Blocking protein may help ease painful nerve condition

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Scientists have identified the first gene that pulls the plug on ailing nerve cell branches from within the nerve cell, possibly helping to trigger the painful condition known as neuropathy.

The condition is a side effect of some forms of chemotherapy and can also afflict patients with cancer, diabetes, kidney failure, viral infections, neurodegenerative disorders and other ailments.

Researchers at Washington University School of Medicine in St. Louis showed that blocking the dual leucine zipper kinase (DLK) gene inhibits degeneration of ailing nerve cell branches, possibly preventing neuropathy.

"Neuropathy can become so extraordinarily painful that some patients stop taking their chemotherapy, regardless of the consequences in their fight against cancer," says co-senior author Aaron DiAntonio, M.D., Ph.D., associate professor of developmental biology. "So we're very excited about the possibilities this gene may offer for reducing that pain."

The findings are published online on March 15 in Nature Neuroscience.

Scientists have known since 1850 that nerve cells have ways to prune branches (also known as axons) that are injured. Although axon pruning is also a normal part of early human development, inappropriate loss of axons in the adult nervous system causes painful sensations that have

been compared to burning, freezing or electric shock and have come to be known as neuropathy.

DiAntonio's lab previously revealed that the fruit fly's version of DLK helps establish synapses, junctures where two nerve cells communicate. But they found the gene doesn't do the same thing in mice.

Curious about DLK's role in mammals, Bradley Miller, an M.D./Ph.D. student in DiAntonio's lab, consulted with co-senior author Jeffrey Milbrandt, M.D., Ph.D., the David Clayson Professor of Neurology. Milbrandt studies the role of various proteins in neurodegeneration. With support from the University's Hope Center for Neurological Disorders, they showed that the long axons of the sciatic nerve in mice with a mutated DLK gene resisted degeneration after it was surgically cut.

In follow-up tests, Miller and Craig Press, an M.D./Ph.D. student in Milbrandt's lab, took nerve cells in culture and treated their axons with the chemotherapy drug vincristine. Normal axons degenerated rapidly after exposure to the drug, but axons where DLK's activity had been blocked were protected from degeneration.

"The pain of neuropathy is often a key factor that limits the dose in cancer chemotherapy," DiAntonio notes. "We know when patients are going to start their treatment, so one day it might be possible to start patients on a DLK-blocking drug before their chemotherapy and spare them considerable pain."

DLK appears to act like a contractor that calls in wrecking crews, DiAntonio notes. It helps make the decision to eradicate an axon, but the actual demolition is left to other processes called up by DLK.

"We want to more fully understand the chain of molecular reactions that carry out DLK's decision, because that might reveal a better opportunity

to block the effect with a drug," says DiAntonio.

DiAntonio and Milbrandt also plan to test if blocking DLK stops neurodegeneration in other forms of injury and stress, including the harm inflicted on the optic nerve by glaucoma and central nervous system phenomena like stroke and Parkinson's disease.

More information: Miller BR, Press C, Daniels RW, Sasaki Y, Milbrandt J, DiAntonio A. A DLK-dependent axon self-destruction program promotes Wallerian degeneration. *Nature Neuroscience*, online March 15.

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