Motor proteins haul precious cargo in neurons. How can we control their movement?

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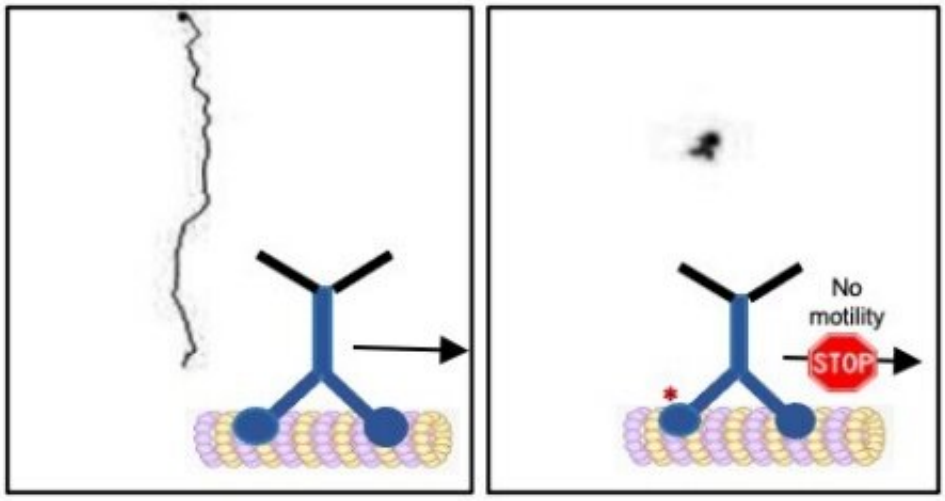

A study describes how an enzyme called GSK3β can act as a stop switch for a motor protein called kinesin 1. The dark line in the left panel shows the trajectory of a kinesin 1 motor protein with normal movement. The dark spot in the right panel shows the trajectory of a kinesin 1 motor protein whose motion has been stalled. Credit: Rupkatha Banerjee, adapted from a figure published in *Development* in a Dec. 23, 2021 article by Banerjee et al.

Inside neurons, motor proteins haul precious cargo, moving essential goods along thread-like roadways called microtubule tracks.

This miniature highway system is vital for keeping neurons healthy:

When traffic is flowing well, critical materials are able to reach distant areas of the cells where they're needed. When the system breaks down, it can impede cellular function and lead to cell death.

Now, scientists have identified a new tool for traffic control. In a study published in December 2021 in the journal *Development*, researchers describe how an enzyme called GSK3β can act as a stop switch for a type of motor protein called kinesin 1.

"Our publication details how GSK3β attaches a molecular tag to kinesin 1 motors, which causes the motors to stop without detaching from microtubule tracks. We are super excited, since now we know how to control the 'engine' while it is moving on a track," says senior author Shermali Gunawardena, Ph.D., an associate professor of biological sciences in the University at Buffalo (UB) College of Arts and Sciences.

"Transport of cargoes by motors is a tightly coordinated process, and yet the molecular mechanisms that control these 'engines' along the microtubule tracks remain largely unknown," says the study's first author, Rupkatha Banerjee, Ph.D., a postdoctoral research associate at Scripps Research in Florida who completed her doctorate in biological sciences at UB.

"Our work provides an in-depth understanding of how the enzyme GSK3β acts as a key regulator of the kinesin 1 motor," Banerjee adds. "Specifically, we have identified a precise site on kinesin 1 that is modified by GSK3β. Using molecular biology, in vitro analysis and fly genetics, coupled with in vivo imaging techniques, we were able to tease out the mechanistic details by which disruption of this particular site impacts motor movement and motor attachment to cargoes or microtubule tracks in a whole organism."

The findings—based on laboratory experiments, including some in the

neurons of fruit fly larvae—could open the door for future research on pausing motors as a mechanism for treating diseases.

Gunawardena highlights cancer as one potential example. "In cancer, cells are rapidly dividing, and motors are involved in this. So if you can stop the motors, you can impact this continuous division of cells," she says.

From a different angle, she notes that "in some neurodegenerative diseases, you see blockages of cargo within neurons because things are getting stuck on the road. If we can control the motors and stop them, maybe we can help to clear the track and get rid of these blockages. In parts of California, at rush hour, you have traffic lights that only let so many cars in at a certain time to prevent the highway from getting too full, which would slow down traffic and cause traffic blocks. Perhaps we can also apply this concept in neurons, too, if we can control motors by turning them on or off."

Co-authors of the study also include Piyali Chakraborty, a MS graduate of UB's neuroscience program, and Michael C. Yu, Ph.D., associate professor of biological sciences at UB.

In addition to detailing how GSK3β can stop kinesin 1 motors, the research explored other aspects of the enzyme's interaction with the motors, with results underscoring the idea that GSK3β plays an important role in fine-tuning kinesin 1 motor movement within neurons inside a living organism.

"This publication emphasizes fine-tuning of motor function as a potential approach for restoring transport defects that contribute to neurodegeneration and cancer," Banerjee says.

More information: Rupkatha Banerjee et al, A stop or go switch:

glycogen synthase kinase 3β phosphorylation of the kinesin 1 motor domain at Ser314 halts motility without detaching from microtubules, *Development* (2021). DOI: 10.1242/dev.199866

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