In This Issue

**Growth factors attract mRNAs**

Transcripts are drawn to—or repulsed by—extracellular signals, report Willis et al. Unique sets of mRNAs, the findings show, are brought to or warded off from axon sites in contact with neuronal growth factors.

Axons have their own translational machinery that allows them to respond to stimuli rapidly. Stores of transcripts lie in wait near axonal ribosomes, ready to be translated when called upon. The make-up of these stores, the new results reveal, can be changed locally by extracellular cues.

To measure store changes, the group first took an inventory of messages that are translated in injured axons, which ramp up local protein synthesis. Using this baseline, the authors then calculated transcript changes at sites also exposed to extracellular growth factors.

Growth-promoting neurotrophins caused some nearby transcript levels to increase and others to decrease. Growth inhibitors such as myelin-associated glycoprotein often had the opposite effects on those same transcripts.

Not all mRNAs were affected equally by growth promoters. The GAP43 transcript was attracted by NGF but not BDNF. And the necessary signaling pathways also differed. Trk neurotrophin receptors were commonly required, but only some transcript changes also required either or both PI3K and MAP kinase signaling.

The attraction of messages by neurotrophins required transport along microtubules both back to the cell body and out to the axon. This messaging system probably tells the cell body to send out the necessary new recruits. Indeed, levels of specific transcripts in the cell body dropped as they increased in the axon.

Changes in transcripts that were repulsed by growth inhibitors did not require microtubule transport back to the body. These axonal transcripts might be either degraded, sent further out into the axon, or transported along actin instead.

In addition to neurons, fibroblasts and muscle cells also locally translate specific messages. Although isolating small areas of their cytoplasm would be difficult, these and other cell types probably also change transcript stores in response to extracellular cues. **JCB**

Reference: Willis, D.E., et al. 2007. *J. Cell Biol.* 178:965–980.

**Kinesin-5 reins in axon branching**

The motor that puts a brake on spindle microtubule sliding also decelerates axon branching, report Myers and Baas.

The spindle brake is kinesin-5. Unlike most microtubule-based motors, the “cargo” of kinesin-5 is more microtubules. In dividing cells, this motor bundles oppositely oriented spindle microtubules and seems to help drive them apart. Recent work shows that kinesin-5 can also prevent them from sliding past each other too quickly, thus preventing premature pole separation.

Kinesin-5 also has a strong presence in developing neurons, which are done dividing and would thus seem not to need a spindle brake. Because its inhibition creates longer axons, Myers and Baas imagined that kinesin-5 normally transports short microtubule building blocks from the axon back to the cell body. In its absence, they figured, more blocks would be available for axon growth.

Instead, the authors found that short microtubules were transported twice as frequently without kinesin-5, both into and out of axons. The increase in transport and axon length was accompanied by an increase in axon branching. Normally, axons send out many new branches, most of which collapse back into the growth cone. But these retraction events were rare without kinesin-5.

Retraction is a result of myosin-2’s pulling force on the actin cytoskeleton. Dynein can counteract this force by hooking actin to long structural support microtubules. The authors now hypothesize that kinesin-5 opposes dynein, thus allowing retraction to occur. They suggest that it might do so by physically replacing dynein or by bundling microtubules, thereby increasing dynein’s load.

Drugs that block kinesin-5 activity are already in use as cancer therapies, thanks to their antimitotic effects. If kinesin-5 is also expressed in adult axons, the drugs might find secondary uses in prodding the regeneration of damaged axons. **JCB**

Reference: Myers, K.A., and P.W. Baas. 2007. *J. Cell Biol.* 178:1081–1091.

Axons branch wildly without kinesin-5 (bottom).
Pyk2 for perfect bones

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nstable microtubules create dense-boned mice, according to Gil-Henn et al. The authors show that bone-eating osteoclasts go hungry without the stabilizing activity of the Pyk2 tyrosine kinase.

