In This Issue

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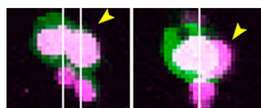
Walking a fine caspase line



DIAP1 (green) turnover means the shaft cell (arrows) can survive and form a proper bristle.

Whether caspase enzymes perform developmental tasks or cause cell death can depend on the timing with which a caspase inhibitor protein turns over, find Koto et al. They show that the inhibitor protein follows a dramatic temporal regulation specific to cell type and maturity.

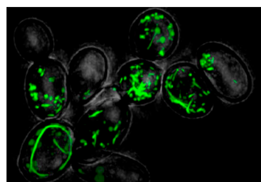
In the last decade, researchers realized that the destructive capabilities of caspase enzymes can be harnessed to carry out certain developmental events, such as dendrite pruning and sperm individualization. But how the caspases are put to work in these scenarios without turning deadly remains a mystery.

Koto et al. devised a fluorescent version of the caspase inhibitor DIAP1 to follow its fate in live *Drosophila* cells during sensory organ bristle development. Surprisingly, the inhibitor vanished altogether in the midst of cell differentiation, without activating cell death, and then reappeared in two cells, including the shaft cell, which spurts forth the bristle. An excess of DIAP1 in the shaft cell gave shorter, thicker bristles, whereas knocking down *diap1* resulted in the loss of the shaft cell to programmed cell death. DIAP1's timely reappearance in this cell followed by a second quick departure appears to ensure the delicate balance between caspase-driven bristle formation and the cell death cascade. The nonlethal nature of the DIAP1 disappearances in these cells indicates other survival strategies exist.

The researchers propose that DIAP1's degradation promotes activation of the initiator caspase, Dronc, without waking up the downstream executioner caspases. Whereas other studies have shown non-death caspase activities sequestered to subcellular compartments, this work hints that caspases can also be activated just a touch, before being turned back down.

Koto, A., et al. 2009. *J. Cell Biol.* doi:10.1083/jcb.200905110.

Securing the next generation's peroxisomes



Deleting Pex3B, a paralogue of Pex3, causes stretched, tubular peroxisomes (green) and inheritance defects.

The same protein that directs the biogenesis of peroxisomes, essential detoxifiers of the cell, also hitches the organelle to its myosin motor for transport into daughter cells, show Chang et al.

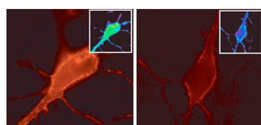
The beloved model *Saccharomyces cerevisiae* does have limitations—one being that its peroxisome receptor for the myosin V motor has no known homologues outside of this fungus family. To figure out how other eukaryotes accomplish peroxisome inheritance, Chang et al. turned to the yeast *Yarrowia lipolytica* and a new player, Pex3B.

Pex3B was recently identified as a paralogue of Pex3, the highly conserved protein responsible for the earliest stages of peroxisome genesis—forming new membrane at the ER. Chang et al. found that, like Pex3, Pex3B is a peroxisomal integral membrane protein. Deleting Pex3B resulted in long, tubular peroxisomes, which were conspicuously absent from the bud tips of dividing cells. Closer inspection of inheritance in *pex3BΔ* cells revealed that the organelles had trouble entering the bud and, once there, ceased moving altogether, with the stretched peroxisomes often straddling the mother-bud neck.

These movement troubles hinted at a role for Pex3B as the organelle's myosin V receptor. Not only did Pex3B bind to the motor, but the team showed that Pex3 did as well. In fact, when overexpressed, Pex3 compensated for the inheritance defect of the *pex3BΔ* cells. Pex3's paralogue allowed Chang et al. to uncover its hidden talent as a myosin receptor, which establishes a direct temporal link between biogenesis and transfer. The authors propose Pex3's dual activities ensure that new, fresh peroxisomes move into new cells, while old, oxidatively damaged organelles remain behind.

Chang, J., et al. 2009. *J. Cell Biol.* doi:10.1083/jcb.200902117.

PIKfyve promotes neuron self-preservation



With glutamate stimulation (right), $Ca_V1.2$ channels (red) are internalized and degraded by cortical neurons under PIKfyve's direction.

Tsuruta et al. find that a lipid kinase directs a voltage-gated calcium channel's degradation to save neurons from a lethal dose of overexcitement.

An important player in cellular signaling, calcium is also terribly toxic at high levels. Neurons have evolved ways to protect themselves against the calcium influxes that come during periods of intense electrical activity. One way to limit the calcium flood is to remove the gatekeepers, calcium channels, from the cell surface. How neurons direct this is clinically important in a range of disorders from stroke to Alzheimer's disease.

In a proteomic screen for binding partners of the $Ca_V1.2$ channel, Tsuruta et al. extracted what seemed a strange companion at first: PIKfyve, the lipid kinase that generates PtdIns(3,5)P_2 and promotes the maturation of endosomes into lysosomes. Other groups had recently shown that mutations affecting PtdIns(3,5)P_2 production cause degeneration of excitable cells in both mice and humans, including mutants found in ALS and Charcot-Marie-Tooth disease. The team hypothesized that PIKfyve might be directing $Ca_V1.2$ degradation. Using glutamate excitation to simulate excitotoxic stress, the authors showed that $Ca_V1.2$ is internalized, associates with PIKfyve, and is degraded in the lysosome. When Tsuruta et al. squelched levels of PIKfyve or PtdIns(3,5)P_2, excess channels stayed at the surface and left neurons vulnerable to apoptosis.

The findings clarify how this neuroprotective mechanism unfolds and suggest that existing calcium channel–blocking drugs might aid patients with neurodegenerative disorders stemming from a PtdIns(3,5)P_2 defect.

Tsuruta, F., et al. 2009. *J. Cell Biol.* doi:10.1083/jcb.200903028.

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