Scientists determine the mechanism of a drug that protects cell mitochondria from damage by aggressive oxygen

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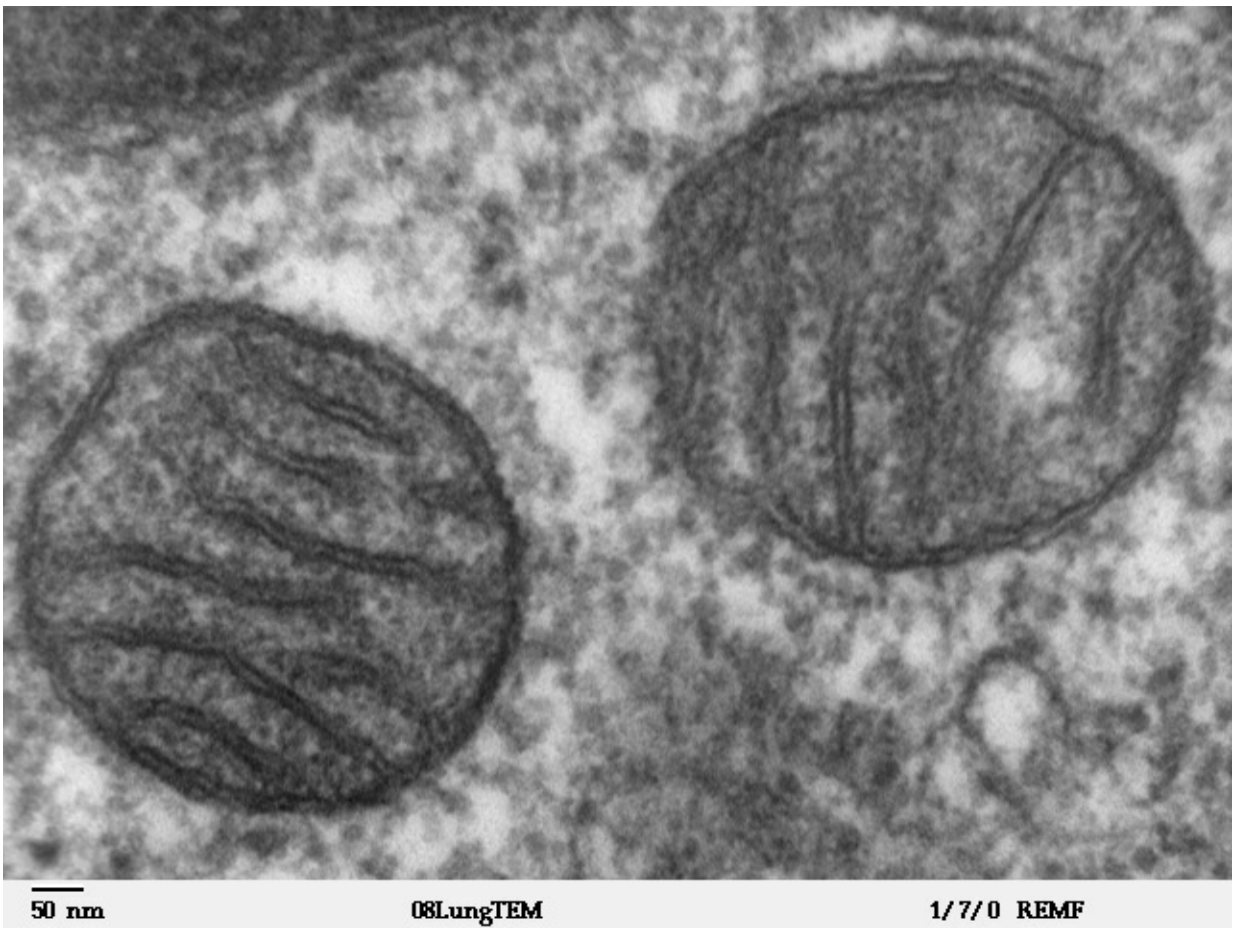

Mitochondria of a mammal. Credit: Louisa Howard

An international team of scientists led by researchers from the Lomonosov Moscow State University clarified the molecular mechanism of a drug created in Russia and designed to prevent the damaging of cell mitochondria by reactive oxygen species. This work is published in the journal *Oxidative Medicine and Cellular Longevity*.

