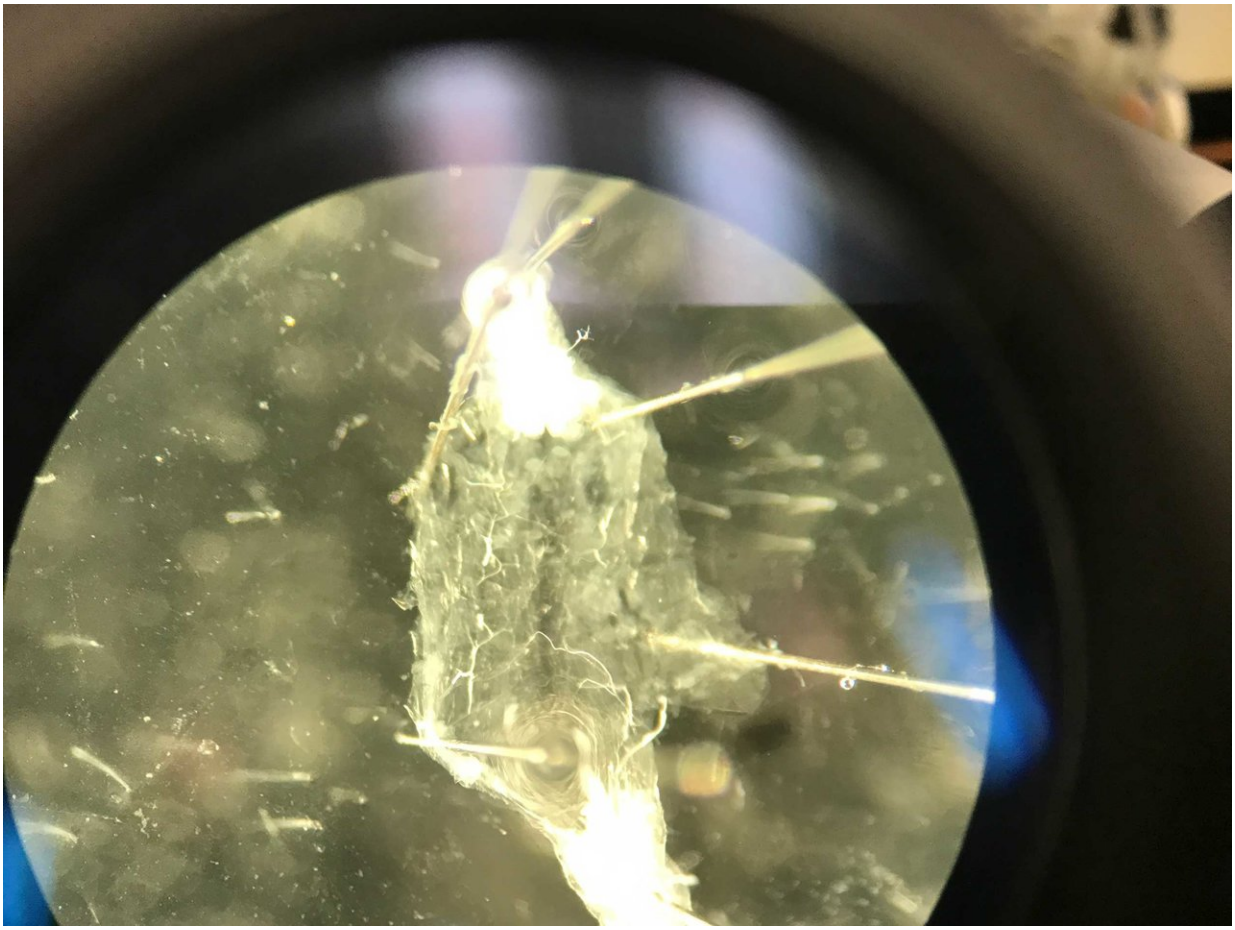
Medical Xpress

Pathway in neurons may contribute to neurodegenerative disease

October 4 2017, by Morgan Sherburne



Researchers in Catherine Collins' lab dissect fruit fly larvae, seen here through a microscope. Credit: Michigan News

