plasma membrane are enriched in an ER transmembrane protein called Scs2. Loewen et al. now show that Scs2 probably links the two membranes together. ER cortical distribution, they found, was abnormal in yeast lacking the protein. This phenotype was exaggerated in the bud. The team shows that this more serious defect occurs because Scs2 is normally enriched at the bud tip, where it is needed to set up the initial attachment point for the ER.

In the Scs2 mutants, cell division often arrested before cytokinesis. Cytokinesis requires the formation of a ring of cytoskeletal septin proteins around the bud neck. But in Scs2 mutants, the septins were disorganized. Septin disorganization sets off a pathway known to halt the cell cycle. The team suggests that cells activate this pathway to stall division until the ER is correctly located in the bud. How the mispositioned ER interrupts proper septin deposition is yet unclear. One possibility is that a septin regulator called Cdc28, which is found on the ER, is in the wrong position to operate correctly.

The authors also found that the human homologue of Scs2, called VAP, shares the same unique polarized distribution in yeast, suggesting a conserved function. VAP mutations are associated with the motorneuron disease amyotrophic lateral sclerosis. Whether wrongly placed ER in the neurons of these patients could be part of the cellular pathology—perhaps by perturbing neurotransmitter vesicle release—remains to be seen.

Reference: Loewen, C.J.R., et al. 2007. J. Cell Biol. 179:467–483.