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Biologists identify a key enzyme involved in protecting nerves from degeneration

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- A new animal model of nerve injury has brought to light a critical role of an enzyme called Nmnat in nerve fiber maintenance and neuroprotection. Understanding biological pathways involved in maintaining healthy nerves and clearing away damaged ones may offer scientists targets for drugs to mitigate neurodegenerative diseases such as Huntington's and Parkinson's, as well as aid in situations of acute nerve damage, such as spinal cord injury.

University of Pennsylvanian biologists developed the model in the adult fruit fly, Drosophila melanogaster.

"We are using the basic power of the fly to learn about how neurons are damaged in acute injury situations," said Nancy Bonini, senior author of the research and a professor in the Department of Biology at Penn. "Our work indicates that Nmnat may be key."

The research was published in Current Biology. First author on the study is postdoctoral researcher Yanshan Fang, with additional contributions from postdoctoral researcher Lorena Soares and research technicians Xiuyin Teng and Melissa Geary, all of Penn's Department of Biology.

When a nerve suffers an acute injury -- as might be caused by a penetrating wound, for example, or a broken bone that damages nearby tissues -- the long projection of the nerve cell, called the axon, can become injured and degenerate. The process by which it disintegrates is known as Wallerian or Wallerian-like degeneration and is an active,

orderly process.

Though this function of eliminating damaged nerve cells is crucial, biologists do not have a clear understanding of all of the molecular signaling pathways that govern the process.

Bonini's lab has previously focused on chronic neurodegenerative diseases but made this foray into acute nerve injury to determine if mechanistic overlaps exist between acute axon injury and chronic neurodegeneration. They first searched for an appropriate nerve tract to target and identified the wing of adult flies as a prime option.

The fly wing is not only translucent and a site of lengthy nerve fibers that can be easily observed, but it can also be cut to cause injury without killing the fly. That way, the researchers can follow the animal's response to nerve injury for weeks.

Using various reagents to manipulate the fly's genetic traits, the team confirmed that the cut wing nerve underwent Wallerian degeneration. They then tested versions of Nmnat and another protein called WldS, all of which had previously been shown to protect nerves from degeneration, to see if any of these might stop the process. All significantly delayed neurodegeneration. Even a form of Nmnat that hadn't worked in other animal models suppressed degeneration, although to a lesser extent.

"That indicates that our assay is really sensitive," Bonini said. "This sensitivity could help us identify genes that have moderate although important functionality at protecting against nerve degeneration."

Their investigations into the wing nerve also showed that the degenerating axon "died back," fragmenting first from the axon terminals, the side farthest from the nerve cell body—a pattern similar to

what has been seen in other disorders.

Doing more genetic tinkering, the researchers showed that when the animal's own Nmnat was depleted, the nerves fragmented in the same way as if the axon was physically cut. And when Nmnat and the other "rescue" proteins were added back to these genetically modified flies, they were able to block degeneration, highlighting that Nmnat is critical to maintaining healthy axons.

In a final set of experiments, the biologists sought to narrow where in the nerve cells Nmnat might be working. They focused on mitochondria, the powerhouses of cells. When they created a genetic line of flies that blocked mitochondria from entering the axon fibers, the nerve tract degenerated, again, in a dying-back fashion. Yet now WldS and Nmnat failed to prevent axon degeneration, suggesting that those proteins may act on and require the presence of axonal mitochondria to maintain healthy nerves in normal flies.

Flipping that scenario around, they looked to see what happened to the mitochondria of flies upon nerve injury. When they cut the wing nerve axons, the mitochondria rapidly disappeared. Yet they can largely preserve the mitochrondria by increasing expression of Nmnat.

Their results, taken together with the findings of other studies, suggest that Nmnat may stabilize mitochondria in some way in order to keep axons in a healthy state.

"We have some hope that these proteins or their activity may someday serve as drug targets or could provide the foundation for a therapeutic advance," Bonini said. "But right now, my hope is that the power of the fly model will open up a lot of new directions of research and new pathways that could be targets for development in the future."