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Tiny worm sheds light on giant mystery about neurons

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Scientists have identified a gene that keeps our nerve fibers from clogging up. Researchers in Ken Miller's laboratory at the Oklahoma Medical Research Foundation (OMRF) found that the unc-16 gene of the roundworm *Caenorhabditis elegans* encodes a gatekeeper that restricts flow of cellular organelles from the cell body to the axon, a long, narrow extension that neurons use for signaling. Organelles clogging the axon could interfere with neuronal signaling or cause the axon to degenerate, leading to neurodegenerative disorders. This research, published in the May 2013 Genetics Society of America's journal *Genetics*, adds an unexpected twist to our understanding of trafficking within neurons.

Proteins equivalent to UNC-16 are present in the neurons of all animals, including humans And are known to interact with proteins associated with neurodegenerative disorders in humans (Hereditary Spastic Paraplegia) and mice (Legs at Odd Angles). However, the underlying cause of these disorders is not well understood.

"Our UNC-16 study provides the first insights into a previously unrecognized trafficking system that protects axons from invasion by organelles from the cell soma," Dr. Miller said. "A breakdown in this gatekeeper may be the underlying cause of this group of disorders," he added.

The use of the model organism *C. elegans*, a tiny, translucent roundworm with only 300 neurons, enabled the discovery because the researchers

were able to apply complex genetic techniques and imaging methods in living organisms, which would be impossible in larger animals. Dr. Miller's team tagged organelles with fluorescent proteins and then used time-lapse imaging to follow the movements of the organelles. In normal axons, organelles exited the cell body and entered the initial segment of the axon, but did not move beyond that. In axons of unc-16 mutants, the organelles hitched a ride on tiny motors that carried them deep into the axon, where they accumulated.

Dr. Miller acknowledges there are still a lot of unanswered questions. His lab is currently investigating how UNC-16 performs its crucial gatekeeper function by looking for other mutant worms with similar phenotypes. A Commentary on the article, also published in this issue of *GENETICS*, calls the work "provocative", and highlights several important questions prompted by this pioneering study.

"This research once again shows how studies of simple model organisms can bring insight into complex neurodegenerative diseases in humans," said Mark Johnston, Editor-in-Chief of the journal *Genetics*. "This kind of basic research is necessary if we are to understand diseases that can't easily be studied in more complex animals."

More information: Edwards, Stacey L., Szi-chieh Yu, Christopher M. Hoover, Barret C. Phillips, Janet E. Richmond, and Kenneth G. Miller. An Organelle Gatekeeper Function for Caenorhabditis elegans UNC-16 (JIP3) at the Axon Initial Segment Genetics, May 2013, 194:143-161.

Commentary: Zheng, Qun and Michael L. Nonet. Title: UNC-16/JIP3/Sunday Driver: A New Cop on the Organelle Highway Genetics, May 2013, 194:35-37.

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