

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.

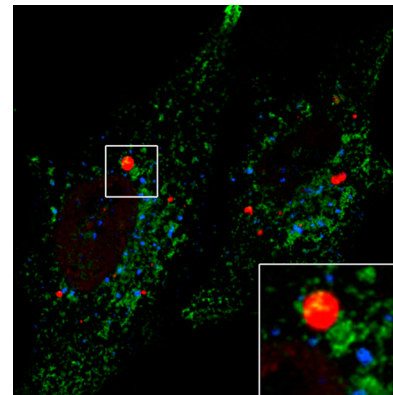
To investigate the molecular basis of disease in patients with CHMP2B mutations, Filimonenko and colleagues knocked down different ESCRT subunits or overexpressed CHMP2B mutants in cultured cells. Tracking the progress

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.

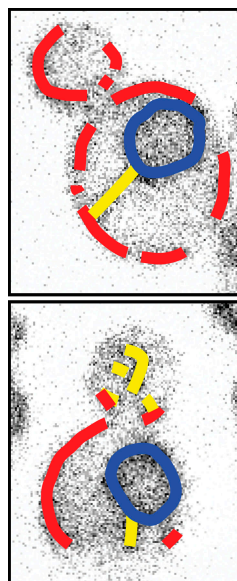
The autophagy-deficient cells seemed to be trying to compensate by ramping up a second protein-degradation pathway, headed by the proteasome. This was insufficient to compensate for the autophagy deficiency, however.

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. **JCB**

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



Ubiquitinated protein deposits (red) build up in the absence of autophagy.



The ER in budding yeast (colored lines) has less cortex (red) and more cytoplasmic (yellow) association when Scs2 is missing (bottom). Nuclear-associated ER (blue) appears normal.

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.

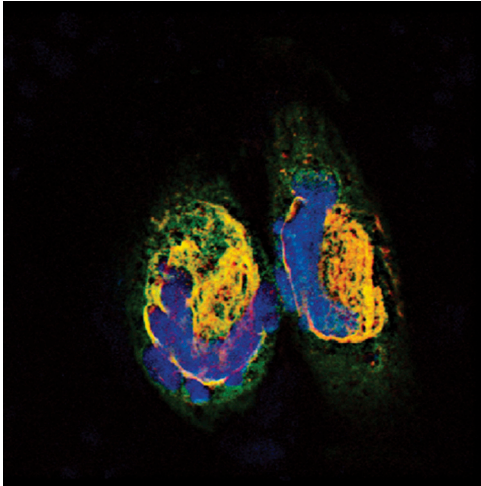
The positioning of particular organelles can often be important for cell function. How a cell senses organelle positioning, however, is unknown. The budding yeast is a useful model organism for getting to the bottom of this question, as its organelles move into the bud in a highly ordered manner. The 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. **JCB**

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



RRP17 (red) binds CAPS1 (green) to help the heart pump out hormones.

Heart hormone release

Problems of the heart may be healed by brain matter, if findings from Rybkin et al. are any indication. Proteins that normally instigate neurotransmitter release help the heart calm down during times of stress and high blood pressure.

Rybkin et al. deal with matters of the heart. In a search for novel heart-specific signaling proteins that might regulate functions such as heart rate, they previously found one that was similar to the signal-transducing small G-protein, Ras. They called the newbie RRP17, for Ras-related protein on human chromosome 17.

RRP17 binds to a protein called CAPS1, which enhances neurotransmitter vesicle release. The team now shows that CAPS1 levels rise in heart cells in response to cardiac stress. RRP17 levels did not increase during the stress, but what was already there promoted CAPS1 to drive the release of secretory vesicles containing a blood pressure-reducing hormone.

Mice lacking RRP17 secreted less of the hormone and consequently had higher blood pressure. Although RRP17, like CAPS1, was also abundant in the brain, the team has yet to observe any neurological impairment in the mice lacking the protein. Although the mice function just fine in their cage, explain the authors, whether they would perform normally in cognitive tests remains to be determined. **JCB**

Reference: Rybkin, I.I., et al. 2007. *J. Cell Biol.* 179:527–537.

Constructing P-bodies

Putting together a P-body requires both building blocks and glue. Decker et al. now show that a yeast mRNA decapping activator protein contributes to both jobs: it forms part of the building block and also helps to glue those blocks together.

P-bodies are cytoplasmic granules that contain unused mRNAs with their associated proteins (complexes known as mRNPs) and mRNA decay factors. Much of the team's previous work investigated how the mRNPs—which form the building blocks—affect mRNA function. How and why mRNPs assemble into P-bodies was unclear.

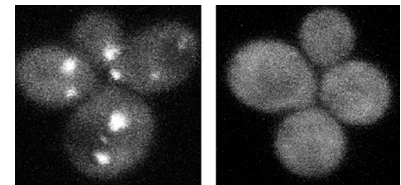
The new work further reveals the inner organization of the building blocks by identifying how an mRNA decapping activator, called Edc3p, brings together the mRNP components. Edc3p bound to two protein complexes that associated with P-body-bound mRNAs: a complex of 5' decapping enzymes and a complex of other decapping activators.

mRNPs then came together into large, visible P-bodies via specific domains of Edc3p, which the team identified through deletion analysis. Removing either of these gluing domains or the entire Edc3p protein resulted in a loss of visible P-bodies from yeast cells.

Yeast unable to assemble large P-bodies just as easily repressed translation and degraded some mRNAs, showing that neither Edc3p or visible P-bodies are required for these functions.

Although the team has yet to identify abnormalities in yeast that are unable to assemble P-bodies, the fact that visible P-bodies are a conserved phenotype of multiple species suggests that aggregation is indeed important. Aggregation might affect specific mRNAs or be needed to prevent mRNPs from interacting with other cellular proteins, say the authors. **JCB**

Reference: Decker, C.J., et al. 2007. *J. Cell Biol.* 179:437–449.



Construction of P-bodies (white) stops in the absence of Edc3p (right).

A polarity/proton loop

Pushing protons out of a cell's leading edge prompts a positive feedback loop for polarity, according to a new report by Frantz et al.

An important polarity protein in numerous cell types is a Rho GTPase called Cdc42, which transduces signals to the cytoskeleton to maintain polarized growth. Now, Frantz and colleagues show that Cdc42 also maintains polarity during fibroblast migration.

Migration is thought to be regulated by intracellular pH. The team found that Cdc42 caused an increase in intracellular pH by activating a sodium/hydrogen exchanger called NHE1, which drives protons out of the cell.

This increase in pH was necessary to activate Cdc42 at the leading edge of the cell. The pH increase was needed to bring Cdc42's activator, a guanine nucleotide exchange factor (GEF), to the membrane, allowing the GEF to pass a new GTP to Cdc42 for hydrolysis.

The team is currently investigating what kicks off this positive feedback loop for polarity. They are also intrigued that, given the pH dependency of GEF activity, numerous cell signaling pathways that also require GEFs and GTPases might be regulated by proton flux. **JCB**

Reference: Frantz, C., et al. 2007. *J. Cell Biol.* 179:403–410.