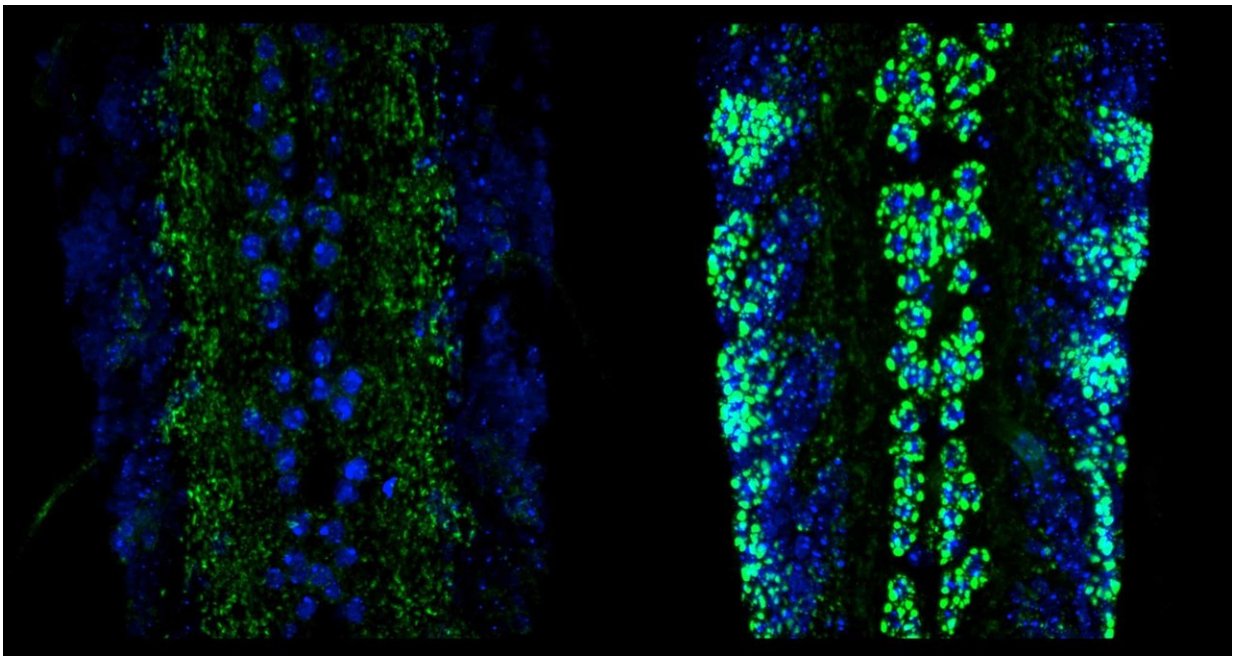
An injury pathway in the neurons of fruit flies may cause the loss of synapses in diseases such as Alzheimer's and ALS, according to University of Michigan researchers.

This pathway, called DLK, has received recent attention as a candidate drug target because it contributes to the deterioration of damaged neurons. The new findings further expand that interest by suggesting that inhibiting DLK may help neurons to maintain working synapses, which is more useful than simply preventing damaged neurons from dying.

The pathway, studied here in fruit flies, is similar to the pathway in the neurons of mammals and humans. The U-M team, which includes former doctoral student Jiaxing Li and Catherine Collins, associate professor of molecular, cellular and developmental biology, found a new relationship between the injury pathway and a protein in neurons called kinesin—specifically, a kinesin called Unc-104.

When neurons communicate with each other, they extend a projection called an axon toward each other and form sites for information exchange called synapses. Transmitting information between synapses requires many protein molecules, which are manufactured within the neuron cell body and ferried over long distances within axons by kinesins such as Unc-104. The Unc-104 kinesin seems to carry many of the proteins needed for the neuron to release neurotransmitters for information exchange.

The U-M researchers found that the injury pathway is triggered when Unc-104 is damaged or mutated. This builds upon previous knowledge that the pathway is required for the key responses neurons make when damaged, including initiating the neuron to repair itself or die, depending on the context.



Nerve cords from the Drosophila larvae, analogous to the spinal cord, are stained to show a synaptic vesicle protein in white. Synaptic proteins build up in cell bodies when an injury pathway is mutated (image on left). Credit: Jiaxing Li

When Unc-104 is damaged or mutated, synapses become defective. Previously, researchers assumed that this is because of a failure to transport synaptic proteins to synapse sites. However, in their study, Li, Collins and their team found that turning off the neuronal injury pathway can restore the function of these mutant synapses. Their results are published in the journal *eLife*.

