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Neurons let it slide

Study reveals how microtubule sliding affects neuronal migration and morphology.

During mammalian brain development, many neurons migrate away from the site where they are born to settle in distant locations where they send out dendrites and axons to connect with other neurons. Both neuronal migration and axon/dendrite extension depend on forces generated by microtubule-based motor proteins such as cytoplasmic dynein. The effects of these forces depend, however, on the organization of the microtubule cytoskeleton. Rao et al. reveal that a small number of microtubules that aren't attached to the centrosome, and which can therefore undergo motor-driven sliding, help migrating neurons navigate toward their destination and that, when the number of these centrosome-unattached microtubules is increased, neurons come to a halt and begin extending axon-like projections (1).

In migrating neurons, most, if not all, microtubules are attached to the centrosome. Many of them extend into a short leading process at the front of the cell, and, when motors pull on these microtubules, the centrosome is dragged forward, bringing with it the nucleus and the rest of the neuronal cell body. "The lore is that all of the functionally relevant microtubules are attached to the centrosome," says Peter Baas, from Drexel University College of Medicine in Philadelphia, Pennsylvania. "We decided to look, using the most rigorous techniques available, whether they are *really* all attached."

> "The motor-driven forces... can now slide microtubules so that the leading process grows longer."

Baas and colleagues, led by graduate students Anand Rao and Aditi Falnikar, used electron tomography to identify microtubule minus ends in cerebellar granule neurons migrating in vitro and found that a small number of them weren't associated with the centrosome (1). Using EGFP-CAMSAP3, a fluorescent marker of free microtubule minus ends, the researchers confirmed that, indeed, a handful of unattached microtubules are present in both the leading process and cell body of migrating neurons. "Our next question was whether these unattached microtubules matter," says Baas. "Are they functionally relevant?"

Rao et al. found that motor proteins can transport, or slide, unattached microtubules within the leading process of migratory neurons. When the researchers added a drug to cross-link and immobilize these microtubules, the leading process grew shorter and, although the neurons still moved, they frequently changed direction instead of migrating in a simple, straight line. "So we think the sliding of this small number of centrosome-unattached microtubules provides maneuverability to the leading process that can correct small pathfinding defects and keep the neuron migrating smoothly," Baas explains.

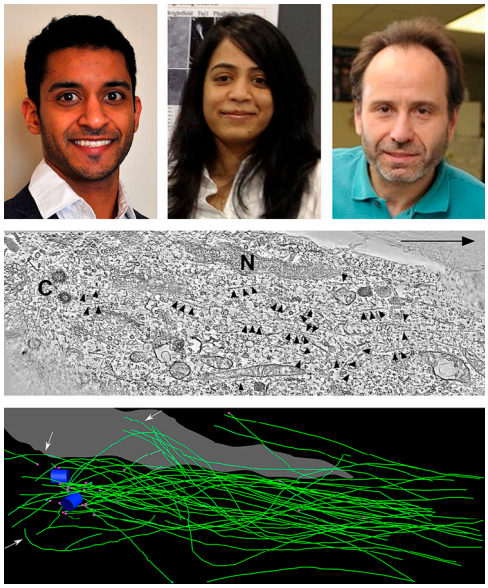
The researchers then investigated the effect of increasing the number of unattached microtubules by knocking down the centrosomal microtubule-anchoring protein ninein (2). Partially depleting this protein enhanced microtubule sliding into the leading process, which therefore grew and took on an axon-like appearance. At the same time, the neurons slowed down or came to a complete halt, as fewer microtubules remained attached to the centrosome in order to drag it, and the neuronal cell body, forward.

Detaching microtubules from the centrosome could therefore promote neurons' transition from a migratory to a stationary phenotype. "The motor-driven forces that were tugging at the centrosome during migration can now slide microtubules so that the leading process grows longer and longer," Baas says. It remains to be seen if ninein itself regulates this transition, though the protein is lost from the centrosome when neurons start to form axons and dendrites (3).

Baas and colleagues now want to study the motor proteins that generate these forces. Cytoplasmic dynein is undoubtedly a major contributor, but other motors, such as kinesin-5, are also likely to have an important role.

1. Rao, A.N., et al. 2016. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201506140
2. Shinohara, H., et al. 2013. *Biol. Open*. 2:739–749.
3. Srivatsa, S., et al. 2015. *Neuron*. 85:998–1012.

FOCAL POINT



PHOTOS COURTESY OF THE AUTHORS

(Top row, left to right) Anand Rao, Aditi Falnikar, Peter Baas, and colleagues investigate the organization of microtubules in migrating neurons. Using electron tomography (center) to construct a 3D model (bottom), the researchers find that, whereas most microtubules (green) are attached to the centrosome (blue), a small number are unattached (white arrows) and are therefore able to undergo motor-driven microtubule sliding in the neuron's leading process. This helps neurons migrate in a straight line but, when the number of centrosome-detached microtubules is increased, neurons come to a halt and extend their leading processes into longer, axon-like projections. By favoring microtubule sliding over centrosome pulling, microtubule detachment from the centrosome may therefore help developing neurons transition from a migratory to a stationary phenotype.