

High glucose-induced ROS activates TRPM2 to regulate organelle zinc homeostasis and mitochondrial fragmentation

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Mitochondria plays a central role in oxidative stress induced cell death. By increasing the production of reactive oxygen species, such as H₂O₂, oxidative stress causes mitochondrial fragmentation and apoptosis. Mechanisms by which oxidative stress leads to apoptosis, however, are not fully understood. Here we hypothesised that Transient Receptor Potential Melastatin 2 (TRPM2) channels play a role in mitochondrial fragmentation. The rationale behind this is the previous evidence that TRPM2 channels are activated by H₂O₂ and conduct ions (Ca²⁺ and Zn²⁺) that affect mitochondrial health and cell survival. To test our hypothesis we have used live-cell imaging, immunostaining, biochemical techniques and cell death assays. Exposure of Human Umbilical Vein Endothelial Cells (HUVECs) to H₂O₂ led to an increase in Zn²⁺ levels in the mitochondria and a reduction in lysosomes. This redistribution was accompanied by an extensive fragmentation of mitochondria and an increase in cell death. Silencing of TRPM2 channel prevented intracellular Zn²⁺ redistribution, mitochondrial fragmentation and cell death. TRPM2 activation increased recruitment of Dynamin-Related protein 1 (Drp1) to mitochondria, thereby increasing mitochondrial fission. Moreover, the data indicated that TRPM2 is expressed in lysosomes presumably to mediate Zn²⁺ release. Endothelial cells derived from TRPM2 knock-out mice were resistant to oxidative stress-induced mitochondrial fragmentation. In conclusion, our data revealed a novel mechanism where H₂O₂ activation of TRPM2 causes a redistribution of Zn²⁺ from lysosomes to mitochondria, resulting in mitochondrial fragmentation and endothelial cell death. Since mitochondrial fragmentation is associated with several age-related chronic illnesses including neuronal (Alzheimer's, Parkinson's), cardiovascular (atherosclerosis, myocardial infarction) and metabolic/inflammatory (diabetes) disorders, our results reveal TRPM2 channel as potential therapeutic intervention of age-related illnesses.

Biography

Nada Abuarab has completed her MSc in Bioscience and PhD in Philosophy from School of Biomedical Sciences, University of Leeds, UK. She is currently working as an Assistant Professor in Basic Science Department, King Saud Bin Abdul-Aziz University for Health Sciences, Saudi Arabia. She has also obtained a second Master's degree in Medical Education from College of Medicine, King Saud Bin Abdul-Aziz University for Health Sciences.

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