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Potential new target for treatment of spinal muscular atrophy discovered

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For the first time, scientists found that in spinal muscular atrophy (SMA), the affected nerve cells that control muscle movement, or motor neurons, have defects in their mitochondria, which generate energy used by the cell. Impaired mitochondrial function and structure in motor neurons were discovered before symptoms occurred, suggesting a role in disease development.

These findings, published in *Human Molecular Genetics*, point to new possibilities for targeted therapy for SMA.

"Restoring mitochondrial function might be a new treatment strategy for SMA," said Yongchao Ma, PhD, senior author and Ann Marie and Francis Klocke, MD Research Scholar, Stanley Manne Children's Research Institute at Ann & Robert H. Lurie Children's Hospital of Chicago. He also is Assistant Professor of Pediatrics, Neurology and Physiology at Northwestern University Feinberg School of Medicine.

Infants born with SMA are not able to hold up their heads or sit up on their own, and they rarely survive beyond 2 years of age.

"While the genetic cause of this devastating disease has been identified, our study describes how mitochondrial dysfunction might contribute to motor neuron destruction even before the onset of symptoms," said Ma. "Our findings provide new insights into SMA pathogenesis, which is crucial to developing new therapies."

Ma and colleagues first discovered that mitochondria was involved in SMA when they analyzed gene expression profiles of motor neurons from SMA and control mice. They observed that the genes related to many mitochondrial functions were significantly dysregulated in SMA motor neurons.

"This discovery was unexpected and led us to test whether mitochondrial functions were changed in motor neurons from SMA mouse models," said Ma.

Using sophisticated technology, the study found that mitochondria in SMA motor neurons produce energy at a slower rate, depleting the nerve. SMA mitochondria was less healthy, as evidenced by its decreased membrane potential. It also had increased oxidative stress level, which is toxic to the neuron. The movement of mitochondria was impaired as well, which would cause it to get stuck at the junction between nerve and muscle, leaking toxins and eventually disrupting the connection. Mitochondria in SMA motor neurons was also fragmented and swollen, which is consistent with the functional defects measured by the study.

"Motor neurons have high energy demands, which would make them highly sensitive to defects in their mitochondria," says Ma. "These defects might lead to the symptom of motor neuron degeneration in SMA," says Ma.

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More information: Nimrod Miller et al. Motor Neuron Mitochondrial Dysfunction in Spinal Muscular Atrophy, *Human Molecular Genetics* (2016). DOI: 10.1093/hmg/ddw262

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