In This Issue

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Low pH puts proteasomes in storage

Peters et al. describe how starving yeast cells regulate the formation of proteasome storage granules (PSGs).

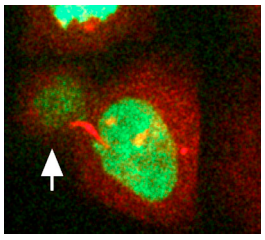
The proteasome is a large, multisubunit protease essential for many cellular functions including proliferation. In the absence of glucose or other carbon sources, budding yeast aggregate their proteasomes in PSGs, which may help protect the complexes until conditions improve. When glucose becomes available again, PSGs disperse, allowing cells to quickly reenter the cell cycle without waiting for new proteasomes to be built from scratch. How glucose levels regulate PSG assembly is unclear, however.

By screening a library of yeast deletion mutants, Peters et al. found that yeast lacking components of the vacuolar ATPase (V-ATPase) formed PSGs more quickly upon glucose starvation but took longer to disassemble the granules when glucose supplies were restored. The V-ATPase pumps protons out of the cytosol and into the vacuole, so yeast lacking this complex have a lower cytoplasmic pH. Lowering intracellular pH in other ways—by mutating the plasma membrane proton pump Pma1, for example—also promoted PSG formation, even in the presence of normal glucose levels. Low pH also stimulated the assembly of other cytoplasmic granules, such as actin bodies, that form in starving yeast cells.

Glucose deprivation is known to induce disassembly of the V-ATPase, which would acidify the cytosol and stimulate PSG formation. Senior author Shay Ben-Aroya now wants to determine how low pH promotes PSG assembly and to investigate whether proteasomes are inactive inside PSGs or whether they continue to degrade proteins during cell starvation.

Peters, L.Z., et al. 2013. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201211146.

EB3 helps daughter cells spread their wings



In the absence of EB3, one daughter cell (arrow) often fails to spread out at the end of mitosis.

Ferreira et al. reveal how Aurora B and the microtubule plus-end binding protein EB3 coordinate cytokinesis and daughter cell adhesion at the end of mitosis.

EB3 and its relative EB1 regulate microtubule dynamics in interphase cells, but they seem to be less important during mitosis. Indeed, Ferreira et al. confirmed that, although cells lacking EB1 and EB3 had problems orienting their mitotic spindles, they passed through mitosis with little delay. EB3-deficient cells ran into trouble as they exited mitosis, however.

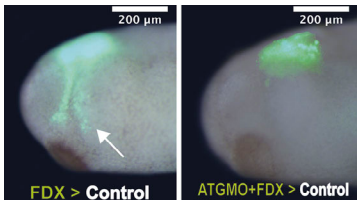
In the absence of EB3, the microtubules that form the midbody between separating daughter cells were unstable, causing the midbody to oscillate and partially inhibit cytokinesis. The mitotic kinase Aurora B, which concentrates at the midbody during anaphase, phosphorylated EB3 and promoted its ability to stabilize midbody microtubules.

Most cells lacking EB3 still completed cytokinesis but their daughter cells often failed to spread out and reattach to the underlying substrate. Cortical microtubules grew more in these cells, preventing them from forming stable focal adhesions. In this case, unphosphorylated EB3 was required to restrict cortical microtubule growth and promote daughter cell spreading.

The gradient of Aurora B activity that emanates from the spindle midzone therefore allows phosphorylated EB3 to regulate midbody microtubules, while unphosphorylated EB3 controls cortical microtubule dynamics. By endowing these two microtubule pools with distinct dynamics, EB3 and Aurora B allow cells to coordinate cytokinesis and daughter cell adhesion. Senior author Helder Maiato now wants to investigate how EB3's numerous binding partners contribute to the protein's function at different locations of the cell.

Ferreira, J.G., et al. 2013. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201301131.

Hif-1α provides a Twist to neural crest migration



The emigration of neural crest cells (green) seen in control embryos (arrow, left) is inhibited when the cells lack Hif-1α (right).

Barriga et al. reveal that a pathway that drives cancer cell metastasis also operates during development to promote the migration of neural crest cells.

Low oxygen levels stimulate cancer cell metastasis by stabilizing the transcription factor Hif-1α, which up-regulates genes that promote epithelial to mesenchymal transition (EMT), migration, and invasion. Barriga et al. wondered whether hypoxia and Hif-1α might also regulate similar processes during development, such as the migration of neural crest cells from the neural plate into other embryonic tissues.

Inhibiting Hif-1α expression blocked neural crest cell migration in *Xenopus* and zebrafish embryos. The researchers identified two key genes that were down-regulated in the absence of Hif-1α. One of these was the gene encoding the chemokine receptor Cxcr4, which binds to the chemoattractant SDF-1. Neural crest cells lacking Hif-1α couldn't migrate toward an SDF-1 source in vitro, but chemotaxis was restored by the expression of exogenous Cxcr4.

The second key target of Hif-1α was the gene encoding Twist, a transcription factor that promotes EMT by repressing the adhesion molecule E-cadherin. E-cadherin was up-regulated in the neural crest cells of *Xenopus* embryos lacking Hif-1α or Twist, inhibiting their dispersal from the neuroepithelium. Because *Twist* and *Cxcr4* are both regulated by Hif-1α in cancer cells undergoing EMT and chemotaxis, it seems that tumors can metastasize by hijacking the developmental program of neural crest cells. Senior author Roberto Mayor now wants to understand how Hif-1α, which is expressed ubiquitously, has such specific effects on the neural crest.

Barriga, E.H., et al. 2013. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201212100.