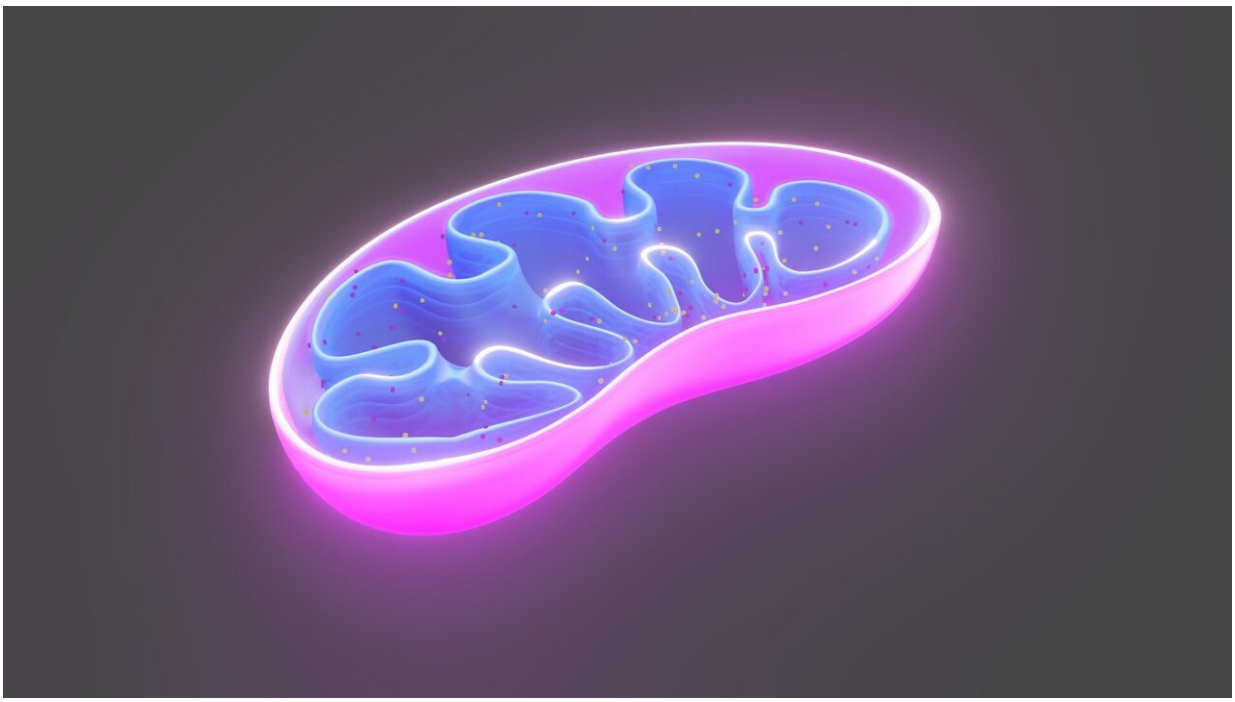
New drug-like molecule extends lifespan, ameliorates pathology in worms and boosts function in mammalian muscle cells

November 13 2023



Credit: Pixabay/CC0 Public Domain

Having healthy mitochondria, the organelles that produce energy in all our cells, usually portends a long healthy life whether in humans or in C. elegans, a tiny, short-lived nematode worm often used to study the aging process.

Researchers at the Buck Institute have identified a new drug-like molecule that keeps mitochondria healthy via mitophagy, a process that removes and recycles damaged mitochondria in multicellular organisms. The compound, dubbed MIC, is a natural compound that extended lifespan in C. elegans, ameliorated pathology in neurodegenerative disease models of C. elegans, and improved mitochondrial function in mouse muscle cells. Results are published in the November 13, 2023, edition of *Nature Aging*.

The impact of mitochondrial dysfunction in age-related disease

Defective mitophagy is implicated in many age-related diseases. It's tied to neurodegenerative disorders such as Parkinson's and Alzheimer's; it plays a role in cardiovascular diseases including heart failure; it influences metabolic disorders including obesity and type 2 diabetes; it is implicated in muscle wasting and sarcopenia and has a complex relationship with cancer progression.

