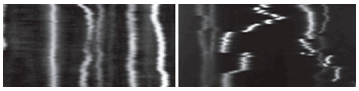
In This Issue

Text by Ben Short
bshort@rockefeller.edu

Opposing motors take the strain



Peroxisomes are immotile in the absence of kinesin-1 (left), but a distinct motor, Unc104, restores normal back-and-forth movement (right).

Molecular motors show an odd sense of teamwork during cargo transport, say Ally et al. In order to get somewhere, they have to pull in opposite directions.

Many types of cargo move through the cell along microtubules, but rather than smoothly gliding to their final destinations, they stutter back and forth due to motor proteins that pull in opposite directions. These bi-directional movements may help cargo navigate through a crowded cytosol. Surprisingly, the opposing motors seem to rely on each other—if one motor is removed, its rival seizes up instead of victoriously hauling its cargo to the microtubule's end.

To investigate how such pairs of motors might communicate, Ally et al. wondered whether any two opposite polarity motors could combine to transport peroxisomes. These organelles are paralyzed in the absence of the plus end–directed motor kinesin-1, even though dynein—the protein that would usually shunt them to microtubule minus ends—is still present. Peroxisome movement in both directions was restored when a different kinesin, Unc104, was artificially targeted to the organelle, suggesting that dynein can pair up with any plus end–directed motor. Similarly, kinesin-1 can partner with minus end motors other than dynein, the researchers found.

Kinesins lacking motor activity couldn't restore peroxisome movements, indicating that transport in one direction is required to activate transport in the other. The mechanical tension produced by one motor might activate its opposing partner, says author Shabeen Ally. Once running, however, the opposing motor activities must be carefully balanced: the slow kinesin Eg5 could replace kinesin-1 and activate dynein, but was powerless to resist the minus end motor's faster movement, causing peroxisomes to incorrectly accumulate in the center of the cell.

Ally, S., et al. 2009. *J. Cell Biol.* doi:10.1083/jcb.200908075.

IKK cuts both ways in Huntington's disease

The kinase IKK phosphorylates the protein mutated in Huntington's disease to promote its removal and neuron survival, say Thompson et al. But IKK may be a double-edged sword that increases neurotoxicity in later stages of the disease.

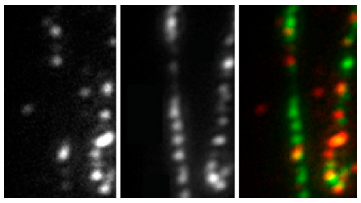
Huntington's disease is caused by an expanded polyglutamine repeat in the protein Huntingtin (Htt), which causes the protein to aggregate and damage neurons. Ubiquitination and SUMOylation of Htt's N-terminal domain affect the protein's stability and toxicity, but other post-translational modifications in this region of the protein might be important as well.

Thompson et al. discovered that the inflammatory kinase IKK phosphorylates Htt, altering the complex pattern of SUMOylation, ubiquitination, and acetylation on neighboring lysine residues. The net result was to promote Htt's degradation by both the proteasome and lysosomes. Lysosome-mediated degradation of Htt was blocked by knocking down the autophagy proteins LAMP-2A and Atg7. Compared to wild type, mutant Htt with an expanded polyglutamine stretch was degraded inefficiently, but a version that mimicked IKK phosphorylation with negatively charged aspartate residues was still less toxic to neuronal slice cultures.

But there may be a darker side to IKK phosphorylation—it also targets Htt to the nucleus where, says senior author Joan Steffan, a particularly toxic fragment that enhances neurodegeneration may accumulate. IKK may thus be involved in both clearing Htt and in generating a more dangerous version of the protein. The latter pathway would predominate in older patients because proteasome and lysosome function declines with age. Therapies aimed at IKK might need to either enhance or block the kinase's function, depending on the patient's age and stage of disease.

Thompson, L.M., et al. 2009. *J. Cell Biol.* doi:10.1083/jcb.200909067.

BBS proteins run an export business



The BBSome (red) removes signaling proteins from flagella by linking them to a subset of IFT particles (green).

A protein complex mutated in human disease removes excess signaling molecules to prevent them from damaging cilia, say Lechtreck et al.

Defective cilia cause a range of diseases including Bardet-Biedl syndrome (BBS), a rare, multi-tissue disorder linked to mutations in 12 different proteins. Seven of these form a complex called the BBSome, but the function of this protein assembly in cilia and flagella is unclear. In worms, the complex glues together the intraflagellar transport (IFT) machinery that assembles and maintains cilia by hauling cargo back and forth along the organelle's microtubules. But most mammalian cell types can still form cilia in the absence of BBS proteins, suggesting that the BBSome isn't essential for IFT.

Lechtreck et al. turned to the green alga *Chlamydomonas*, and found that BBS proteins were only present on a subset of IFT particles in each of the alga's two flagella. Strains lacking components of the BBSome showed normal rates of IFT and proper flagellar structure, but couldn't steer away from bright light like wild-type cells could. Mutant flagella accumulated several signaling-related proteins, which the researchers think may disrupt the alga's response to light.

The researchers speculate that a similar buildup of disruptive proteins causes cilia dysfunction in BBS patients; the BBSome may remove excess signaling proteins from flagella by linking them to a subset of IFT particles undergoing retrograde transport out of the cilia. Author Karl Lechtreck says that the next step is to fluorescently tag the signaling proteins and compare their movements to BBS and IFT proteins.

Lechtreck, K.-F., et al. 2009. *J. Cell Biol.* doi:10.1083/jcb.200909183.