Self-cannibalizing mitochondria may set the stage for ALS development

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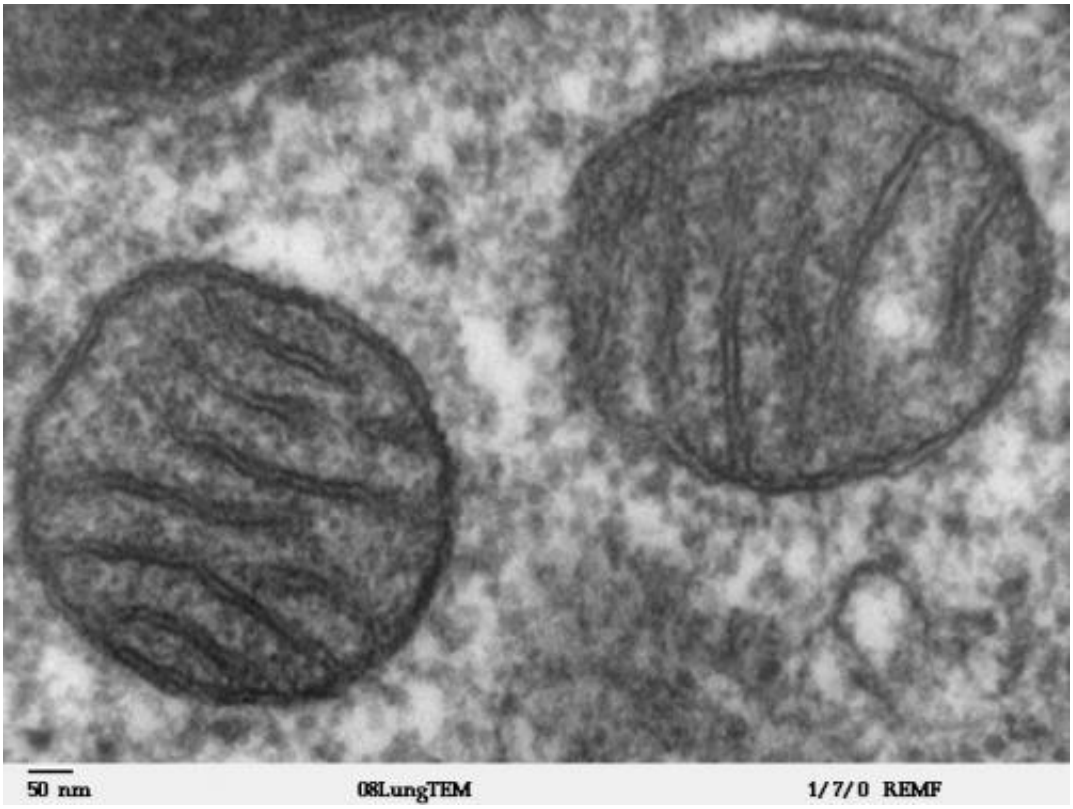

Mitochondria. Credit: Wikipedia commons

Northwestern Medicine scientists have discovered a new phenomenon in the brain that could explain the development of early stages of neurodegeneration that is seen in diseases such as ALS, which affects voluntary muscle movement such as walking and talking.

The discovery was so novel, the scientists needed to coin a new term to describe it: mitoautophagy, a collection of self-destructive mitochondria in diseased upper motor neurons of the brain that begin to disintegrate from within at a very early age. Upper motor neurons in the brain are responsible for initiating muscle movement and relaxation and are one of the first to break down in neurodegenerative diseases.

The study will be published on November 7 in the journal *Frontiers in Cellular Neuroscience*.

The phenomenon is observed mainly in one of the most common pathologies observed in neurodegenerative diseases, TDP-43 pathology, which is seen in more than 90% of ALS cases. When a pathology is present in the body, it indicates that something is wrong or functioning abnormally.

"I think we have found the culprit that primes neurons to become vulnerable to future degeneration: suicidal mitochondria," said senior study author Hande Ozdinler, associate professor of neurology at Northwestern University Feinberg School of Medicine. "The mitochondria basically eat themselves up very early in the disease. This occurs selectively in the neurons that will soon degenerate in patient's brains."

"This type of degeneration begins much earlier than previously thought," said study lead author Mukesh Gautam, the A Long Swim (ALS) Ellen Blakeman fellow at Northwestern.

Using a process called immuno-coupled electron microscopy, the scientists investigated the cellular events that go wrong inside the neurons that become vulnerable to disease. After analyzing more than 200 neurons, they observed the self-destruction of mitochondria only in the diseased neurons, and especially within the context of TDP-43

pathology.

Mitochondria are powerhouses of the cell that create and maintain energy in the cells. In the diseased upper motor neurons, mitochondria self-destruct first by elongating, then forming a ring-like structure, until they finally disintegrate from the inside out.

It is a type of degeneration never been seen before, and it is different from previously described stages of mitochondrial degeneration.

The study analyzed mitochondria in the upper motor neurons of three different mouse models of ALS at only 15 days old—equivalent to a toddler in humans. While the study was in mice, Ozdinler and her team showed many times before that the upper neurons even in different species are almost identical at a cellular level, especially within the context of TDP-43 pathology.

These self-destructive mitochondria could become a future target for drug therapies to treat ALS and other neurodegenerative diseases in which a person's movement is affected, Ozdinler said. They are currently working with drug companies to see if drugs used for human patients with mitochondrial disease could in fact improve the health of diseased motor neurons.

"Many of the drugs currently on the market that target the health and the integrity of mitochondria may well be repurposed and considered for neurodegenerative diseases in the future," Ozdinler said. "Maybe we don't need to reinvent the wheel to cure ALS and other neurodegenerative diseases.

"To overcome neurodegeneration, we need to improve the health and the stability of mitochondria. If we improve the health of the mitochondria early, we may even eliminate protein aggregate formation, a pathology

broadly observed in many diseases."

More information: Mukesh Gautam et al, Mitoautophagy: A Unique Self-Destructive Path Mitochondria of Upper Motor Neurons With TDP-43 Pathology Take, Very Early in ALS, *Frontiers in Cellular Neuroscience* (2019). DOI: 10.3389/fncel.2019.00489

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