Mitochondrial distress signaling pathway revealed in new study

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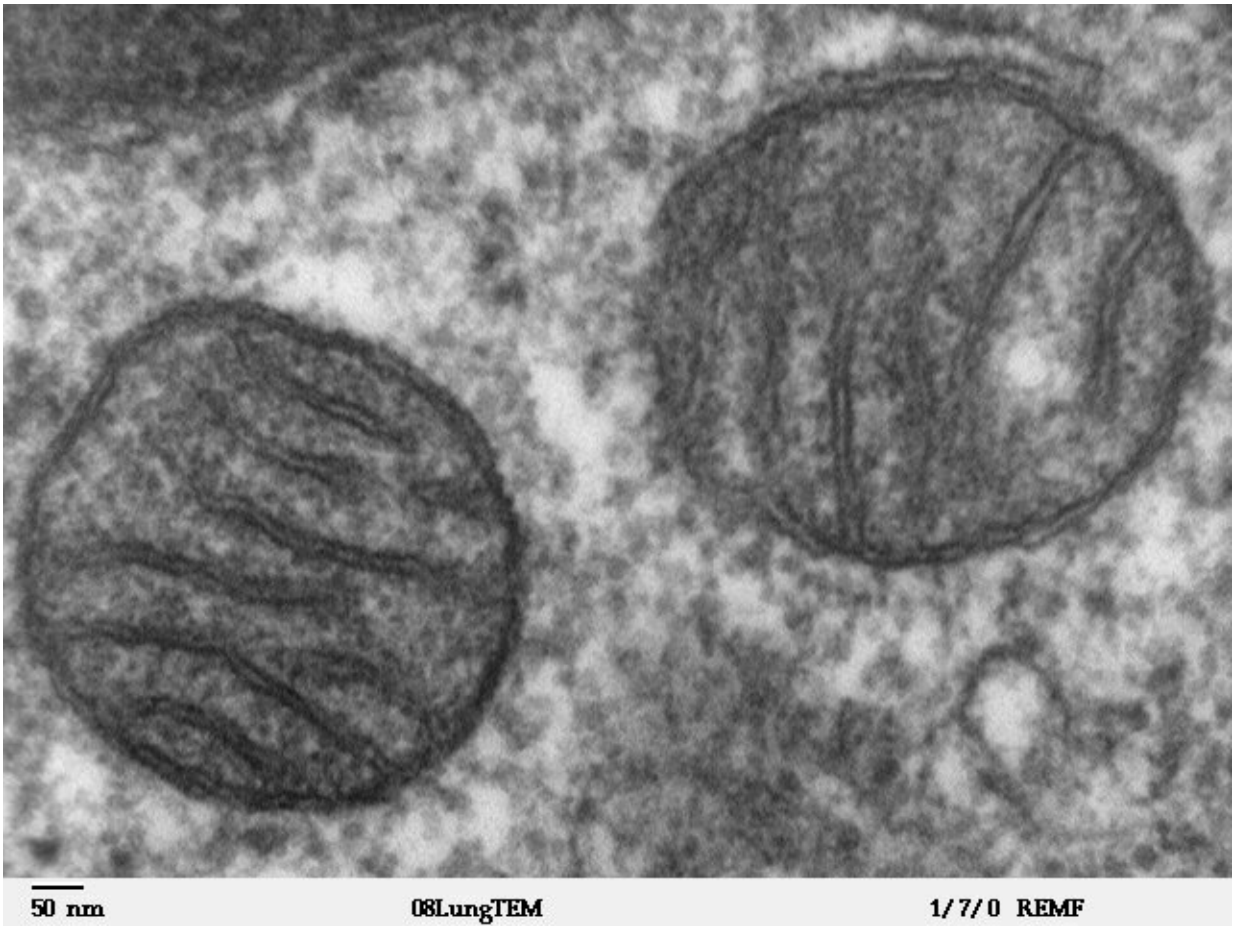

The mitochondrion (plural mitochondria) is a double-membrane-bound organelle found in most eukaryotic organisms. Transmission electron microscope image of a thin section cut through an area of mammalian lung tissue. The high magnification image shows a mitochondria. JEOL 100CX TEM. Credit: CC0 Public Domain

Mitochondria cannot autonomously cope with stress and must instead call on the cell for help. Molecular geneticists at LMU have identified the long-sought signaling pathway which enables the organelles to do so.

