LIS-less neurons fall behind

IS1, the protein that is affected in the developmental disorder Lissencephaly, interacts with cytoplasmic dynein in several cell systems. As neuronal positioning is disrupted by this disease, LIS1 and dynein are assumed to be involved in neuronal migration. Now, live in vivo images from Tsai et al. (page 935) reveal that migration is just one facet of LIS1 function.

Neuronal development was blocked at multiple stages following the loss of LIS1, probably depending on the efficiency of RNAi uptake in a cell. The earliest defect was seen in the proliferation of neural progenitors. The nuclei of these precursors normally oscillate in the neural tube and divide when they reach the ventricular surface. But nuclei of cells lacking LIS1 did not oscillate and never divided. The authors suspect that nuclear positioning dictates cell division in these precursors, perhaps via a mitosis-promoting signal at the ventricular surface.

LIS1-lacking neurons also stalled at the transition to a migratory bipolar state. After mitosis, differentiating neurons work their way out from the ventricles, but then pause and extend multiple processes, one of which becomes an axon and extends further. In time, the cell becomes bipolar (keeping only its axon and one migratory process) and migrates to peripheral regions of the cortex. Multipolar cells lacking LIS1, however, never converted to the expected bipolar form and remained immobile. Their axons persisted, but did not elongate like those of normal cells.

Some LIS1-lacking cells with the classic bipolar state did appear further out in the cortex. These cells were also immobile, although their migratory processes elongated normally.

The defects are probably by-products of altered dynein activity, although the specific effects of LIS1 on dynein are not well understood. Nuclear oscillation, for example, might require the linkage of nuclei via microtubules to cortical dynein/LIS1. Dynein and LIS1 are found at the leading edge of migrating fibroblasts, and the group has new evidence that they might also be in neuronal growth cones, where they could promote cell migration or axon extension. JCB

Formin steps and slips

On page 889, Shemesh et al. suggest how formin builds actin filaments without tangling them. Formin, according to the new theory, slowly winds the filament and then undoes the twist with one big slip. Formin caps the barbed ends of actin filaments, yet allows more monomers to be added. It has been proposed that a formin dimer works as if climbing stairs. The formin dimer initially contacts the terminal actin monomers but then releases its grip on the actin monomer second from the top, allowing it to bind a new actin monomer. When that new actin monomer is added, the free half of the formin dimer attaches to it. The other half of formin then releases its actin, and so on.

The model made sense but did not explain how torsion was accommodated. Each added actin monomer induces a slight rotation. As formin is often fixed in place at adhesion junctions, it cannot rotate. Actin filaments attached to both formin and the cytoskeleton cannot rotate freely either. Polymerization should thus induce torsional strain and cause supercoiling, but that is not seen. Now, the authors propose that formin periodically switches from stair stepping to a screw mode to release the accumulated strain.

A recent crystal structure revealed that formin dimers make a ring that hugs the barbed end like a screw cap, prompting the authors to imagine that the cap could turn either way. In their stair model, formin twists slightly in one direction (the shorter distance from monomer to monomer, ~14°). But the cap might also turn the long way around (~166°) in a screw-like mode if both halves of the formin dimer transiently release actin. The group modeled this theory using an elastic energy analysis.

The authors propose that torsional stress builds up with stair stepping until it is energetically favorable for formin to slip into screw mode. They estimate that every 12 steps should be followed by one screw mode slip. Although the prediction still awaits experimental verification, the regulation of polymerization mode by stress might apply to more than just actin. JCB