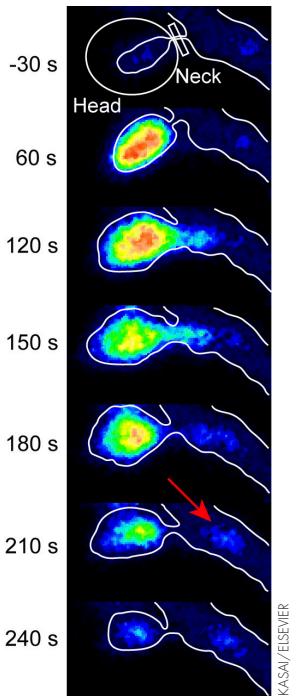
Research Roundup



Stimulated spines do not remain enlarged if the enlargement pool (colored) is quickly extruded through the spine neck.

Spine actin for memory

Tiny spines on dendrites harbor three separate pools of actin, say Naoki Honkura, Haruo Kasai (University of Tokyo, Japan), and colleagues. The trapping of one pool helps form memory.

Memory is thought to stem from long-term potentiation (LTP)—the lasting enhancement of communication between two neurons at a synapse. On the postsynaptic side, information is collected in tiny bulbous membrane protrusions called spines, whose enlargement helps create LTP. Enlargement requires actin polymerization, prompting the authors to examine spine actin organization in brain slices before and after synaptic stimulation.

Unstimulated spines contained a stable pool of actin filaments near the base of the spine and a more dynamic pool throughout. The behavior of the dynamic set resembled that of actin in axonal growth cones, where actin is assembled by Rac at the leading edge and disassembled further back.

A third actin pool appeared in spines that swelled after repeated stimulation with glutamate. Polymerization of this pool seemed to cause the spine expansion, as its appearance correlated with membrane ruffling at spine edges. Its polymerizing enzyme is not yet known, but the group found that it required calcium and especially high concentrations of actin monomers.

In some spines, the enlargement-associated pool was quickly pushed out en masse into the dendrite body through the bud neck, and the spine shrunk back to its former size. The pushing force probably stems from surrounding glia and other neurons.

Lasting growth required more of the stable actin filaments, which might originate from the enlargement pool. Only spines that held onto their enlargement pool for longer than six minutes were still enlarged an hour later. Confinement of the pool required CaM-dependent kinase II, which the authors hypothesize helps cross-link the new filaments, making them stiffer and more difficult to squeeze through the bud neck. Smaller spine necks also helped hold them in.

The findings explain why larger spines have proportionately more glutamate receptors, since the receptors dock to the ends of actin filaments. The resulting increased responsiveness to glutamate in turn helps LTP set in. Enlargement itself probably assists. "So many enzymes are needed for LTP," says Kasai. "The spine becomes a sort of incubator, and the extra space allows subsequent events to happen." JCB

Honkura, N., et al. 2008. *Neuron.* 57:719–729.

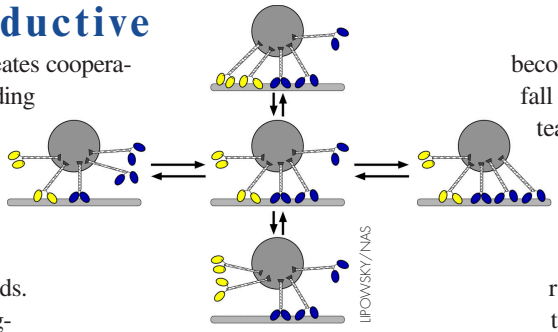
Motor tug-of-war is productive

A tug-of-war between microtubule motors creates cooperation that makes cargo transport a snap, according to a mathematical model from Melanie Müller (Max Planck Institute of Colloids and Interfaces, Potsdam, Germany) and colleagues.

Microtubule-based transport runs in two directions: motors such as kinesin pull cargo toward filament plus ends, whereas dynein heads to minus ends. Both motor types can bind at once to a single cargo, suggesting that they should hinder each other's progress.

Some researchers propose that the two motor sets are coordinated by a regulatory complex to ensure that only one team is bound to the track at a given time. But the new model indicates that motors can fight it out themselves and still bring cargo to its destination.

The motors were characterized mathematically using previously measured properties such as motor speed, strength, and binding and unbinding rates. The calculations revealed that fast, directional transport was possible due to what the authors call an unbinding cascade. Random fluctuations in the number of motors bound to the microtubule give one motor team an advantage. If the force generated by the winning team is enough to detach a losing motor, each remaining losing motor bears a greater force and thus becomes even more likely to fall off until only the winning team is attached.



A cargo with both plus-end (blue) and minus-end (yellow) motors can be pulled by a fluctuating number of motors bound to the track. Motor properties determine which configuration is most likely.

Small variations in the properties of one motor, such as might be caused by mutations or cellular regulatory pathways, altered the probability that one team or the other would win. Plugging such alterations into the model reproduced actual changes in transport behavior seen in developing fly embryos.

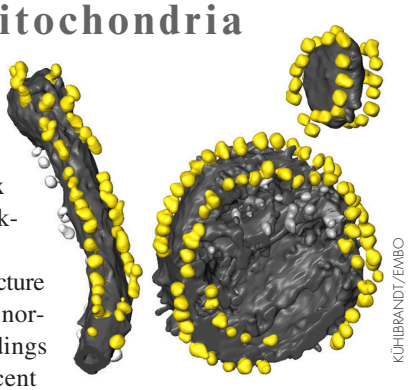
Müller would like to see the model tested further. "I'm not an experimentalist," she says. "So I hope someone else builds an in vitro assay—bind microtubules to a surface and add beads with both motors attached. If you lower ATP concentrations to decrease motor velocity, does it then do what our model predicts?" The biggest obstacle might be getting dynein, which Müller calls the "diva" of motors, to behave reproducibly in vitro. JCB

Müller, M.J.I., et al. 2008. *Proc. Natl. Acad. Sci. USA.* doi:10.1073/pnas.0706825105.