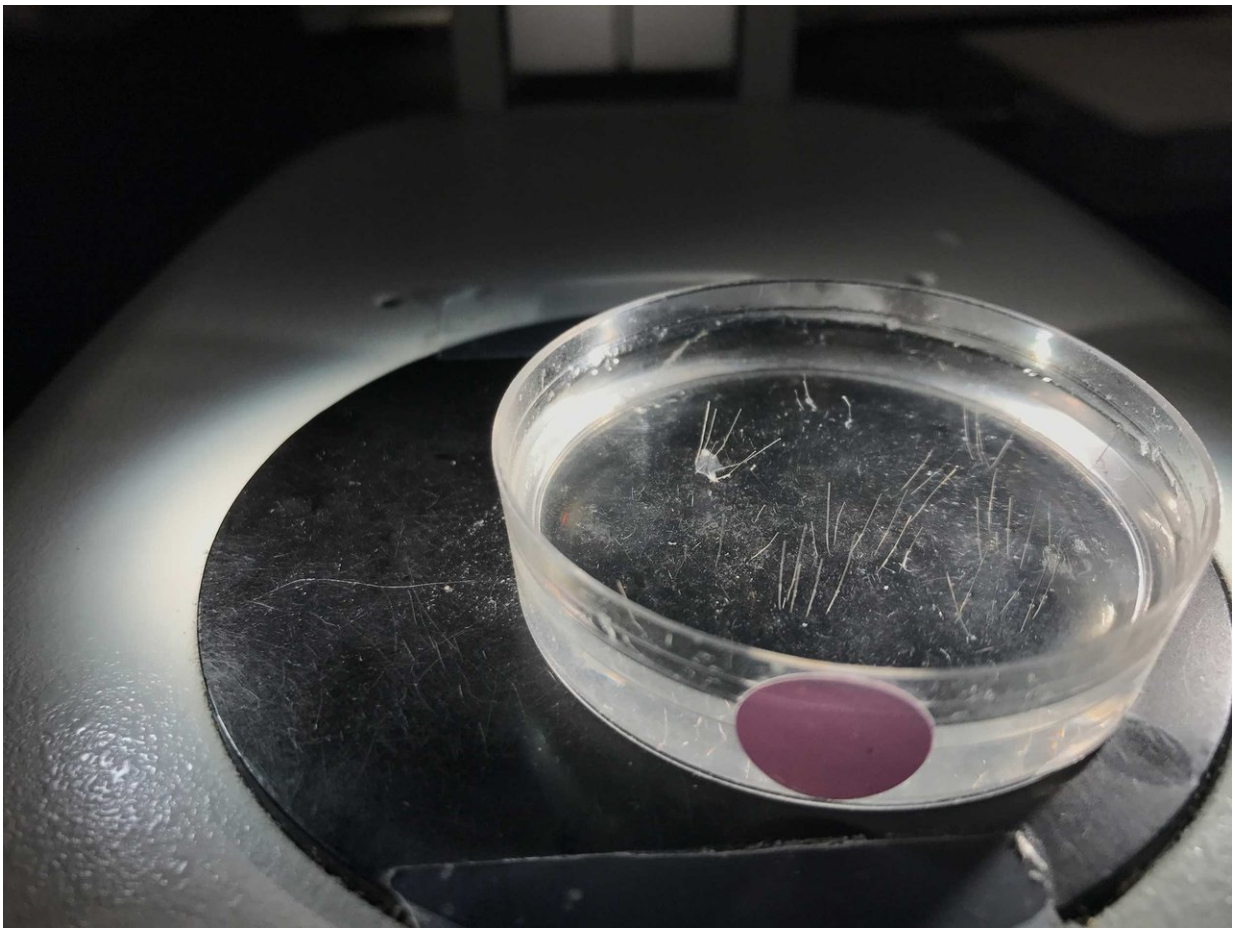
To study the role of the kinesin and the injury pathway in the malfunction of synapses, the researchers imaged the synapses of dissected fruit fly larvae using a confocal microscope. Working in the neighboring lab of U-M professor Richard Hume, Li also used electrophysiology to measure how well the synapses were firing. The team found that when they shut down the injury pathway, the function of

that synapse was restored.

"That was really striking," Collins said. "It told us that the axon injury pathway was causing these major problems in synapses."

The team found that the pathway becomes activated when the Unc-104 kinesin is impaired, and that once activated, the pathway shuts down the formation of many of the synaptic proteins which are normally transported in axons.

"In the fruit fly system, we know the neuroanatomy really well. We can actually see how impairment of kinesin is affecting things in cell bodies, synapses and neurons," Collins said. "When we turned down the injury pathway in the kinesin mutants, we could see a huge mass of synaptic proteins accumulating in the cell body. That led us to the idea that the injury pathway turns down the levels of many synaptic proteins, leading to synapse malfunction."



Researchers in Catherine Collins' lab pin larvae for dissection under a microscope. Credit: Michigan News

The findings imply that activation of the injury pathway has negative consequences for synapses. Complementing this work, recent findings published in *Science Translational Medicine* suggest that the injury pathway may be activated in patients with neurodegenerative diseases ALS and Alzheimer's disease.

Restricting the pathway can also delay symptoms of these diseases in mouse models. This draws attention to the pathway as a potential therapeutic target.

But this could also hinder beneficial functions of the injury pathway, Collins says.

"When the injury pathway was knocked down in flies, the massive accumulations of proteins in cell bodies suggested to us that it functions as a stress response mechanism, to prevent unwanted build-up of proteins when axonal transport is impaired," she said.

Next, the researchers want to understand why the injury pathway appears specifically tuned to Unc-104 for its activation, and how the pathway reduces synaptic proteins.

More information: Jiaxing Li et al. Restraint of presynaptic protein levels by Wnd/DLK signaling mediates synaptic defects associated with the kinesin-3 motor Unc-104, *eLife* (2017). DOI: 10.7554/eLife.24271

Loss of dual leucine zipper kinase signaling is protective in animal models of neurodegenerative disease. *Science Translational Medicine* doi.org/10.1126/scitranslmed.aag0394

Provided by University of Michigan