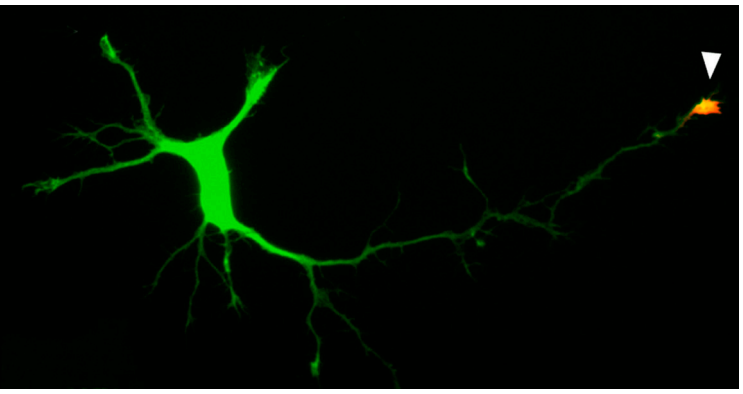
Text by Nicole LeBrasseur
lebrasn@rockefeller.edu

Kinesin switch in neurites

Before axon specification, seemingly identical neurites are not so alike after all. New research from Catherine Jacobson, Bruce Schnapp, and Gary Banker (Oregon Heath & Science Center, Portland, OR) reveals a hitherto unseen biochemical distinction in neurites of developing neurons.

The distinction was noted while visualizing a constitutive version of the Kinesin-1 motor, which in mature neurons is found only in the axon. Because the plus ends of axonal microtubules point away from the cell body, whereas those in dendrites face both directions, Kinesin-1's plus end–directed activity could explain this specific accumulation. But the new results show that Kinesin-1 is found in a subset of young neurites, often in just one, at a time when the microtubules in all neurites are still similarly oriented.

The accumulation of Kinesin-1 in a given young neurite was transient—it periodically switched homes until the time at which the axon was specified. With each switch, only one or two neurites contained the motor at a time. To explain the preference of Kinesin-1 for a given neurite, Banker suggests, "the population of microtubules [in that neurite] is distinct. But I'm pretty mystified as to what that difference is."



BANKER/ELSEVIER

Kinesin-1 (red) accumulates specifically in the axon (arrowhead) even before microtubule polarity differs between axon and dendrites.

One of his theories suggests that tubulin is transiently modified posttranslationally in certain neurites. Because Kinesin-1 has a relatively low affinity for microtubules but travels far with each binding, localized modifications that increase its affinity even slightly might strongly favor its accumulation in that neurite.

Stable accumulation of truncated Kinesin-I within a neurite coincided with that neurite's specification as the axon and is now the earliest marker of this event. But, says Banker, "every time you see one of these molecular distinctions, it takes the question one step higher, to 'what led to that?'" This new question will now haunt neurobiologists, at least for the near future. JCB

Reference: Jacobson, C., et al. 2006. *Neuron.* 49:797–804.

Hedgehog makes giant brains

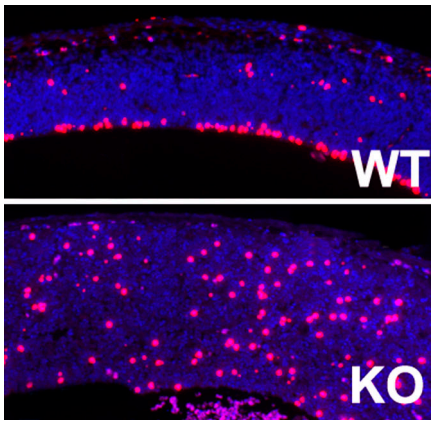
Brain size is kept in check by proteins at cell–cell junctions that act as look-outs for cell density, report Wen-Hui Lien, Olga Klezovitch, Valeri Vasioukhin, and colleagues (Fred Hutchinson Cancer Research Center). The group finds that Hedgehog (Hh)-mediated proliferation is dampened in densely packed cells by an adherens junction component called αE-catenin.

To study the function of adherens junctions, the FHCRC group eliminated αE-catenin, which links the cell junctions to the cytoskeleton. Mutants lacking αE-cadherin in their developing central nervous system had strikingly large brains, with twice as many cells than wild-type controls. Much of this massive—and lethal—excess was due to rapid mitotic cycling of neural progenitor cells.

Microarrays revealed that the expression of fewer than ten genes was altered by the loss of αE-catenin. Several of the up-regulated genes are activators or targets of Hh signaling, which induces hyperproliferation. Blocking this pathway rescued the brain size defect of the αE-catenin mutants. This study provides the first link between Hh signaling and contact-mediated inhibition of proliferation, although just how αE-catenin inhibits Hh is not yet clear.

Junctions in other organs might also pressure cells into down-regulating proliferation via Hh. "In an organism," says Vasioukhin, "space is a commodity that you have to be aware of. Obviously, cells don't have eyes, so they need another way to 'see' how dense the cell population is." Adherens junctions are the perfect candidate to relay this information, as junctions expand with increasing cell density.

Epithelial tumors often down-regulate cell adhesion proteins, including α-catenin, and may thus bypass the density-dependent Hh control. "When you remove this brake," says Vasioukhin, "you blind [the cells]. They cannot find out what's happening around them. They wrongly perceive that neighbors are missing and therefore that cell density must be low, so they continue proliferating." JCB



VASIOUKHIN/AAAS

More mitotic cells (pink) are found in developing brains lacking αE-catenin (bottom).

Reference: Lien, W.-H., et al. 2006. *Science.* 311:1609–1612.