In osteoclasts, Pyk2 resides mainly in podosomes, actin-rich structures that help attach osteoclasts to the underlying bone. Organized in a beltlike structure at the cell periphery, podosomes create a sealed zone between the cell and the bone. Beneath this zone, osteoclasts lower the pH and secrete enzymes that degrade bone to counter its production by osteoblasts.

Podosome belts and sealing zones form by the fusion of small actin rings at the cell periphery. This fusion appears to fail in osteoclasts from mice lacking Pyk2 due to instability of their microtubule network, causing faulty bone destruction and thick-boned mice.

Microtubule instability was accompanied by a reduction in the acetylation of microtubules in osteoclasts lacking Pyk2. Additionally, Rho activity was enhanced. The authors suggest that Rho somehow inhibits acetylation and thereby reduces microtubule stability until turned off by Pyk2 or one of its targets. This switch might be thrown when integrins turn on Pyk2 upon osteoclast adhesion to the bone surface. JCB

Reference: Gil-Henn, H., et al. 2007. J. Cell Biol. 178:1053–1064.

Emerin hooks centrosome to nucleus

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ells lacking emerin, one of the proteins whose loss causes a form of muscular dystrophy, cannot hook their centrosome to the nucleus, show Salpingidou et al. The lost linkage might weaken contractile cells, including those diseased muscles.

Besides harboring the genome, the nucleus is becoming increasingly recognized as a load-bearing structure. By hooking to the cytoskeleton, the nuclear envelope probably helps to absorb mechanical forces. The links that hook the nuclear envelope to the actin and intermediate filament networks are known. Now, the microtubule link is identified as emerin.

In cells lacking emerin, the microtubule-organizing center—the centrosome—drifted away from its usual nucleus-adjacent spot. In normal cells, emerin bound to β-tubulin, a component of both microtubules and centrosomes. Since the centrosome normally lies within 1.5 μm of the nucleus, emerin probably hooks directly to centrosomes rather than to long microtubule filaments.

Emerin was previously found only on the inner nuclear envelope, but closer inspection identified a portion on the outer envelope, where it can reach centrosomes. Other proteins must hold it in place there and link it to the nuclear lamina. The authors would like to identify these proteins and more centrosomal proteins that are part of the linkage. As ~50% of patients with Emery Dreifuss muscular dystrophy do not have mutations in the known causal genes (emerin and lamins A and C), such a list should provide more candidates. JCB

Reference: Salpingidou, G., et al. 2007. J. Cell Biol. 178:897–904.

Katanin cuts some, spares others

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lthough the microtubule-severing protein plays favorites, say Sharma et al. The slicer, called Katanin, builds up microtubules in cilia while it cuts down those in the cell body.

All microtubules are not created equal. In Tetrahymena, for example, the polymers come in many flavors, including ciliary extensions, an internal network, and cortical bundles. These subsets, the new results indicate, are differentially affected by katanin activity.

After knocking out Tetrahymena katanin, the authors found that cilia were missing their central microtubules and had shorter outer doublets. Cortical bundles and internal microtubules, by contrast, were more abundant and unusually stable. These inner polymers were more heavily laden with posttranslational modifications, including acetylation, glutamylation, and glycylation.

These modifications normally increase as microtubules age, so their accumulation might be a simple byproduct of the loss in severing activity, which may keep the polymer dynamic. The katanin mutants, however, resembled a β-tubulin mutant lacking the glutamate and glycy projections. The similarity suggests that microtubule modifications might activate katanin, thereby focusing its activity on long, old filaments.

Why cilia microtubules were shorter or missing is unclear. Cilia that were lopped off regrew to a similarly stunted length, suggesting that free tubulin subunits were available. Perhaps katanin cuts microtubules to a particular length that can be transported into or along the cilia, as has been suggested for axons. JCB

Reference: Sharma, N., et al. 2007. J. Cell Biol. 178:1065–1079.