Text by Mitch Leslie
mitchleslie@comcast.net



# Stay-at-home transcription factor saves axons

Without departing for the nucleus, STAT3 stabilizes microtubules.

The old saw that local actions can have global consequences holds true for neurons, too. Selvaraj et al. show that a transcription factor remains in the axon to help prevent neurodegeneration (1).

In neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS), neurons usually die in stages, with axons deteriorating first and the cells themselves perishing later (2). Axon degeneration may represent a turning point for patients, after which so much neuronal damage has accumulated that treatments won't work. Researchers have tested several proteins for their ability to save axons (3, 4). One of these molecules, ciliary neurotrophic factor (CNTF), rescues axons in rodents and extends their lives. But it caused severe side effects in patients during clinical trials. "Acting on the same pathway but farther downstream could be an ideal way to improve the situation for motor neuron disease" and possibly for other neurodegenerative diseases, says senior author Michael Sendtner.

To discover how CNTF works, Selvaraj et al. studied *pmn* mutant mice that mimic ALS. The researchers found that CNTF not only prevented the shrinkage of the rodents' motor neurons, it also reduced the number of swellings along the axon that are markers of degeneration. Another sign that CNTF was beneficial was the movement of mitochondria, which continually shuttle back and forth along the axons of healthy motor neurons. In axons from *pmn* mice, stalled mitochondria were prevalent, but treatment with CNTF accelerated the organelles to normal speeds.

CNTF indirectly turns on the transcription factor STAT3. To determine whether STAT3 is behind CNTF's protective powers, the researchers tested whether the neurotrophic factor helps motor neurons that lack STAT3. They discovered that *pmn* axons lacking STAT3 were half as long as those from control *pmn* mice after CNTF treatment.

> "We found that most of the axonal STAT3 does not move to the nucleus and has a local effect."

After it has been activated, STAT3 typically travels to the nucleus to switch on genes. "We found that most of the axonal STAT3 does not move to the nucleus and has a local effect," says Sendtner. "That is the most surprising finding of this study." The local effect involves stathmin, which stimulates microtubule breakdown by capturing tubulin heterodimers and preventing them from joining growing fibers. STAT3 latches onto stathmin and forces it to let go of the tubulin heterodimers, the researchers showed. To determine whether release of the dimers spurs axon growth, Selvaraj et al. knocked down stathmin in motor neurons from *pmn* mice. The axons grew at the same rate as axons from normal mice. But they didn't elongate any faster after doses of CNTF, suggesting that CNTF mainly stimulates axon growth by thwarting stathmin.

The researchers next investigated CNTF's effect on microtubule behavior. Dynamic microtubules, such as those at the tip of a rapidly growing axon, are typically decorated with tyrosine groups, whereas stable microtubules typically carry acetyl groups. Axons from *pmn* mice showed more tyrosinated microtubules than did motor axons from normal mice. Adding CNTF reduced the amount of dynamic microtubules in the mutant mice. However, the levels of acetylated microtubules didn't differ between *pmn* mice and controls. To gauge another aspect of microtubule dynamics, Selvaraj et al. tested how rapidly microtubules rebound after a dose of nocodazole, which causes the fibers to collapse. CNTF spurred faster regrowth in *pmn* animals.

The results indicate that, by enlisting STAT3, CNTF inhibits stathmin and boosts the stability of microtubules in motor neurons. The neurotrophic factor also speeds microtubule regrowth. Those positive effects suggest that drugs to block stathmin could slow neuron breakdown in patients with neurodegenerative diseases. Sendtner notes that about 2% of the population carries mutations that leave them with no CNTF. These natural knockouts seem to suffer no ill effects unless they develop multiple sclerosis, which is more severe than usual. The question is whether the increased severity of the disease in these people stems from a flaw in their microtubules.

## Focal Point

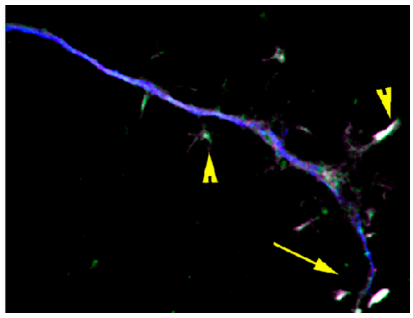

PHOTO COURTESY OF ROBERT BLUM

**Nicolas Frank (front row, left), Bhuvaneish Thangaraj Selvaraj (front row, right), Michael Sendtner (back row, left), and colleagues (not pictured) determined how ciliary neurotrophic factor (CNTF) protects axons. The protein activates the transcription factor STAT3 (green), which lingers in the axon (blue) and helps stabilize microtubules by inhibiting a protein called stathmin (magenta). STAT3 and stathmin colocalize in axonal branch points (arrowheads) and growth cones (arrow).**

1. Selvaraj, B.T., et al. 2012. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201203109.
2. Sendtner, M., et al. 1992. *Nature*. 358:502–504.
3. Sagot, Y., et al. 1995. *J. Neurosci.* 15:7727–7733.
4. Sagot, Y., et al. 1996. *J. Neurosci.* 16:2335–2341.