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Research Paper: Disease-associated mutations hyperactivate KIF1A motility and anterograde axonal transport of synaptic vesicle precursors

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Dr. Kyoko Chiba

Kyoko earned her Ph.D. in the lab of Dr. Toshiharu Suzuki at Hokkaido University in Japan, where she studied the mechanism of kinesin-based transport of the Azheimer's disease protein APP. Kyoko then became a postdoctoral scholar in the lab of Dr. Richard McKenney at the University of California – Davis, where she combines biochemistry and biophysics to study the molecular mechanisms of kinesin-based transport in cells and their relationships to human disease.

Dr. Richard J. McKenney

Richard earned his Ph.D. at Columbia University where he studied the biophysical properties of the cytoplasmic dynein motor with Professor Richard B. Vallee. Richard then moved to the laboratory of Dr. Ronald Vale, where he continued to research the mechanism and regulation of the dynein motor. The McKenney lab at the University of California – Davis maintains a strong interest in the biochemical and biophysical mechanisms of the molecular motor proteins dynein and kinesin, and how these mechanisms relate to human diseases.

Dr. Shinsuke Niwa

Shinsuke earned his Ph.D. in the lab of Dr. Nobutaka Hirokawa, a world-renowned leader in the biology of kinesin motor proteins. Shinsuke studied molecular and cellular aspects of various classes of kinesin motors before moving to do a postdoc in the lab of Dr. Kang Shen at Standford University. There, Shinsuke utilized the genetically tractable worm C. elegans to perform genetic screens to uncover regulatory mechanisms of kinesin movement in cells. Shinsuke now heads his own laboratory at Tohoku University in Japan. The Niwa lab continues to study diverse aspects of kinesin-based transport in cells utilizing genetics, cell biology, biochemistry and biophysics to address these questions.

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Understanding How Molecular Motor Proteins Work in Cells

Kinesin and dynein are molecular motors, protein machines that harness chemical energy to produce directed movement along filamentous tracks called microtubules within cells. Molecular motors function analogously to delivery trucks within a city, ferrying specific cargos to their proper destinations. The function and regulation of molecular motor activity is critical for cell health, and dysfunction of molecular motor activity leads to a variety of human diseases. The Niwa lab at Tohoku University (Japan), and the McKenney lab at the University of California – Davis (USA) study the mechanisms of molecular motor movement and how cells harness this ability to perform vital processes to keep cells healthy and alive. To ensure accurate delivery of cargos, molecular motor movement must be tightly regulated, turned on and off at the appropriate times to pick up and drop off their cargos. Our labs are particularly interested in how cells are able to control molecular motor activity to ensure the fidelity of cargo delivery as needed.

The KIF1A Molecular Motor

KIF1A is one molecular motor belonging to the large and diverse kinesin motor family of genes. Mutations in the KIF1A gene lead to defects in the ability of the KIF1A motor to properly deliver cargo within cells, particularly in neurons, which rely heavily on the long-distance transport via KIF1A. How KIF1A motor activity is regulated, turned on and off, is an area of active investigation. We, and others, have found that, similar to other kinesin motors, KIF1A predominantly exists in an autoinhibited state. This means that, in the absence of cargo, the motor tends to change its shape resulting in the inhibition of its motor activity. The binding of cargo to the motor changes the motor's shape again to allow it to move along microtubule tracks and thus deliver the cargo to its appropriate destination. The ability to self-regulate motor activity appears to be a common principle across different classes of molecular motor proteins and suggests that motor activity is tightly controlled in cells. Loss of the ability to properly control when and where a motor protein becomes active or inactive means cells lose the ability to control cargo pickup and delivery, leading to drastic consequences for cell health and viability.

What We've Discovered About KIF1A & Hereditary Spastic Parapalegia

Mutations in KIF1A that lead to hereditary spastic paraplegia (HSP) are thought to result in a loss of KIF1A motor activity, due to the damaging effects of the mutation on the motor's ability to adopt it's appropriate three-dimensional shape. However, our study has provided new evidence that this notion is not true for a subset of KIF1A mutations that lead to HSP. Our labs have combined our expertise in protein biochemistry and biophysics, genetics, and cell biology to study the effects of several KIF1A mutations that cause a specific subtype of HSP called "uncomplicated" or "pure" HSP (that is HSP symptoms that are limited to the lower extremities). We have found that these mutations in KIF1A actually lead to over-activation of motor activity, in contrast to loss of motor activity. That is, KIF1A motors harboring these specific mutations lose the ability to adopt their autoinhibited shape and shut off their motor activity in the absence of cargo.

What We've Discovered About KIF1A & Hereditary Spastic Parapalegia (Continued)

We directly observed the motion of isolated KIF1A motors using single molecule imaging, a technique that allows us to monitor the movement of individual KIF1A molecules in real time. We were able to directly observe that the HSP mutant motors had much more motor activity compared to the normal KIF1A molecule. We then established a genetic model of HSP using the worm *C. elegans*, in which we could monitor the movement and delivery of specific cargos within live neurons inside the worms. Introduction of the HSP-causing mutations in KIF1A lead to the over active transport of KIF1A cargo inside of these neurons, further indicating that the mutations result in KIF1A motors that are defective in shutting off their motor activity in live neurons.

Together our data suggest a new paradigm about the proper activity of molecular motors in cells. It was previously known that mutations that result in loss of motor activity are detrimental to cell health, but our new data now suggest that too MUCH motor activity is equally as detrimental, and can result in human diseases such as pure HSP. These findings highlight the fact that transport of cargo within cells by molecular motors such as KIF1A is a delicate balance of activity, and that too little or too much motor activity can be equally detrimental to cell health. Further, our findings suggest that, for some specific types of HSP, future treatment efforts should be focused on how to attenuate the over active KIF1A motor.

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