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Microtubules slide neurons home

Brain development requires neurons, the most sophisticated information-carrying cells in the body, to migrate from where they are born to faraway destinations where they finally settle down and take up residence. During its journey, a young neuron extends a short leading process which drags along the cell body as it lunges forward. Microtubules are struts inside the neuron that connect the leading process with a structure called the centrosome inside the cell body so that it can be dragged along. When the neuron reaches its home, the microtubules detach from the centrosome and then move freely to populate the axon, which is an elongated process that is very different from the leading process. Unlike the leading process, which is short and tows the cell body, the axon can grow enormously long so that it can reach a target tissue, such as a muscle, without dragging along the cell body. In the axon, the microtubules are free to slide down its length, and this is what enables the axon to grow longer and longer. While this scenario makes good sense, there had been no direct test of it, with some controversy from investigators who have had other ideas. In our recent article, published in the *Journal of Cell Biology* (Rao et al., 2016), we wanted to investigate the situation, using contemporary cellular, molecular and pharmacologic tools. In so doing, we confirmed that the scenario described here is essentially correct, but we also found an exciting surprise that may tell us how the sliding of microtubules also controls the journey of the neuron to its home.

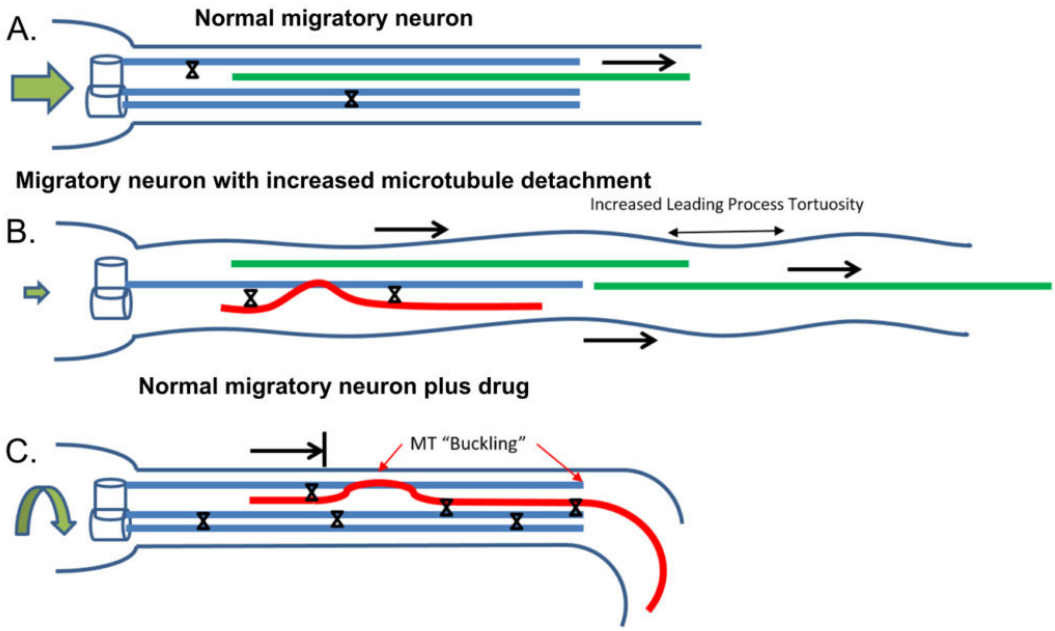

Fig. 1. A. Migrating neurons display a small amount of microtubule sliding (green microtubule = sliding microtubule) and migrate on a consistent path (represented by large green arrow in cell body). B. After microtubules are detached from the centrosome, microtubule buckling is observed, the leading process becomes a bit wavy, and migration is compromised (represented by smaller green arrow in cell body). C. When a drug is used to prevent microtubule sliding (represented by 'X'), more of the microtubules in the leading process become buckled (curved red microtubule), and the neuron's migratory path becomes abnormal (represented by curved green arrow in cell body). Schematic adapted from (Rao et al., 2016).

We started out by testing the long-standing idea that all of the microtubules in the migrating neuron are attached to the centrosome. We found that almost all of them are indeed attached to the centrosome, but some of them are not (schematic; 'A'). Then, we used some molecular tricks to detach more of the microtubules from the centrosome, and when we did this, we found that the cell body of the neuron stopped moving, exactly as we had predicted. In addition, with the microtubules free to slide more, the leading process grew longer and longer, much like an axon (schematic; 'B'). Using fluorescence microscopy to observe living neurons on the microscope stage, we are able to observe microtubules sliding. We documented that the microtubules slide just a little bit in the normal migrating neuron but quite a lot after our experiments had detached greater numbers of microtubules from the centrosome. Some of the microtubules buckled, due to natural brakes on their sliding. We were excited about these findings because they satisfied our predictions, namely that microtubules attached to the centrosome cannot slide while those that are not attached to the centrosome can slide.

The surprise came when we applied a drug to the neurons that inhibits microtubule sliding. We had not suspected that the small amount of microtubule sliding during neuronal migration had any purpose. However, when microtubule sliding was inhibited by the drug, even more of the microtubules buckled as they were stopped while sliding, and the neuron lost its normal trajectory of migration (schematic; 'C'). This indicates that the little bit of microtubule sliding that normally occurs in the migrating neuron is important for the neuron to keep on its appropriate path, rather than losing its way. Thus, microtubule sliding is important not only for making an axon, but also for the migratory neuron to find its way home.

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Publication

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