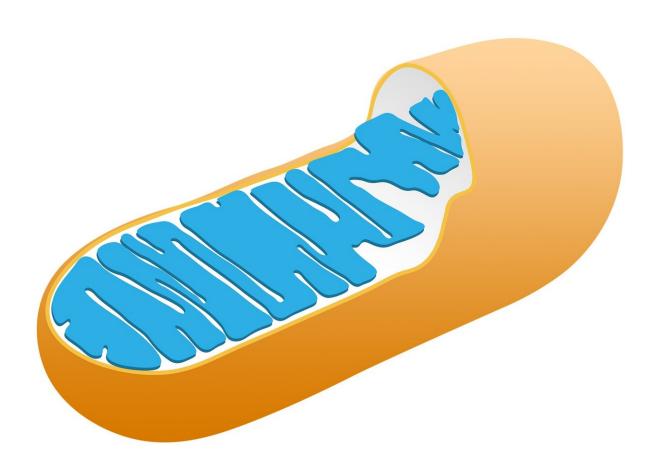


Protein protects the mitochondria and surprisingly rescues neurons from stroke-like damage

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A protein newly discovered by scientists in China is aiding in the dramatic reversal of stroke-like damage in laboratory animals and may one day rescue humans from neurological injury, the research team is predicting.

Their work is based on a series of breakthrough studies involving mitochondria, bean-shaped structures that are often called the powerhouses of <u>cells</u> because they are the source of adenosine triphosphate (ATP), the basic fuel for the myriad processes of life itself.

When the mitochondria are damaged, <u>neurological diseases</u> proceed on a rapid downhill course. Such is the path for patients in the aftermath of a severe stroke; irreversible neurological damage likewise afflicts patients with Parkinson's disease.

Xiaodong Wang of the National Institute of Biological Sciences in Beijing has completed a series of elegant experiments involving mitochondria based on a deceptively simple question: Is there a way to prevent the downward course of neurological conditions by stopping damage within the mitochondria?

Reporting in the *Proceedings of the National Academy of Sciences*, Wang and colleagues examined an important pathway that leads to programmed <u>cell death</u>—apoptosis—when the mitochondria are damaged.

"Mitochondria in mammalian cells play many functional roles in



maintaining the well-being of the organism, acting as the major bioenergy source, as well as a signaling compartment that can trigger apoptosis and inflammation," Wang wrote in PNAS.

A mitochondrion is an organelle, a constituent in a mammalian cell that has a specific job—<u>energy production</u>. It also has its own DNA, and is the only organelle with DNA other than the nucleus.

Other organelles have different, specialized roles. The Golgi apparatus, for example, modifies, sorts and packages proteins for secretion. The nucleus provides the inner sanctum for the cell's genetic material, DNA.

Working with a team of researchers from throughout China, Wang isolated a minuscule protein that not only blocks apoptosis, but additionally protects mitochondrial integrity and function. The result, the scientists say, is preserved neurological function. The work to date has been conducted only in laboratory animals, but the team foresees possible extension of their work in human clinical trials.

The protein isolated by the team has been dubbed Compound R6, which not only prevents apoptosis, but the activation of autophagy, the body's process of clearing out damaged cells. Blocking apoptosis allowed damaged cells to recover and regain some of their healthy functions.

Wang discovered that Compound R6 prevents apoptosis through the inhibition of mTOR, a major signaling pathway. Supplying the protein to animals with cerebral ischemia, for example, produced neuroprotective effects that were dose-dependent. That means the more Compound R6 that was provided, the better the brain was protected from neurological injury.

"Given increasing appreciation that mitochondrial damage affects the etiology of several common and devastating neurodegenerative diseases,



Compound R6's ability to pass the <u>blood-brain barrier</u> and confer strong anti-apoptotic effects should encourage preclinical and medicinal chemistry research efforts," Wang reported, noting, "perhaps even extending—as with other known mTOR inhibitors—into evaluation of possible anti-aging effects."

Because mitochondria are the energy producers in cells, they are associated with the overall health and vigor of the organism. A single human muscle cell can contain 5,000 or more mitochondria, as can a fragile nerve cell or an insulin-producing cell in the pancreas.

But these tiny, oblong energy producers are not only subject to damage in age-related diseases, such as stroke and Parkinson's, they decline in the natural process of aging. When these mini factories decline or fail in the pancreas, the result can be type 2 diabetes, a condition diagnosed most frequently among older patients.

Damage and loss of mitochondria in nerve cells, also documented to occur with age, is associated with dimmer vision and foggier minds. For example, studies have long suggested that fewer energy-producing mitochondria are present in neurons throughout the brains of people with Alzheimer's disease. The Parkinson's and stroke-related research of Wang and colleagues add to the growing catalog of data on the importance of the mitochondria to neurological health.

The mitochondria, scientists theorize, hail from a misty primordial past. They are believed to be descendants of ancient aerobic bacteria that insinuated themselves—DNA and all—into early mammalian and plant cells. Scientists say they may have been purple bacteria that possessed a superior ability to utilize oxygen in an ancient stew where complex cells—forerunners to those that would one day make up complex organisms—were struggling.



Wang's research, meanwhile, stems from a long series of experiments that reveal the intimate link between the <u>mitochondria</u> and the health of nerve cells. Compound R6 offers a potential path to ameliorate damage to the organelle and rescue severely injured nerve cells. Compound R6, however, is not the team's first major discovery.

"Previously, we reported the discovery of a small molecule, Compound A, which blocks dopaminergic neuron death in a rat model of Parkinson's disease," Wang said.

More information: Ran Cao, et al. A small molecule protects mitochondrial integrity by inhibiting mTOR activity, *PNAS*, (2019). Doi.org/10.1073/pnas.1911246116

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