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New therapeutic modes of action of the anti-cancer agent 2-Hydroxyoleic Acid (2OHOA) are revealed in isolated mitochondria of U118MG glioblastoma cells**Kumudesh Mishra***Israel*

2-Hydroxyoleic acid (2OHOA) is a synthetic fatty acid used as an anti-cancer agent based on its capacity to regulate membrane lipid composition and structure. A major effect of 2OHOA is its incorporation into pre-existing lipids, thus generating hydroxylated lipids, which can activate sphingomyelin synthase 1 and elevate sphingomyelin levels. However, while this effect was challenged, another effect of 2OHOA is its ability to depolarize the inner mitochondrial membrane. In a previous study, we investigated a new anti-cancer modality of 2OHOA as an OxPhos uncoupler. That work demonstrated that beyond acting as a cancer cell selective OxPhos uncoupler, 2OHOA can also compromise the capacity of cancer cells to compensate for the OxPhos deficiency by activating glycolysis. In the present study, we mechanistically explored how 2OHOA can compromise mitochondrial function. Shotgun lipidomics, spectrophotometric assays of respiratory complex activity, mass spectrometry for assessing beta oxidation and bioenergetic profiling by Seahorse technology were used to analyze mitochondria isolated from 2OHOA-treated glioblastoma cells. Lipidomics analyses showed that 2OHOA treatment led to mitochondrial lipid hydroxylation. This hydroxylation, as revealed by molecular dynamics, decreased co-enzyme Q (CoQ) diffusion in the liquid disordered membrane domain, which embeds respiratory complexes.

Biography

Dr. Kumudesh Mishra is presently working as a Postdoc Research Fellow in Dr Or Kakhlon's Lab, Department of Neurology, Hadassah Medical Center, The Hebrew University of Jerusalem, Israel. He did his PhD from SGPGIMS Lucknow UP INDIA after obtaining a Senior research fellowship from ICMR, New Delhi, Government of India, in the area of Gallbladder Cancer. He received prestigious "Golda Meir Postdoctoral International Research Fellowship-2021-2022" from Lady Davis Fellowship Trust, The Hebrew University, Jerusalem, Israel. His postdoctoral research work is "To study the Molecular mechanism of action of a synthetic fatty acid drug 2OHOA in Glioblastoma; he also screened and tested in-vivo a new molecule 144DG11 to treat adult polyglucosan body disease (APBD), that caused due to lack of glycogen branching enzymes (GBE).