Mitochondria are membrane-bounded intracellular organelles that supply the energy needed to power the biochemical operations required for cell function and survival. The energy is provided in the form of a compound called ATP, which can be hydrolyzed by specific enzymes to drive chemical reactions. When mitochondria are subjected to stress—owing to the accumulation of misfolded proteins, for example—their functional capacities are diminished. Degradation of mitochondrial function can have serious consequences for the affected cells, and potentially for the whole organism. In order to activate protective measures, mitochondria must transmit a distress signal into the surrounding cytosol. In a paper that appears in the leading scientific journal *Nature*, researchers led by Professor Lucas Jae at the LMU Gene Center now report that they have characterized the elusive signaling pathway that triggers the response to mitochondrial stress in human cells. Mitochondrial dysfunction is at the root of many serious disorders, and functional deterioration of these organelles is regarded as a major component of the aging process. The new findings are therefore of considerable significance in the search for new therapeutic approaches to the treatment of age-related diseases.

Although mitochondria retain a small set of genes required for their primary role as energy generators, they are unable to autonomously resolve stress. Instead, they must alert the cell to the developing emergency by sending a specific signal into the cytosol. This signal then triggers mechanisms that either dissipate the source of stress, or activate programmed cell death once the level of stress exceeds a specific threshold. Landmark studies in the nematode worm Caenorhabditis elegans have elucidated how this organism monitors the state of its mitochondria. However, the results show that the mode of action in

worms differs from that in humans. Human cells respond to mitochondrial stress—and various other insults—by inducing a rather unspecific reaction known as the Integrated Stress Response (ISR) in the cytosol. "The signaling pathway that relays mitochondrial stress to the cell has eluded identification through classical biochemical approaches for over 20 years," says Jae. "So we decided to use a genetic strategy to tackle the problem."

Since normal human genomes contain two copies each of virtually every gene, Jae and his colleagues made use of 'haploid' cells, in which genes are present in only one copy. This allowed the researchers to randomly introduce millions of knockout mutations throughout the genome that would not be compensated for by the presence of a second gene copy. They then subjected the resulting mutant cells to mitochondrial stress and recovered mutants that responded aberrantly. "This unbiased genome-wide screening procedure revealed two mitochondrial key factors that are essential for the ability of the mitochondria to activate the cellular stress response. One of these is the enzyme OMA1, which can cleave target proteins, and the other is a barely studied protein called DELE1," Jae explains.

When mitochondria are exposed to stress, OMA1 becomes activated and induces the cleavage of the DELE1 protein into a shorter fragment. This fragment is then redistributed to the cytosol, where it binds to another enzyme called HRI, which in turn triggers the ISR. "HRI was thus far believed to be primarily required for the formation of red blood cells," says Jae. "Our study has now shown that it can also be activated by DELE1 in the context of mitochondrial perturbation."

According to the authors, these findings might open up new opportunities for therapeutic regulation of cellular stress responses. These could be relevant for conditions that are associated with mitochondrial malfunction—including debilitating, age-related

neurodegenerative disorders, such as Parkinson's disease. Recently, drugs have been developed that can globally shut down the ISR. Although not tailored to a specific type of ISR-inducing stress, such compounds have been shown to have positive effects on cognition and learning in mice. However, unspecific inhibition of the ISR might also have undesirable effects, as the ISR, for instance, also mediates antiviral protection during infection. "In an alternative scenario, the cellular response to mitochondrial stress could be selectively modulated by manipulating the factors we have now identified," says Jae.

More information: Evelyn Fessler et al. A pathway coordinated by DELE1 relays mitochondrial stress to the cytosol, *Nature* (2020). DOI: 10.1038/s41586-020-2076-4

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