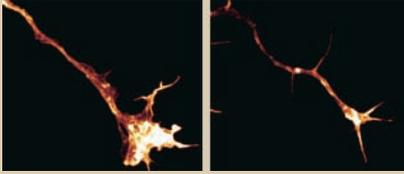


## A disease of actin transport?



SMA neurons (right) have less actin.

Spinal muscular atrophy (SMA), a motoneuron disease that results in paralysis and death usually before age 3, is caused by loss of the *SMN1* gene. But what does the established splicing function of *SMN1* have to do with motoneurons? Perhaps very little, say Rossoll et al., who on page 801 show that *SMN1* is part of a complex that drags  $\beta$ -actin mRNA out to growth cones so that axons can grow and possibly function properly.

The authors first looked at motoneuron survival *in vitro*. Survival of cells from a mouse SMA model was unimpaired, but axon growth, growth cone size, and axonal accumulation of actin was reduced. The *SMN* protein has been shown to associate with the RNA-binding protein hRNP R, and Rossoll et al. found that hRNP R associates, in turn, with  $\beta$ -actin mRNA. The axonal concentration of both hRNP R and  $\beta$ -actin mRNA are lost in cells lacking *SMN1*.

Individuals with SMA apparently live as long as they do because full-length *SMN2* can carry out at least part of the essential splicing function of *SMN* proteins. But most *SMN2* transcripts have a small deletion relative to *SMN1*, and thus are inactive in both splicing and axon localization functions. It is not yet clear if the localization function is the sole determinant of SMA disease, and if it is needed for transport of mRNAs other than  $\beta$ -actin mRNA. But at least in theory the shortage of axonal actin could lead to deficits not just in axonal outgrowth but also in synaptic functioning. One distant option for correcting these defects might be to boost the activity of an mRNA transport component. ■



TGF- $\beta$  signaling (blue) requires Notch cooperation.

then enter the nucleus. And recent microarray results suggested that both pathways converge on at least one common target gene. Now, Blokzijl et al. demonstrate that Notch and Smad3 (a protein released from the transforming growth factor  $\beta$  (TGF- $\beta$ ) receptor after ligand binding) bind each other, and then bind and activate a target promoter. The other two papers describe a similar association between Notch and Smad1 (which is downstream of the bone morphogenetic protein [BMP] receptor) that is enhanced by binding of coactivators (Takizawa et al.) and required for a BMP4-mediated block of muscle differentiation (Dahlqvist et al.).

Such a requirement for two signals could be seen as further reducing the choices available for developmental processes, which use and reuse a limited number of signaling pathways. But senior author Carlos Ibáñez sees the new complexes as the cell's equivalent of a computational AND gate, and anticipates that a closer investigation of signaling complexes will show that the complexes work like small microprocessors. Only with such integration, he says, can cells deal with all the complexity that surrounds them. ■

## Notch gets transformed

Cells exist in complicated environments filled with reinforcing and conflicting signals. Three recent papers (Blokzijl et al., page 723; Takizawa et al., 2003. *Nucl. Acids. Res.* 31:5723–5731; Dahlqvist et al., 2003. *Development.* 10.1242/dev.00834) describe a link between pathways downstream of two of the most important of these signals: Notch and the TGF- $\beta$ /BMP systems.

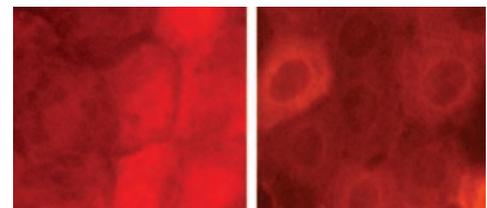
Both signaling pathways trigger the release of initially receptor-localized species—the Notch intracellular domain (NICD) and the Smads, respectively—that

## Barriers to export

Nuclear pores facilitate transport into and out of the nucleus. But now Roth et al. report that cells with more of the nucleoporin DNup88 do less nuclear export (page 701). DNup88 exerts this negative effect by sequestering the exportin DCRM1 so that it can no longer do its job.

Roth et al. first established that cells with DNup88 were compromised for nuclear export but not import. The overactive export in cells lacking DNup88 could be prevented by inhibiting DCRM1, which shuttles its cargos out of the nucleus. DNup88, DCRM1, and the nucleoporin DNup214 are normally found in a complex on the cytoplasmic face of the nuclear pore, but loss of DNup88 frees up DCRM1 so that it can enter the nucleus and help export more proteins.

The authors found a correlation between DNup88 levels and the effectiveness of nuclear export at different stages of fly development. Such alterations of DNup88 levels may be one way of altering the rates of export of many substrates, rather than tweaking the binding of individual substrates to DCRM1 by, for example, phosphorylation. But Roth et al. are also on the lookout for phosphorylations or other modifications of the DNup88/DCRM1 system that may alter export capability in response to specific signals. ■



Loss of a Nup (right) leads to excessive nuclear export.