Text by Nicole LeBrasseur
lebrasn@rockefeller.edu

Enzyme shapes mitochondria

ATP synthase bends the mitochondrial membrane to improve its performance, say Mike Strauss, Werner Kühlbrandt, and colleagues (Max Planck Institute of Biophysics, Frankfurt, Germany).


KÜHLBRANDT/EMBO

Ribbons of ATP synthase (yellow) dimers can be seen by electron tomography in curved membranes derived from mitochondria.

Kühlbrandt is interested in the structure of membrane proteins, which are normally extracted from their surroundings before examination. But with the recent emergence of electron tomography, Kühlbrandt realized, "if a protein is large enough, it should be possible to visualize it in situ without taking the whole thing apart." His team tried its luck on ATP synthase embedded in bits of mitochondrial membrane.

The images revealed long ribbons of ATP synthase dimers in highly curved membranes. Previous work suggests that the curvature is created by the dimers: yeast mutants lacking dimerization subunits are missing the elaborate mitochondrial membrane invaginations called cristae. And the massive synthase leaves little room for anything else to do the bending.

The curves, the group suggests, make the synthase more efficient by increasing the local pH gradient, which helps drive ATP synthesis. The gradient is created by the pumping of protons into the inner membrane space. Mathematical calculations revealed that those protons can be more densely packed along membrane curves, thereby increasing the pH gradient there, where ATP synthase is situated.

Bacteria get by with only monomeric ATP synthase in flat membranes. But eukaryotes probably evolved dimers rapidly, as they are found in yeast, unicellular ciliates, and mammals. JCB

Strauss, M., et al. 2008. *EMBO J.* doi:10.1038/emboj.2008.35.

Stem cells sport longest telomeres

Adult stem cell hideouts can be identified by the presence of extra long telomeres, according to findings from Ignacio Flores, Maria Blasco (Spanish National Cancer Center, Madrid, Spain), and colleagues.

Because of their location at chromosome tips, telomeres shorten with every cell division. Stem cells divide more slowly than other cell types, so Blasco's group reasoned that they might have the longest telomeres. Using a precise, quantitative version of FISH with telomere sequences, the group found that cells with the longest telomeres corresponded to known stem cell niches in skin, brain, testis, and other tissues.

The approach bypasses the need to identify distinguishing stem cell markers in each tissue type. Until now, the only other generally applicable method was the slower label-retaining technique. The authors will now test other tissues to identify unknown stem cell populations or resolve controversial ones.

Telomeres in the stem cell niches and elsewhere were dramatically shorter in two-year-old mice than in those just a year younger. The group hypothesizes that telomere maintenance mechanisms may go awry in old age. If stem cells with stubby telomeres are unable to function normally, this shortening may be a cause of aging. The group would now like to try to extend lifespan in mice by delaying telomere shortening. JCB

Flores, I., et al. 2008. *Genes Dev.* 22:654–667.

Myosin and kinesin collaborate

Motors band together to improve each other's performance, based on findings from Yusuf Ali, Kathleen Trybus, and colleagues (University of Vermont, Burlington, VT).

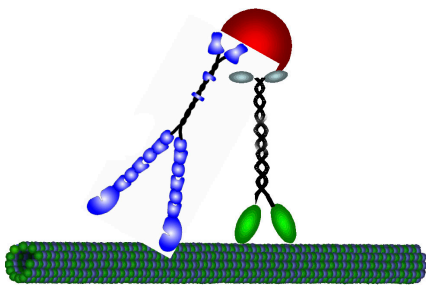
Molecular motors each have their favorite tracks. Kinesin tugs cargo along microtubules for long distance transport, and myosin continues the haul on actin at the cell edges. But recently the group found that myosin also diffuses along microtubules. "At the time," says Trybus, "we supposed that the diffusion might help myosin hook up with kinesin and its cargo, but the idea wasn't very satisfying." They now find a more gratifying explanation.

Using an in vitro system, the group showed that myosin's interactions with microtubules enhanced kinesin's processivity. When both motors were hooked to a cargo, kinesin took longer trips made up of several short runs linked by pauses. Dual-motor cargo might exist in vivo, given that large cargos such as melanosomes harbor dozens of motors.

The improved kinesin run lengths stemmed from electrostatic interactions between myosin and microtubules. Adding more positively charged residues to myosin further improved kinesin's performance, whereas removing them blunted its effects. The findings suggest that myosin tethers a detached kinesin near the microtubule while it finds a site to rebind. "Without the tether," says Trybus, "kinesin and the cargo are more likely to simply diffuse away."

Kinesin returned the favor by increasing myosin's run lengths, again through electrostatic effects. If charge is the decisive characteristic, any positively charged cargo can lend a hand to its own transport. JCB

Ali, M.Y., et al. 2008. *Proc. Natl. Acad. Sci. USA.* 105:4691–4696.


TRYBUS/NAS

Kinesin (green motor) runs farther along microtubules when its cargo (red) is also bound to myosin (blue motor).