Scientists discover structural clues to calcium regulation in cells

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Inside almost every cell in the human body, tiny mitochondria are continuously generating energy to power countless cellular activities. That process of energy generation also happens to be closely tied to intracellular calcium regulation by a membrane gateway inside mitochondria known as the mitochondrial Ca2+ uniporter (MCU), which has critical roles in both bioenergetics and cell death. How MCU

regulates calcium uptake has been unclear, but the recent structural discovery of a key MCU domain by scientists at the Lewis Katz School of Medicine at Temple University points toward the involvement of not one, but two ions - calcium and magnesium - opening new paths to the development of MCU-modulating agents for the treatment of diseases involving mitochondrial dysfunction.

"Calcium is a key regulator of energy production in mitochondria, but too much of it can trigger cell death," explained senior investigator on the study, Muniswamy Madesh, PhD, Professor in the Center for Translational Medicine and the Department of Medical Genetics and Molecular Biochemistry at the Lewis Katz School of Medicine (LKSOM) at Temple University. Dr. Madesh and colleagues are the first to solve the crystal structure of the MCU N-terminal domain, which they detail in an article published online August 25, by the journal *Cell Chemical Biology*.

Mitochondrial calcium regulation can set in motion signaling pathways that control cytosolic calcium levels, as well as pathways that influence cell death and energy production and expenditure. Hence, MCU activity is vital to calcium homeostasis and cell survival. "But if the pore fails to close," Dr. Madesh explained, "mitochondria retain the energy they synthesize in the form of ATP. The resulting accumulation of oxidants and calcium overload lead to mitochondrial swelling and cell stress."

Such abnormalities in mitochondrial function occur in a variety of diseases, including cardiovascular diseases, such as stroke and heart attack, and certain neurological conditions such as Parkinson's and Alzheimer's diseases. As a result, insight into MCU structure could help researchers find ways to modulate the gateway's activity and potentially restore its function in disease states.

In the new study, Dr. Madesh and colleagues describe the atomic

structure of the MCU N-terminal domain and report the discovery of a "grasp" region of the domain dedicated specifically to the binding of calcium and magnesium ions. They found that interaction of the ions with the region destabilizes the MCU channel, causing the gateway to close.

In experiments in human cells, mutations introduced into the grasp region disrupted MCU assembly and greatly attenuated mitochondrial calcium uptake through the channel. The researchers further discovered that MCU activity could be blocked both by bathing mitochondria in magnesium and by preventing mitochondrial calcium displacement. The discovery supports previous studies, suggesting that MCU is autoregulated via a mechanism involving either calcium-dependent inactivation or magnesium-induced inhibition.

According to Dr. Madesh, the new structural and mechanistic insights from his team's study help fill in gaps in scientists' understanding of the role of MCU in controlling mitochondrial calcium uptake. The new findings also have important implications for the understanding of diseases involving mitochondrial dysfunction.

"In identifying a region of MCU that directly controls its activity, we have created a framework for modulating MCU function through the development of a small molecule," Dr. Madesh said.

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