Fission and disease

Proper regulation of mitochondrial fusion and fission is required for both neurons and Schwann cells, report Niemann et al. on page 1067.

Charcot-Marie-Tooth disease (CMT) is subdivided into axonal or demyelinating phenotypes, depending on whether the neurons or the myelinating Schwann cells are most affected. However, mutations in a single gene, GDAP1, can cause both phenotypes, muddying the distinction.

Niemann et al. found that GDAP1 is localized to the outer membrane of mitochondria. Overexpression of wild-type GDAP1 caused excessive fragmentation of mitochondria, whereas knock-down of GDAP1 expression resulted in long tubular mitochondria. Disease-causing mutations also impaired mitochondrial fission. However, mitochondrial physiology was not obviously disrupted in the presence of excess GDAP1 or GDAP1 mutations, leaving open the question of why the mutations induce degeneration.

GDAP1 is not the first protein involved in mitochondrial dynamics to be associated with CMT. Mutations in Mfn2, a protein required for mitochondrial fusion, are found in some patients with axonal CMT, but again, what causes the degeneration is unclear. Nor is it clear why Mfn2 primarily results in neuronal damage, whereas GDAP1 affects both neurons and Schwann cells.

To find out, Niemann et al. are using conditional knock outs to determine whether neurons are most sensitive to a loss of GDAP1 activity or whether myelinating Schwann cells are the primary targets of the mutations. JCB

Calcium, direct from the source

Cell adhesion proteins determine the direction of turning during axon guidance by altering downstream signaling, report Ooashi et al. on page 1159.

Axon guidance cues, such as netrin-1, stimulate growth cone turning by altering intracellular calcium levels. However, no simple correlation exists between the location of calcium increase within the growth cone and the direction of movement. Previous data suggested that the type of cell adhesion matrix influences the direction of movement.

Ooashi et al. tested the effects of calcium release in dorsal root ganglia neurons by uncaging NP-EGTA in a small region of the growth cone. Axons grown on N-cadherin or on L1 immunoglobulin superfamilies protein turned toward the side of calcium release and exhibited an increase in cAMP. Blocking cAMP caused the cell to turn away from the stimulus. Meanwhile, cells on laminin turned away from the site of calcium release and did not show an increase in cAMP.

cAMP stimulates protein kinase A activity, which phosphorylates ryanodine receptors (RyRs) and triggers calcium-induced calcium release. When the team blocked RyR activation, axons on N-cadherin or L1, which would normally turn toward the stimulus, turned away, suggesting that both the initial calcium release and a subsequent downstream influx was required for attractive turning. Blocking RyR had no effect on repulsive turning seen in cells on laminin.

The authors conclude that the system enables cells to modify their responses to soluble cues based on their local environment, including the type of cell adhesion molecules present. JCB