Research Simplified

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Research Paper: *Kinesin-3 Responds to Local Microtubule Dynamics to Target Synaptic Cargo Delivery to the Presynapse*

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Research Simplified By: *Pedro Guedes-Dias*
Pedro conducted this work in Prof. Erika Holzbaur's laboratory at the Perelman School of Medicine, University of Pennsylvania. He combines biophysical and cell biology approaches to advance our understanding of how the activities of motor proteins and microtubules are coupled to regulate the maintenance of synapses in neurons.

How Nerve Cells Talk to Other Nerve Cells

Neurons communicate with other neurons through specialized structures called “synapses”. Each synapse can be divided in two main parts: the “presynapse” and the “postsynapse”. The presynapse is located in a long cable called “axon” in the presynaptic neuron and contains hundreds of synaptic vesicles loaded with neurotransmitters; the presynapse is where information is conveyed. The postsynapse is located on the opposing postsynaptic neuron and is where information is received.

Proper communication between neurons requires presynapses to have an appropriate number of synaptic vesicles. Over time, synaptic vesicles are used up and the presynapse needs to be replenished with new ones.

How KIF1A Helps Neuron Communication

This is where KIF1A comes in. As the main motor protein that transports synaptic vesicles from the neuronal cell body – where vesicles are produced – to the presynapse, KIF1A plays a critical role in this important process: while one end of KIF1A binds to synaptic vesicles, the other end binds to microtubules, which act as roads on which KIF1A moves along the axon.

Although we have known for some time the basic way KIF1A moves synaptic vesicles along microtubules down the axon, important details concerning the local delivery of these vesicles to presynapses remain unknown.

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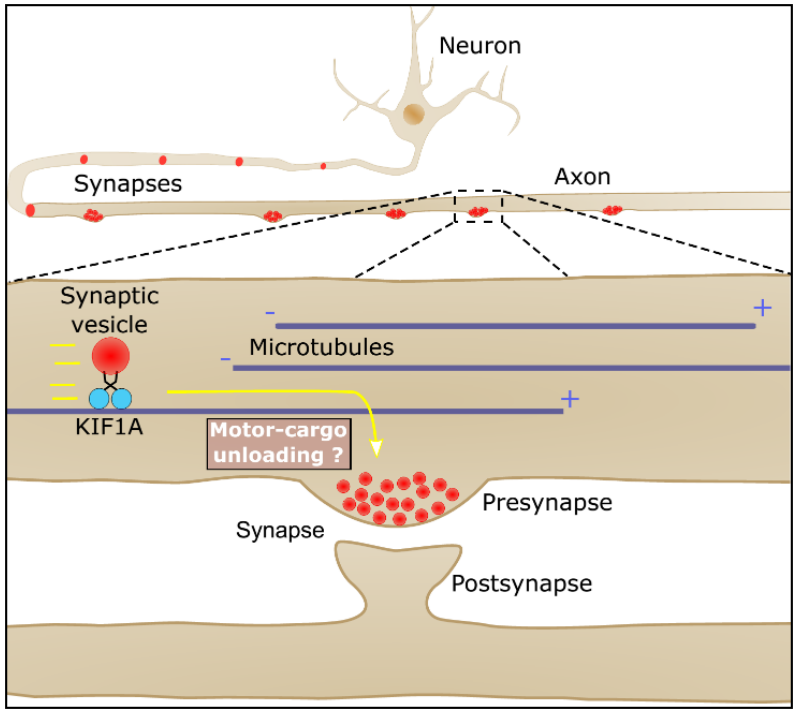
In the brain, the axon of a single neuron can follow an extremely tortuous path and branch several times. Single axons can extend for several meters in total length and establish hundreds of thousands of synapses along its course. These presynapses sit next to the microtubule array on which KIF1A moves, so one intriguing question is how do synaptic vesicles in transit along the microtubules in the axon "know" where to stop?



Microtubules are rod-like structures that are arranged as a tiled array along the axon. One of the extremities of the microtubule is considered relatively stable (the minus-end), while the other extremity (the plus-end) can be highly dynamic, frequently growing and shrinking. We are still not sure exactly how the average length or the number of microtubules vary along the axon, but in this work we have identified presynapses as sites rich in dynamic microtubule plus-ends.

What We've Learned About KIF1A Mutations & Neuron Communication

We discovered that KIF1A reacts to this region by rapidly detaching from the microtubule, and conclude that the high number of dynamic microtubule plus-ends at presynapses define an unloading zone for precise delivery of synaptic vesicles by KIF1A and is important to keep proper synaptic communication between neurons.

In an effort to identify what parts of the KIF1A protein are important for this response to the microtubule plus-end region, we screened eighteen disease-causing KIF1A mutants. We found that some KIF1A mutants that are known to cause severe neurological symptoms lost the ability to bind microtubules. Others were capable of binding to microtubules but were unable to move. Some KIF1A mutants associated with milder phenotypes however, retained their ability to bind and move on microtubules.

With this work, we now understand better how KIF1A carries on its important function of transporting synaptic vesicles to the synapse and how specific disease-causing mutations on KIF1A affect its molecular behavior and lead to disease.

Questions or comments about this research? Send an email to shannon@KIF1A.ORG.