RESEARCH HIGHLIGHTS

Germline determinants clean-up

Autophagy, long viewed as a bulk catabolic pathway, was recently implicated in the selective degradation of damaged organelles such as the endoplasmic reticulum and mitochondria. Zhang and colleagues have now found that autophagy selectively eliminates aggregates formed in somatic cells by proteins normally associated with germline determinants, in the nematode *Caenorhabditis elegans* (*Cell* **136,** 308–321; 2009). In worms, germline determinants, including PGL-1 and -3, form aggregates that are selectively segregated into the germ line through their asymmetric distribution during cell divisions; remnants in somatic cells are removed by a hithero undefined mechanism. Autophagy was first linked to this process through a genome-wide RNAi screen aimed at identifying genes whose loss of function lead to upregulation of PGL-1 in somatic cells. In worms harbouring mutations in genes required for autophagy, somatic cells accumulate a subset of maternal germline determinants in distinct aggregates called PGL granules, indicating that autophagosomes participate in their clearance. This hypothesis is supported by the colocalization of PGL granules with autophagosomal markers. To gain insight into PGL granule recognition by the autophagy machinery, the authors looked for suppressors of PGL accumulation in autophagy mutants. They found that the protein SEPA-1 was essential for the appearance of PGL granules. SEPA-1 directly interacts both with PGL-3 and the autophagosome component LGG1–ATG8, serving as an adaptor for the recognition of the PGL granules by the autophagy machinery. Whether autophagy prevents accumulation of germline determinants in the somatic lineage of other organisms remains to be explored. NLB

Microtubules take path into dendritic spines

The morphological remodelling of neuronal dendritic spines is associated with synaptic plasticity. Remodelling is based on the rearrangement of actin filaments, which are predominantly concentrated in the spines, whereas microtubules are confined to the dendritic shaft, with no reported role in regulation of synaptic plasticity. Hoogenraad and colleagues (*Neuron* **61,** 85–100; 2009) now show that growing microtubule plus ends that associate with the protein EB3 enter dendritic spines and modulate their morphology through the regulation of actin dynamics. EB proteins are key regulators of microtubule-associated signalling pathways. In mature neurons, EB3 associated with dynamic microtubule tips, which extended into the spines, and colocalized with synaptic markers. Knockdown of endogenous *EB3* reduced the spine size and impaired synaptic transmission, while also decreasing levels of F-actin. EB3 was found to interact with the synaptic protein and actin regulator p140Cap, which in turn interacted with the F-actin-binding protein cortactin. In EB3-depleted neurons p140Cap was delocalized from the dendritic protrusions; p140Cap depletion resulted in decreased spine density and F-actin levels, whereas overexpression of p140Cap or cortactin rescued the EB3 depletion phenotype. These newly identified interactions between EB3, p140Cap and cortactin point to a function of EB3-positive microtubules in mediating signalling to the actin cytoskeleton within dendritic spines, to regulate synaptic plasticity and hence learning and memory. SG

CCM controls vascular integrity

Mutations in the CCM2 (cerebral cavernous malformation) gene leads to enlarged thin-walled blood vessels, but the function of this putative adaptor protein is unknown. Two studies in Nature Medicine demonstrate a role of CCM2 in endothelial barrier function. In zebrafish, loss of *ccm2*, *krit1* (Krev interaction trapped 1, another gene associated with the disease) or *heg* (heart of glass, a transmembrane receptor) leads to a dilated heart phenotype. Kahn and colleagues (*Nature Med.* doi: 10.1038/nm.1918; 2009) find that depletion of *heg1* in mice leads to loss of vascular integrity; simultaneous mutation of *ccm2* leads to a more severe phenotype, suggesting that these proteins function in the same signalling pathway. In an accompanying study Li and colleagues (*Nature Med.* doi: 10.1038/nm.1911; 2009) show that the defective vascular development in *ccm2* mutant mice is endothelial cell-autonomous and not mediated by neural or smooth muscle cells, as had been suggested. Both studies demonstrate a requirement for CCM2 in endothelial lumen formation. Previous ultrastructural studies of human CCM disease biopsies indicated abnormal endothelial cell–cell junctions. A junctional role is supported by Kahn and colleagues, who describe shortened endothelial junctions in both Heg1- and CCM-deficient mice. Li and colleagues find that CCM2-deficient human microvascular edothelial cells show reduced cortical actin and decreased barrier function. Biochemically, Kahn and colleagues show that the intracellular tail of Heg1 binds CCM2 in a manner facilitated by KRIT1. Although the Heg1-KRIT1-CCM2 signalling pathway needs to be defined in more detail, Li and colleagues demonstrate that CCM binds RhoA and Rac1, and that CCM2-depletion leads to elevated RhoA and JNK activity. Indeed, RhoA inhibition rescues the milder phenotype seen in mice heterozygous for the CCM2 mutation. CKR

EGFR puts the brakes on Notch and Wingless signalling

A study by Nagaraj and Bannerjee reveals crosstalk between several key developmental signalling pathways. They report that *phyllopod* (*phyl*), a transcriptional target of the epidermal growth factor receptor (EGFR) signalling pathway, restrains Notch and Wingless signalling (*EMBO J.* doi: 10.1038/emboj.2008.286; 2009). Endocytosis of the Notch receptor, its ligand Delta and Wingless (Wg) is essential for promoting signalling through Notch and Wg pathways. In the developing *Drosophila* eye disc, the authors find that Notch and Wg proteins are upregulated and signalling from both pathways is enhanced, in *phyl* mutants. A series of elegant genetic experiments revealed that the upregulation was probably due to a post-internalization block in trafficking, specifically at the early endosome stages, in *phyl* mutants. Overexpressing Delta to enhance Notch signalling phenocopied the effect of *phyl* mutants in the developing eye. EGFR signalling is known to result in transcriptional activation of *phyl*. Consistent with the idea that the effect of EGFR on these two pathways is mediated by Phyl, the authors find that Phyl overexpression phenocopies the suppressive effect of EGFR upregulation on Notch and Wg signalling. Conversely, both pathways are upregulated in *phyl* and *EGFR* mutants. While Phyl is known to promote degradation of the transcriptional repressor Tramtrack through the ubiquitin ligase Sina, regulation of Notch and Wg signalling by *phyl* is independent of both Sina and Tramtrack. SS

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