LIS-less neurons fall behind

LIS1, 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, \( \sim 14\)°). But the cap might also turn the long way around (\( \sim 166\)°) 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
eIF2 activated in spots

The eIF2 translation initiation factor travels to a cytoplasmic focus for activation, according to Campbell et al. (page 925). In stressed cells, which turn down translation, the same foci soak up eIF2.

Stressed yeast cells shut down general translation so they can concentrate on making proteins that will help them adapt. One highly regulated protein during this inhibition is eIF2, which is active only in its GTP-bound form. The GDP-to-GTP exchange is done by eIF2B, about half of which the authors now show aggregates in a cytoplasmic blob in yeast.

Under normal conditions, eIF2 shuttled quickly in and out of the foci, presumably getting activated and sent on its way. But when cells were stressed (e.g., by low amino acid levels), eIF2 was less able to escape the foci. This trapping depended on eIF2 phosphorylation. Translation inhibition also depends on eIF2 phosphorylation, which locks eIF2 in an inactive complex with eIF2B, but it is not clear whether eIF2B must be in foci for inhibition to occur.

The concentration of some eIF2B in foci might make translation more efficient or more easily regulated. The group suspects that the foci themselves move around the cell, like a mop for GDP-bound eIF2. Although no one has seen these foci in mammalian cells, they might have been easily missed: only actively translating yeast cells contained them. JCB

A Notch outlier

Notch is activated by ligands on opposing cells. When expressed in the same cell as Notch, some DSL (Delta, Serrate, Lag2) ligands become inhibitors. On page 983, Ladi et al. show thatDll3 is the only known DSL ligand that is dedicated solely to Notch inactivation, leaving the job of activator behind.

Dll3 seems to be important for somitogenesis, as its loss disrupts somite patterning. But since cycles of Notch activity control somite formation, it has not been clear whether the important function of Dll3 is to turn Notch on or off. The new findings show that Dll3 must be turning down Notch signaling.

Unlike all other known DSL ligands, Dll3 was unable to activate Notch in apposing cells. In fact, Dll3 and Notch did not even interact unless they were in the same cell. When the authors examined the Dll3 structure, they found that most of the conserved activating regions of DSL ligands had been lost.

Notch is widely expressed in mammals, and the mechanism for turning on its pathway is rather simple—the receptor itself is also the signal transducer. Perhaps for this reason, says principal investigator Gerry Weinmaster, “several levels of negative regulation must be superimposed on its activation scheme to keep it under tight control. Notch seems to have more ways to turn off signaling than to turn it on.” The evolution of a dedicated Notch inhibitor that resembles its activators seems to be one more way to keep Notch in check. JCB

An actin ruler

On page 947, McElhinny et al. suggest that nebulin is a molecular ruler for actin filaments in muscle cells.

Muscle physiology depends on the precise alignment, length, and overlap of thin (actin) and thick (myosin) filaments. Capping proteins such as Tmod stop the growing and shrinking of dynamic thin filaments but lack the innate ability to know when to do so. The new results show that the capping proteins know when to act because of nebulin, a giant protein that spans the length of thin filaments.

Nebulin’s size varies by muscle cell type, and the variation correlates with thin filament length. McElhinny et al. removed nebulin from cultured heart muscle cells by RNAi and found that the actin filaments became unruly. Their pointed ends (which overlap with thick filaments) were no longer decorated by Tmod and thus grew past their normal lengths. Barbed ends were also disorganized in the absence of nebulin.

As expected, muscle contraction was impaired by the uneven, elongated thin filaments. Muscle development might also depend on thin filament precision, as skeletal myotube maturation was blocked by nebulin RNAi. Alternatively, nebulin might harbor an undiscovered signaling function.

Nebulin was also detected in nonmuscle cells, where it might set the lengths of actin filaments of cilia and microvilli. Some researchers remain skeptical of the ruler theory unless mutant nebulins of various sizes can be shown to dictate filament lengths. Nebulin’s large size and modular structure, however, make this a challenging experiment. JCB

Thin filaments (red) become elongated when nebulin is lost. Titin (blue) and thick filaments (green) are unaffected.