Researchers uncover vital role for mitochondrial calcium exchange in heart function

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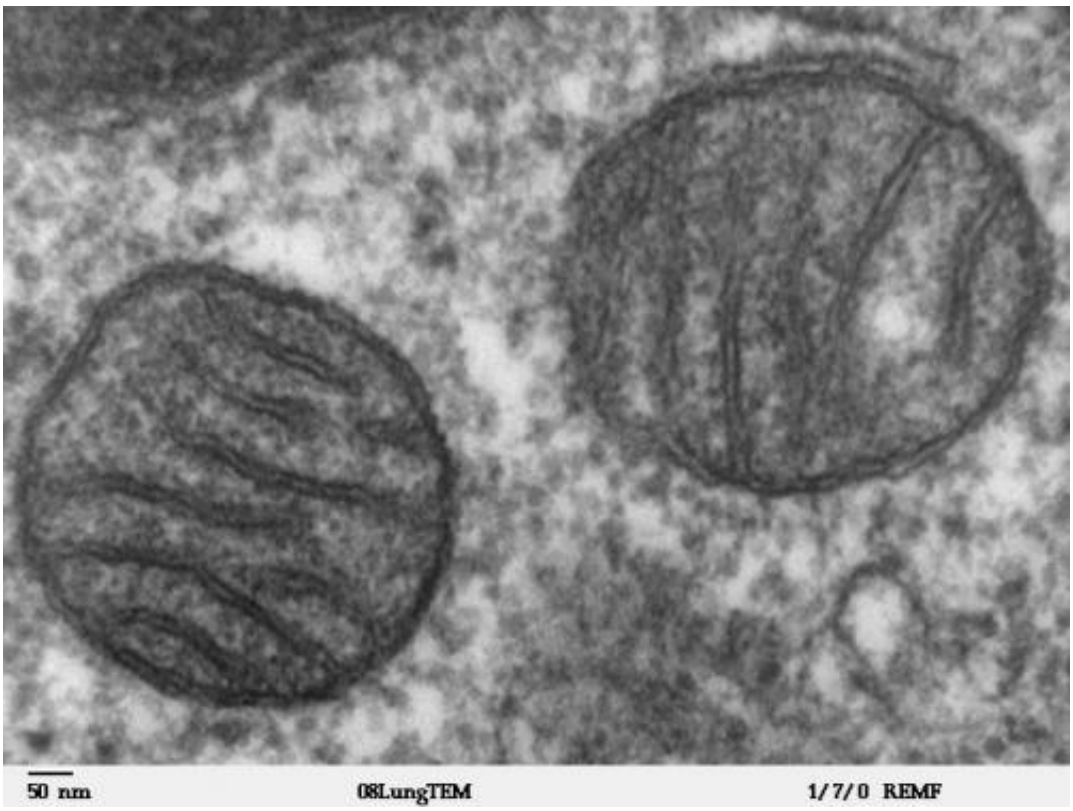

Mitochondria. Credit: Wikipedia commons

Scientists have long thought that calcium transport into mitochondria - the powerhouses of cells - is a key signal linking cardiac workload, or how hard the heart pumps, with energy production. Studies at the Lewis

Katz School of Medicine at Temple University (LKSOM) and elsewhere have shown the importance of this pathway during stress, but they have also questioned the dogma that mitochondrial calcium exchange is necessary for normal cardiac function. Now, in a major breakthrough, LKSOM researchers show that the exit of calcium from mitochondria serves a critical role in heart function and may represent a powerful therapeutic approach to limit heart disease.

Using a newly developed mutant mouse model, researchers led by John W. Elrod, PhD, Assistant Professor in the Center for Translational Medicine at LKSOM, and senior investigator on the new study, demonstrate that a mitochondrial transporter encoded by the gene Slc8b1 (referred to as the mitochondrial sodium-calcium exchanger, or NCLX) is necessary for proper heart function. Without NCLX, animals suffer sudden death. The study, published online April 26 by the journal *Nature*, is the first to look at the necessity of mitochondrial calcium efflux in living animals.

Mitochondrial calcium exchange - the flow of calcium in and out of the energy-generating organelle - is fundamental to both cell death and pro-energetic signaling pathways. "We know from our previous work that the inhibition of calcium uptake results in a loss of stress response signaling in the heart," Dr. Elrod explained. "We found that mitochondrial calcium uptake was required for the heart to beat harder in response to stress and that excessive mitochondrial calcium uptake could trigger the death of heart cells. But those same animals had normal heart function in the absence of stress, suggesting the existence of a separate homeostatic, basal mechanism of calcium signaling."

To circumvent possible alternative mitochondrial calcium uptake pathways, Dr. Elrod and colleagues developed a conditional knockout mouse model, in which the NCLX gene was deleted after treatment with the drug tamoxifen, enabling mice to reach adulthood before the

knockout was induced.

"By deleting NCLX, we were able to determine the necessity of mitochondrial calcium efflux," Dr. Elrod said.

When the gene was switched off in adult mice, the animals began to suddenly die from massive heart failure. Examination of cardiomyocytes from the animals revealed swollen and dysfunctional mitochondria, a sign of mitochondrial permeability transition pore (MPTP) activation, a mechanism known to be activated by calcium overload and to induce cell death. By genetically inhibiting MPTP activation, the researchers were able to rescue the NCLX knockout mice from death and prove the essential nature of mitochondrial calcium exchange in the heart.

Dr. Elrod and colleagues then explored the effects of augmenting NCLX expression in the mouse heart using genetic techniques. As anticipated, NCLX overexpression increased mitochondrial calcium efflux. It also prevented cell death in mice that suffered heart attacks and protected against the progression of heart failure by reducing reactive oxygen species production and limiting cardiomyocyte death and fibrosis (tissue stiffening).

"Targeting NCLX was effective in preventing cardiomyocyte death and maintaining heart function during the progression of heart failure," Dr. Elrod said. "Our findings suggest that mitochondrial calcium efflux is a promising therapeutic target, with the potential to lessen the severity of cardiac disease states."

Dr. Elrod plans to investigate NCLX activation further. Understanding its regulation at the molecular level could help identify additional mechanistic targets for the development of novel drug therapies.

More information: Timothy S. Luongo et al, The mitochondrial

Na+/Ca2+ exchanger is essential for Ca2+ homeostasis and viability, *Nature* (2017). DOI: 10.1038/nature22082