Mouse model sheds light on role of mitochondria in neurodegenerative diseases

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A new study by researchers at the University of Utah School of Medicine sheds light on a longstanding question about the role of mitochondria in debilitating and fatal motor neuron diseases and resulted in a new mouse model to study such illnesses.

Researchers led by Janet Shaw, Ph.D., professor of biochemistry, found that when healthy, functioning mitochondria was prevented from moving along axons – nerve fibers that conduct electricity away from neurons – mice developed symptoms of neurodegenerative diseases. In a study in the *Proceedings of the National Academy of Sciences*, Shaw and her research colleagues said their findings indicate that motor neuron diseases might result from poor distribution of mitochondria along the spinal cord and axons. First author Tammy T. Nguyen, is a student in the U medical school's M.D./Ph.D. program, which aims to produce physicians with outstanding clinical skills and rigorous scientific training to bridge the worlds of clinical medicine and basic research to improve health care.

"We've known for a long time of the link between mitochondrial function and distribution and neural disease," Shaw says. "But we haven't been able to tell if the defect occurs because mitochondria aren't getting to the right place or because they're not functioning correctly."

Mitochondria are organelles – compartments contained inside cells – that serve several functions, including making ATP, a nucleotide that cells convert into chemical energy to stay alive. For this reason mitochondria

often are called "cellular power plants." They also play a critical role in preventing too much calcium from building up in cells, which can cause apoptosis, or cell death.

For mitochondria to perform its functions, it must be distributed to cells throughout the body, which is accomplished with the help of small protein "motors" that transport the organelles along axons. For the motors to transport mitochondria, enzymes known as Mitochondrial Rho (Miro1) GTPases act to attach mitochondria to the motors. To study how the movement of mitochondria is related to motor neuron disease, Nguyen developed two mouse models in which the gene that makes Miro1 was knocked out. In one model, mice lacked Miro1 during the embryonic stage. A second model lacked the enzyme in the cerebral cortex, spinal cord and hippocampus.

The researchers observed that mice lacking Miro1 during the embryonic stage had motor neuron defects that prevented them from taking a single breath once born. After examining the mice, Nguyen, Shaw and their colleagues discovered that neurons required for breathing after birth were missing from the upper half of the mice's brain stems. The phrenic nerve, also important for breathing, was not fully developed, either.

"We believe the physical difficulties in the mice indicated there were motor neuron defects," Shaw says.

Conversely, the mice without Miro1 in their brain and spinal cord were fine at birth but soon developed signs of neurological problems, such as hunched spines, difficulty moving and clasping their hind paws together, and died around 35 days after birth. Those symptoms appeared similar to motor neuron disease, according to Shaw.

"The mitochondrial function in the cells appeared to be fine, and calcium levels were normal," she says. "This shows for the first time that

restricting mitochondrial movement and distribution could cause neuronal disease."

Stefan M. Pulst, M.D., Dr. med, professor and chair of the University's neurology department and a co-author on the study, says the mitochondrial transport process is important not just for motor neurons but other neurons as well. "The Miro1 proteins and the respective animal models represent a breakthrough for studying ALS (Lou Gehrig's disease) and other neurodegenerative diseases."

Although much more research must be done, the study opens the possibility of developing new drugs to partially correct the mitochondrial distribution defects to slow the progression of motor neuron diseases. First, Shaw wants to generate a model to knock out the Miro1 gene in adult mice to see if the results mimic neurological diseases.

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