In This Issue

Held back by a finger

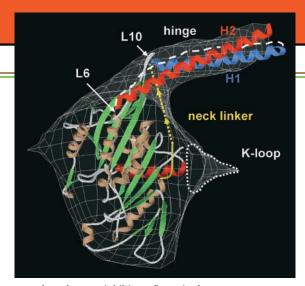
The familiar arm-over-arm kinesin swing was recently challenged by proposals that KIF1A acts as a processive, but monomeric, kinesin motor. The proposal involved a rotation of the motor that, along with a microtubule-binding patch, would bias further movement in one direction.

But now Al-Bassam et al. add to the growing evidence that the KIF1A orthologue in worms, Unc104, may function as a dimer, like conventional kinesin (page 743). The monomer, they propose, is instead a regulated form whose full activity is only restored when motors are crowded onto cargo vesicles.

The unusual prospect of a monomeric motor, and expression problems that had led to the use of a KIF1A/conventional kinesin hybrid in the earlier work, led the authors to study Unc104. Images obtained by cryo-EM revealed a motor domain with a protruding finger that the group identified as representing two neck helices, paired in parallel.

Under other conditions, the finger unfolds (i.e., disappears in the EM), and its helices pair intermolecularly with neck helices from another Unc104 motor. The dimeric motor that is now visible by EM should move vesicle traffic along axons processively.

Dimerization would be favored when the motor is at high concentrations on vesicle cargo surfaces. But more sparsely spaced Unc104 may stay monomeric because the two neck helices pair with each other. Al-Bassam et al. prevent this inhibitory pairing, and thus the formation of the finger, by



H1 and H2 form an inhibitory finger in the Unc104 monomer.

deleting a hinge between the two helices. This deleted protein can move well in vitro, but is a poor replacement for wild-type gene function in worms. Perhaps this motor is activated too easily, and therefore whizzes out to the axon before it has cargo.

An important question remains: does any kinesin truly operate as a monomer? The sizeable rotation seen in the KIF1A studies (which was proposed to drive monomeric movement) is minimal in Unc104, based on the new structures. But a decisive conclusion may require further experiments. If dimerization is required for movement, then mutations in neck helices that disrupt dimerization should always destroy movement. Many such correlations may be necessary before the monomeric camp gives up its cause.

Cautious apoptosis

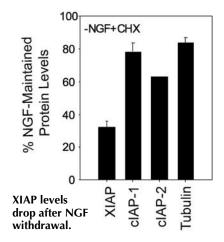
I t is not easy to convince sympathetic neurons to commit suicide. Potts et al. (page 789) now show that a caspase inhibitor called XIAP acts as a safety brake so that these terminally differentiated cells do not take the death decision too lightly.

Earlier studies established that injection of cytochrome c, which is normally released from mitochondria to activate caspases and thus apoptosis, can kill most cell types but not sympathetic neurons. This resistance can be overcome by coinjection with excess Smac, which shuts down caspase inhibitors including XIAP. Potts et al. now show that cells lacking XIAP no longer need Smac, and succumb to cytochrome c injection alone.

This clean result from a single gene deletion was surprising because there are a number of XIAP-like inhibitors, or IAPs,

that have until now been largely undifferentiated. The entire family of proteins has been plagued by the absence of knockout phenotypes (although their overexpression clearly inhibits apoptosis); this situation has now been rectified for XIAP.

As postmitotic cells that are not easily

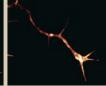


replaced, sympathetic neurons must resist most toxic insults without resorting to apoptosis. These insults can breach mitochondria, releasing not only cytochrome *c* but also Smac. But Potts et al. find that these endogenous levels of Smac are not sufficient to shut off XIAP, unlike the excess injected Smac.

Only when survival factors such as NGF are withdrawn do the neurons finally give up the ghost. The mechanism of XIAP downregulation is not yet clear. After NGF withdrawal, XIAP mRNA levels are reduced. But XIAP protein degradation may also occur, as XIAP levels drop more after NGF withdrawal than after a protein synthesis shut-off with cycloheximide. A mystery also surrounds the specificity of the phenotype: both why XIAP is the critical IAP in sympathetic neurons, and why the similar levels of XIAP found in other cell types do not have a similar safety brake effect.

A disease of actin transport?





SMA neurons (right) have less actin.

S pinal 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 β-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 $\beta\text{-actin mRNA}$. The axonal concentration of both hRNP R and $\beta\text{-actin mRNA}$ 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- β signaling (blue) requires Notch cooperation.

Notch gets transformed

ells 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-β/BMP systems.

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

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 β (TGF- β) 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.

Barriers to export

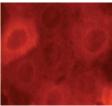
Nuclear pores facilitate transport into and out of the nucleus. But now Roth et al. report that cells with more of the nucleoporin DNup88 do less nuclear export (page 701). DNup88 exerts this negative effect by sequestering the exportin DCRM1 so that it can no longer do its job.

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.