Recently, Russian researchers, led by Prof. Vladimir P. Skulachev, created an antioxidant drug that selectively accumulates within mitochondria and protects them from oxidative damage. Under the trade name "Visomitin" the drug was approved for treatment of such eye diseases as cataracts and dry eye. Prof. Armen Mulkidjanian of the Faculty of Bioengineering and Bioinformatics of the Lomonosov Moscow State University and the University of Osnabrück, Germany, and his colleagues have explained why very small doses of synthetic antioxidants such as Visomitin offer a pronounced therapeutic effect, despite the presence of large quantities of natural mitochondrial antioxidants.

Mitochondria are intracellular structures that conduct respiration. Respiration, however, is accompanied by formation of reactive oxygen species (ROS) as by-products. The ROS are capable of damaging the mitochondria. Damaged mitochondria produce even more ROS, which can destroy cells and tissues. Nature has special mechanisms, including mitophagy and apoptosis, for elimination of damaged mitochondria and cells. These mechanisms are triggered after a distress signal passes through the double membrane surrounding the mitochondria. Several laboratories have shown that it is possible to avoid the decay of cells and tissues by preventing the oxidation of a particular component of the mitochondrial membrane—cardiolipin, as oxidized molecules of cardiolipin trigger this signal chain.

The group of Prof. Vladimir Skulachev at Lomonosov Moscow State University has developed a line of mitochondria-targeted antioxidants,

the so-called SkQ-ions, specifically protecting the molecules of mitochondrial cardiolipin from oxidation. In animal trials, the SkQ-ions cured inflammatory eye diseases, helped to overcome ischemia-simulating conditions, and even reduced the manifestation of senescence. Although similarly acting drugs have been developed and studied in U.S. and U.K. laboratories, the Russian group was the first to obtain approval for their drug as eye drops. The researchers hope that SkQ-based drugs, in the form of pills and injections could eventually attenuate the pathological symptoms that accompany strokes, heart attacks and serious traumas.

Armen Mulkidjanian and his collaborators have suggested answers to some intriguing questions. Specifically, it was not clear why cardiolipin, of all the components of the membrane, becomes oxidized. Molecules of cardiolipin, while comprising only 10 to 20 percent of total membrane lipids, are specifically targeted by ROS and, after oxidization, trigger the self-destruction of cells. Secondly, it was not clear why the natural antioxidants, namely coenzyme Q (ubiquinol) and vitamin E (alpha-tocopherol), which are present in mitochondrial membranes in large quantities, fail in the case of cardiolipin. Researchers wondered why these substances could not protect cardiolipin from oxidation, whereas artificial, mitochondria-targeted antioxidants perfectly coped with this task, in spite of very small doses of the administered drugs.

Armen Mulkidjanian says that the goal of the study was set by Prof. Skulachev.

'Prof. Skulachev asked our group in Germany to tackle these puzzles,' says Armen Mulkidjanian. 'We have developed an experimental system to investigate quantitatively the oxidation of the cardiolipin membranes and the ability of various antioxidants to prevent it. It turned out that the SkQ-ions and the molecules of coenzyme Q protected the cardiolipin membranes from oxidation equally well, whereas vitamin E performed

much worse.'

To understand why cardiolipin molecules are the main target of the ROS, the researchers compared the experimental data with their previous results and the structures of respiratory enzymes. A fraction of cardiolipin molecules is occluded within respiratory protein complexes, specifically those that generate ROS. 'These molecules should be the first to be oxidized,' Mulkidjanian says.

The bulky, water-insoluble molecule of coenzyme Q cannot get to these "hidden" cardiolipin molecules, as opposed to small, agile molecules of artificial antioxidants, which, as shown in the study, are capable of protecting cardiolipin molecules from oxidation by accessing them both from the membrane and from the aqueous phase.

"The essence of our work is that we have proposed a mechanism that explains how very low doses of mitochondria-targeted antioxidants could provide a distinct therapeutic effect, even being applied over large amounts of natural antioxidants, which were ineffective in this case. The mechanism should be valid for the whole class of similar drugs. We hope that our findings would help to develop new drugs,' says Armen Mulkidjanian.

Provided by Lomonosov Moscow State University