Even though interventions that restore mitophagy and facilitate the elimination of damaged mitochondria hold great promise for addressing these conditions, not one treatment has been approved for human use despite advances in the field.

What's MIC?

MIC (Mitophagy-Inducing Compound) is a coumarin, which are naturally bioactive compounds that have anticoagulant, antibacterial, antifungal, antiviral, anticancer, and antihyperglycemic properties (among others) as well as being an antioxidant with neuroprotective effects. Coumarin is found in many plants and is found in high concentrations in certain types of cinnamon, which is one of the most

frequent sources for human exposure to the substance.

A new mechanism of action in mitophagy

The project started in a mouse model of Parkinson's disease where researchers in the laboratory of Julie Andersen, Ph.D., a senior author of the paper, were looking at known enhancers of mitophagy, including rapamycin.

"Co-author Shankar Chinta, Ph.D., started screening natural compounds in neuronal cells and MIC came up as a major hit," she said. "Rather than taking MIC immediately into a mouse model we wanted to understand its impact on overall aging and identify its mechanism of action, so we took the work into the worm where we found that MIC is in a different class of molecules that enhance the expression of a key protein, TFEB."

In an effort spearheaded by Andersen and research scientist Manish Chamoli, Ph.D., lead author of the study, researchers found that MIC enhanced the activity of transcription factor TFEB, which is a master regulator of genes involved in autophagy and lysosomal functions. Autophagy is the intracellular recycling process whereby cells clean up damaged proteins; it derives its abilities from the lysosome. Researchers found that MIC robustly increased the lifespan of C. elegans while also preventing mitochondrial dysfunction in mammalian cells.

"This paper helps support the overall notion of TFEB being a key autophagy regulator that extends lifespan," said Buck professor and Chief Scientific Officer Malene Hansen, Ph.D., who collaborated on the paper. She added, "Mitophagy is a selective and very significant form of autophagy. The field has recognized TFEB as a player when it comes to quality control in mitochondria. This study provides a possible translational route to induce mitophagy in a TFEB-dependent fashion."

A link to the brain/gut connection

Mechanistically MIC works upstream of TFEB by inhibiting ligand-induced activation of the nuclear hormone receptor DAF-12 (in worms)/FXR (in humans), which in turn induces mitophagy and extends lifespan.

FXR is best known for its ability to act in the liver and gut to maintain lipid homeostasis, where it acts to regulate levels of TFEB as part of a feed-fast cycle, but recently TFEB was shown to also be present in brain neurons. This provided Andersen with the clue needed to piece together MIC's potential mechanism of action in the latter.

"This study provides another piece of the puzzle when it comes to understanding the brain/gut connection in terms of health and disease," said Andersen.

FXR is regulated by bile salts which are formed in the gut microbiome. "The gut microbiome impacts the body's use of bile acids. Aging impacts our microbiome," said Chamoli.

"If levels of bile acids aren't correct it hinders mitophagy. That's how FXR can impact neuronal health. Neurons have a lot of mitochondria which makes mitophagy important in terms of neurodegeneration," he said, noting that experiments are underway to explore neuronal FXR as a therapeutic target for Alzheimer's disease.

MIC as a general geroprotective therapeutic

"There's a bottleneck in efforts to develop potential therapeutics in the field of geroscience, and the bottleneck is that we don't have enough molecules in the pipeline," said Gordon Lithgow, Ph.D., Buck Professor

and Vice President of Academic Affairs and senior co-author. "MIC is a great candidate to bring forward given its therapeutic effect across multiple models and the fact that it is a naturally occurring molecule."

Chamoli highlighted the direct links between mitophagy and aging, suggesting that drugs enhancing this process could offer treatment well beyond neurodegeneration or muscle wasting. He added, "All these possibilities can be explored at the Buck where the research environment supports such endeavors."

More information: Julie Andersen et al, A drug-like molecule engages nuclear hormone receptor DAF-12/FXR to regulate mitophagy and extend lifespan, *Nature Aging* (2023). DOI: 10.1038/s43587-023-00524-9

Provided by Buck Institute for Research on Aging