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Study sheds light on a 'guardian' protein of brain function

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Mitochondria not only are the cell's main power producers, they are also the chief cooks and bottle washers.

When they get out of whack, the cell can't function normally. In the brain, mitochondrial failure can set the stage for Parkinson's disease, Alzheimer's disease and other forms of neurodegeneration.

Fortunately there is a group of "night watchmen," proteins that monitor mitochondrial function and sound the alarm if a mitochondrion has failed and needs to be replaced.

One of these proteins, called CHIP, is essential for maintaining mitochondrial health. When CHIP is absent or there is not enough of it, nerve cells cannot recover when, for example, a stroke disrupts their supply of oxygen and glucose.

The critical role of CHIP was reported recently in the journal *Antioxidants and Redox Signaling* by researchers at Vanderbilt University. Their report has spurred efforts to develop CHIP-enhancing drugs to help speed recovery from strokes and following neurosurgery, and prevent development of neurodegenerative disorders.

"If we can do a better job of maintaining these mitochondria ... that's a very, very powerful tool to have," said senior author BethAnn McLaughlin, Ph.D., assistant professor of Neurology and Pharmacology.

Among the major findings the authors uncovered "profound impairments" at both the anatomical and biochemical levels in mice with the CHIP gene deleted, or "knocked out."

They're smaller than their normal littermates, their back legs are weak, and they die young. "They're 30 days old and they look like they're 150," McLaughlin said.

Using a mass spectrometry technique developed by Vanderbilt proteomics pioneer and co-author Dan Liebler, Ph.D., and his colleagues, graduate student Amy Palubinsky confirmed for the first time that CHIP goes to the mitochondria when cells are stressed by lack of oxygen, for example.

She also found that in the absence of CHIP, nerve cells from these animals are much more vulnerable to oxygen and glucose deprivation and are "loaded" with damaged proteins that impair their functioning. Palubinsky is first author on the paper and a Vanderbilt Clinical Neuroscience Scholar.

Palubinsky said the cellular changes seen in the CHIP knockout mice were the same as those her group previously detected in postmortem human samples from people who'd had strokes or "transient ischemic attacks," which interrupt the brain's oxygen and glucose supplies.

"That gives us a new model system to ... look deeper and see what the mechanisms" are," she said.

The Vanderbilt team is now collaborating with medicinal chemist Jason Gestwicki, Ph.D., at the University of California, San Francisco, to test potential CHIP-enhancing drugs he has developed. "We're moving (toward) trying that in cells, (and) in animal models of stroke and Parkinson's disease," McLaughlin said.

They also are working with David Charles, M.D., professor of Neurology at Vanderbilt and a pioneer in deep brain stimulation to relieve symptoms of Parkinson's disease, to develop imaging tests that can pick up changes in the mitochondria before the cells die.

Provided by Vanderbilt University Medical Center