Text by Ben Short
bshort@rockefeller.edu

Syntaphilin puts the brakes on axonal mitochondria

Study reveals how an axonal mitochondrial protein arrests the organelles at active synapses.

Mitochondria move around inside neurons to make sure they localize to whichever part of these highly polarized cells they are needed in. For example, mitochondria accumulate in active synapses to facilitate synaptic transmission by providing energy and buffering calcium levels. Chen and Sheng describe how the organelles are immobilized in response to synaptic activity (1).

Mitochondria are ferried back and forth along neuronal axons by the microtubule-based motor proteins dynein and kinesin-1. The plus end–directed kinesin motor is coupled to mitochondria by the cargo adaptor Trak1 or Trak2 and the calcium-sensing protein Miro. In 2009, two papers revealed that, if motile mitochondria pass an active synaptic terminal, the local increase in calcium levels disrupts the Miro–Trak–kinesin complex and arrests the mitochondria at the synapse (2, 3). The papers disagreed, however, as to whether kinesin remained associated with stationary mitochondria (3) or whether the motor was completely decoupled from the organelle upon immobilization (2).

Around the same time, Zu-Hang Sheng and colleagues at the National Institute of Neurological Disorders and Stroke in Bethesda, Maryland, identified syntaphilin (SNPH) as another major regulator of axonal mitochondrial motility (4). Axonal mitochondria are more mobile in neurons lacking SNPH, an axonal mitochondrial membrane protein that anchors the organelle by binding to microtubules. Postdoc Yanmin Chen subsequently discovered that axonal mitochondria aren't arrested by activity-triggered Ca^{2+} influx in SNPH-null neurons (1). "The mitochondria keep moving upon increased neuronal firing," explains Sheng. "The striking dynamics were a real surprise and suggested that SNPH is required for the activity-dependent immobilization of axonal mitochondria."

Chen and Sheng discovered that SNPH bound directly to the kinesin heavy chain KIF5 and that this interaction was required to immobilize mitochondria in response to synaptic activity. Moreover, SNPH competed with the Trak2 adaptor for KIF5's C terminus. Synaptic activity and elevated calcium levels favored the interaction between SNPH and KIF5 by disrupting the Miro–Trak–kinesin complex. In addition, sustained neuronal activity increased SNPH's recruitment to axonal mitochondria.

But the SNPH–KIF5 interaction maintains kinesin-1's attachment to mitochondria, so how does a switch in KIF5 binding partners lead to the activity-dependent immobilization of the organelle?

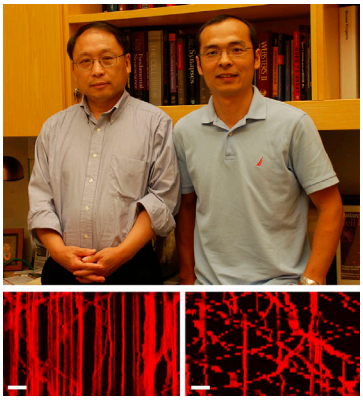
> "We call this the 'engine-switch and brake' model."

One mechanism may involve SNPH's microtubule-binding capacity, which could anchor mitochondria onto microtubules, thus serving as a molecular brake to stop both anterograde trafficking by kinesin-1 and retrograde transport by the minus end–directed motor dynein. However, Chen and Sheng also discovered that SNPH prevents kinesin-1 from moving along microtubules by inhibiting the ATPase activity of KIF5. "We call this the 'engine-switch and brake' model," says Sheng. "In response to a 'stop' sign—elevated calcium levels at activated synapses—SNPH switches off the kinesin motor and puts a brake on mitochondria, thereby anchoring them in place on axonal microtubules."

Because SNPH only localizes to axonal, and not dendritic, mitochondria, Chen and Sheng's results help reconcile the previous models of mitochondrial immobilization (2, 3). In dendrites, synaptic activity disrupts the Miro–Trak–kinesin complex, detaching the motor protein from the mitochondrial surface to immobilize the organelle near postsynaptic terminals. In axons, on the other hand, kinesin-1 remains associated with immobilized mitochondria through its interaction with SNPH. This difference, says Sheng, may help axonal mitochondria be more responsive to changes in synaptic activity. "If the calcium signal is removed, the motor protein can be quickly reactivated to transport mitochondria away to find new active synapses."

Defects in mitochondrial transport have been linked to a variety of neurodegenerative diseases, probably because, as mitochondria age and become dysfunctional, they must be trafficked back from distal axons to the neuronal cell body for degradation through the autophagy–lysosomal pathway before they start deteriorating synapses and damaging the cell (5). "We think SNPH may provide a new molecular target to manipulate mitochondrial motility and enhance the turnover of dysfunctional mitochondria," Sheng says.

Focal Point



Zu-Hang Sheng (left) and Yanmin Chen (right) investigate how the axonal mitochondrial protein syntaphilin immobilizes mitochondria in response to increased synaptic activity. The authors propose an "engine-switch and brake model," in which activity-dependent calcium influx causes the kinesin-1 motor protein to dissociate from its mitochondrial cargo adaptor Trak2 and bind to syntaphilin instead. Syntaphilin inhibits kinesin-1's motor activity and anchors mitochondria to microtubules at active synapses, where they provide the energy and calcium buffering capacity required for synaptic transmission. Kymographs (bottom row) show that, after stimulation, mitochondria (red) are much more mobile in syntaphilin-knockout axons (right) than they are in wild-type axons (left).

PHOTO COURTESY OF TAO SUN

1. Chen, Y., and Z.-H. Sheng. 2013. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201302040.
2. MacAskill, A.F., et al. 2009. *Neuron*. 61:541–555.
3. Wang, X., and T.L. Schwarz. 2009. *Cell*. 136:163–174.
4. Kang, J.S., et al. 2008. *Cell*. 132:137–148.
5. Sheng, Z.H., and Q. Cai. 2012. *Nat. Rev. Neurosci.* 13:77–93.