TRANSPORT

Keeping motors running smoothly

In neurons, neurotransmitter-containing secretory vesicles are transported along microtubules from the proximal golgi apparatus to the distal pre-synaptic membrane, and various signalling molecules are transported from the pre-synaptic membrane to the nucleus. The structurally and functionally diverse molecular motor proteins dynein and kinesin mediate this transport, which is modulated by microtubule-associated proteins (MAPs). A new study by Holzbaur and colleagues further characterizes the role of tau, a MAP that has been implicated in the pathology of several neurodegenerative diseases, in anterograde and retrograde vesicle transport.

Anterograde transport is directed towards the pre-synaptic membrane and is carried out by kinesin, which can move only unidirectionally along microtubules. Conversely, dynein can move bi-directionally *in vitro* but carries out only retrograde transport in the cell. The binding of these motor proteins to microtubules, and their motility once they are bound, is affected by MAPs. Tau is one such MAP, and has been shown to inhibit kinesin activity *in vitro* and *in vivo*; however, the specifics of this inhibition and the effects of tau on dynein were largely unknown. To gain further insight, the authors sought to visualize individual interactions between microtubule-bound tau and kinesin and dynein in cell-free studies *in vitro*.

First they used total internal reflection fluorescence microscopy to visualize the effect of fluorescent Alexa-546-tagged recombinant tau on green fluorescent protein (GFP)-tagged dynein and kinesin. They found that tau affected the binding of kinesin to microtubules, but not that of dynein: kinesin binding decreased as local microtubule-bound tau concentrations increased. Tau also affected kinesin and dynein motility differently: when kinesin motors encountered a high concentration of microtubule-bound tau, they detached from the microtubule. By contrast, dynein motors reversed direction at tau clusters.

There are many neuronal isoforms of tau, all of which are comprised of two domains: a projection domain that is thought to have a role in recruiting dynein activators; and a microtubule-binding domain, which can contain different numbers of repeated elements. The authors wanted to quantify the concentration-dependent effects of tau, and investigate whether the different isoforms produced different effects. When they incubated microtubules with different concentrations of the shortest and longest isoforms — tau23 and tau40, respectively — they found that the binding and motility of both kinesin and dynein decreased in a tau-concentration-dependent manner. However, only kinesin was affected at physiological concentrations of tau23, and neither kinesin nor dynein was affected by physiological concentrations of tau40.

To further characterize these effects, the authors used recombinant tau23 proteins with truncated projection domains but intact microtubule-binding domains. They found that these truncated proteins were stonger inhibitors of kinesin and dynein binding and motility than wild-type tau23, and thus that the microtubule-binding domain of tau is sufficient for its inhibitory effects. The authors posit that the projection domain of tau recruits motor proteins to the microtubule; however, this hypothesis requires further investigation.

This study shows that tau has a modulatory role in axonal transport. A proximal-to-distal gradient of tau, which is known to exist in healthy neurons, would allow kinesin to bind to microtubules at the cell body and then translocate distally, at which point the higher concentration of tau would cause the kinesin to detach. Conversely, dynein would still be able to bind to the microtubules distally and mediate retrograde transport. An additional level of control that might be afforded by modulatory phosphorylation of tau remains to be explored.

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