In This Issue

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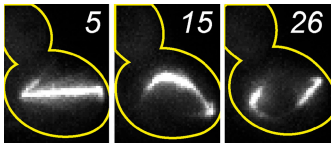
Elm1 sparks the SPOC



This time series shows misalignment of the mitotic spindle in an Elm1-deficient cell.

If the spindle isn't aligned properly, the spindle position checkpoint (SPOC) pauses mitosis so that the cell can make adjustments. Caydasi et al. identify a master switch for the checkpoint.

When a yeast cell begins to bud, the SPOC detects whether the spindle has lined up parallel to the bud–mother cell axis. One of the main SPOC proteins is the kinase Kin4. What controls its activity is unclear, so the researchers looked for proteins that flip on Kin4.

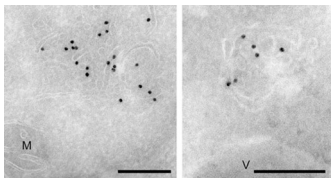
Caydasi et al. started with yeast cells that manufacture extra Kin4, which die because they become stuck in anaphase. The team reasoned that genes whose absence allowed the cells to survive were likely to be Kin4 activators. One of the activators they identified was another kinase called Elm1, which is part of a pathway that helps cells retain their shape.

To determine how Elm1 affects the SPOC, the researchers tested a yeast strain prone to faulty spindle alignment. If the spindle was askew, control cells took at least an hour to complete anaphase because they stopped to make corrections. But Elm1-deficient cells raced through anaphase in only 24 minutes, suggesting that they couldn't activate the SPOC.

Elm1 phosphorylates Kin4 throughout the cell cycle. Where the two proteins interact remains uncertain. Elm1 normally settles at the base of the newly forming bud, but it doesn't have to remain there for Kin4 to switch on. The researchers think that Elm1 activates Kin4 so that the SPOC is primed to act if the spindle misaligns. **ML**

Caydasi, A.K., et al. 2010. *J. Cell Biol.* doi:10.1083/jcb.201006151.

Autophagy membranes held in reserve



Atg9-containing vesicles and tubules reside next to a mitochondrion (M, left) but form a PAS near the vacuole (V) at the onset of autophagy (right).

Cells draw on a reservoir of tubules and vesicles to start building the membranes required for autophagy, Mari et al. say.

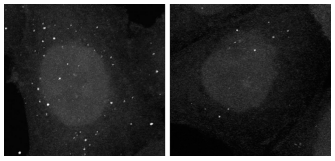
During autophagy, cells form a double-membraned autophagosome to engulf cytoplasmic components and deliver them to the lysosome for degradation. In yeast, autophagosome biogenesis begins at the phagophore assembly site (PAS), a region near the vacuole (the yeast equivalent of lysosomes) where autophagy proteins and lipid bilayers build the phagophore, a membranous sac that expands into a mature autophagosome. Where the PAS membranes come from is unknown. Mari et al. investigated their origin by tracing the movements of Atg9—the only conserved transmembrane autophagy protein and one of the first parts of the machinery to arrive at the PAS.

The researchers found that, before moving to the PAS, Atg9 localized to small clusters of tubules and vesicles that were often next to mitochondria. At the beginning of autophagy, one or more of these clusters moved en bloc toward the vacuole, where they formed the PAS. But where do these Atg9-containing tubules and vesicles come from in the first place? The transport of newly synthesized Atg9 was blocked by mutants preventing traffic through the secretory pathway, suggesting that these "Atg9 reservoirs" arise from the ER and/or the Golgi. Mari et al. think that the reservoirs can rapidly provide a cell with the membranes it needs to initiate autophagy in times of stress.

Senior author Fulvio Reggiori now wants to investigate which other proteins are stored in these unique compartments, and why they tend to wait near mitochondria. **BS**

Mari, M., et al. 2010. *J. Cell Biol.* doi:10.1083/jcb.200912089.

α-Synuclein leaves autophagy feeling compromised



Overexpression of α-synuclein (right) reduces the number of autophagosomes (bright puncta, left).

A protein linked to Parkinson's disease may cause neurodegeneration by inhibiting autophagy, Winslow et al. reveal.

The degradative autophagy pathway clears a variety of toxic waste from cells, including misfolded proteins and defective mitochondria. These two types of cellular trash accumulate in neurons from Parkinson's patients, suggesting that autophagy could be impaired in these cells. A commonly aggregated protein in Parkinson's disease is α-synuclein, whose gene is often mutated or overexpressed in familial forms of the illness. Winslow et al. found that excess α-synuclein inhibits autophagy by blocking formation of the autophagosome—the double-membraned vesicle that engulfs cytoplasmic garbage and delivers it to lysosomes for destruction.

A previous study showed that α-synuclein inhibits Rab1a, a small GTPase that controls secretory transport from the ER to the Golgi. Winslow et al. found that Rab1a knockdown also impaired autophagosome formation whereas overexpression of the GTPase reversed the inhibitory effects of α-synuclein on autophagy. Depleting other Rab proteins involved in ER to Golgi transport failed to block autophagy however, suggesting that Rab1a has a specialized role in autophagosome biogenesis. This function is important at an early step in the pathway: an abundance of α-synuclein or lack of Rab1a mislocalized an early acting part of the autophagy machinery called Atg9 and blocked the formation of putative autophagosome precursors known as omegasomes.

Compromising autophagy in this way could enhance the gradual accumulation of toxic proteins and dysfunctional mitochondria, sensitizing neurons to cell death. Senior author David Rubinsztein now wants to investigate how α-synuclein inhibits Rab1a and how this impairs autophagosome formation. **BS**

Winslow, A.R., et al. 2010. *J. Cell Biol.* doi:10.1083/jcb.201003122.