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Opinion Article

Physiology and Disease Implications of Molecular Regulation of MCU

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DESCRIPTION

Cellular bioenergetics, intracellular cytoplasmic Ca^{2+} signals, and different cell death pathways are all regulated by Ca^{2+} flux across the Inner Mitochondrial Membrane (IMM). Due to the extremely negative membrane potential (m), Ca^{2+} enters the mitochondria through a specific inward rectifying MCU channel. The channel is transcriptionally controlled by upstream Ca^{2+} cascade, post transnational modification, and divalent cations in addition to being regulated by various mitochondrial matrix resident proteins like MICUs, MCUb, MCUR1, and EMRE. The mode of regulation either prevents or promotes the activity of MCU channels, controlling mitochondrial metabolism and cell fate in the process. The Ca^{2+} ion is a flexible second messenger that is necessary for a number of kinetically distinct cellular activities, including cell division and cell death. While certain processes, like endocytosis, take only a few seconds, other processes, like gene transcription, can take up to hours. It is currently unknown how Ca^{2+} governs these various activities. Since no other ions are transported, Ca^{2+} entry into the mitochondria occurs due to the strong electrochemical gradient (180 mV) and is hence an importer.

Early research on mCa^{2+} uptake demonstrated that Ca^{2+} uptake into the mitochondria was m-dependent and lacked anion transport, making it a uniporter. Ruthenium Red was sensitive to the second order kinetics of Ca^{2+} transport (RR). An RR sensitive Tran's membrane protein that is a resident of the IMM and a component of the vast complex known as the MCU was discovered by whole genome phylogenetic profiling, RNA co-expression analysis, and organelle wide protein co-expression analysis. The expression of MCU is conserved among eukaryotes with the exception of yeast, which is consistent with the discovery that all vertebrate mitochondria take up Ca^{2+}. Yeast do not exhibit uniporter activity and lack homologs of the uniporter components, in contrast to their evolutionary sister group Amoebozoa, which has one MCU homolog.

The N-terminal Domain (NTD) of the MCU, which spans exons 3 and 4, adopts a -grasp-like fold with a central core made up of a helix and six strands and two highly conserved leonine-rich loops. A gene duplication event may have led to the evolution of MICU1's two prologues in vertebrates, according to bioinformatics study. It was discovered that MICU2 and MICU3 contained the same conserved domains as MICU1 as well as two canonical EF hand domains with various expression patterns.

For cells to survive, cCa^{2+} regulation is essential. Since it is generally known that mitochondria can influence cytosolic Ca^{2+} transients, one might hypothesise that cytosolic Ca^{2+} might activate the genes involved in mitochondrial Ca^{2+} uptake. It has been demonstrated that the Ca^{2+} regulated transcription factor CREB is responsible for the reduction in MCU protein levels that occurs in the absence of proximal Ca^{2+} signals. Cells have multiple layers of regulation; if one fails, the other layers step in to take over. MicroRNAs serve as one such regulatory mechanism. MiRNAs are short, non-coding nucleotides that bind to their target mRNA through sequence complementarity to control the expression of genes.

MCU RNA and protein are downregulated by miR-25 in in vitro luciferase experiments, but not other MCU complex components. The inverse regulation of MCU by miR-25 in the mucosal tissues of colon cancer was validated by immunohistochemistry. Colon cancer patients had higher amounts of miR-25, which decreased MCU levels and prevented the tumour cells from dying. The mice who received injections of MCU-down regulated or miR-340 overexpressed MDA-MB-231 cells had considerably less metastatic lung nodules than the mice in the control group, showing that miR-340 silencing of MCU inhibits cell migration and metastasis. It was possible to comprehend the physiological importance of the channel thanks to the creation of germline and tissue specific MCU KO animals. There is still much to learn about the function of MCU in pathological situations.

It has been demonstrated that Mg^{2+} binding to the MRAP region in the NTD of the MCU shuts down MCU channel activity. It may be necessary to conduct studies on Mg^{2+} supplements to reduce MCU channel activity when there is a Ca^{2+} overload. Studying whether MCU can act as a matrix ROS set point and comprehending the molecular mechanisms of MCU oxidation in inflammatory disorders may create therapeutic avenues based on studies that have proven for the first

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time that MCU experiences oxidative alterations like most ion channels do. Finally, genetic MCU ablation did not provide a defence against mCa^{2+} overload-mediated mortality. One possible explanation is that MCU KO cells caused MiST to beactivated, which resulted in cell death caused by MiST. Future research on MiST-mediated pathways should be investigated.