Bakovic Marica, Biol Syst Open Access 2015, 4:2
http://dx.doi.org/10.4172/2329-6577.S1.002

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3rd International Conference on
Integrative Biology

August 04-06, 2015 Valencia, Spain

The phospholipid enzyme CTP: Phosphoethanolamine cytidylyltransferase (Pcyt2) is a new target for oxidative stress therapy and ischemia

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It is well-known that is beneficial to transiently block respiration during ischemia/reperfusion; however there is an unmet clinical need for discovering new compounds and targets that can inhibit the respiration. We established that the 'over-the-counter' anti-histaminergic drug Meclizine could inhibit mitochondrial respiration (uncoupling the OXPHOS) by elevating the levels of phosphoethanolamine, an intracellular metabolite in phospholipid biosynthesis and the exclusive substrate of Pcyt2. That phosphoethanolamine was the only elevated intermediate (35-fold) during the inhibition of respiration with Meclizine strongly directed towards Pcyt2 as the drug target. The extensive metabolic studies as well as studies on recombinant Pcyt2 protein provided strong evidence for direct inhibition of Pcyt2 with Meclizine. The impact of our discovery is not only how to expand the future use of Meclizine but also to offer the first inhibitor for the CDP-ethanolamine Kennedy pathway to continue to investigate the regulation of the membrane phospholipid synthesis and the basic function of Pcyt2. This is the first time to be demonstrated that the membrane biogenesis impacts mitochondrial OXPHOS and that the inhibition of the CDP ethanolamine pathway at the level of Pcyt2 is protective under pathological conditions of oxidative stress and ischemia.

Biography

Bakovic Marica completed her BSc in Chemistry and PhD in Biological Chemistry at the University of Alberta. She received Post-doctoral awards from Medical Research Council and Alberta Heritage Foundation. Before coming to the University of Guelph, she worked in the area of molecular and cell biology of lipid metabolism at the Faculty of Medicine, University of Alberta. Currently, she is a Professor in the Department of Human Health and Nutritional Sciences at the University of Guelph. She has a long-lasting interest in nutrition and metabolism especially in the area of regulation of membrane phospholipids, fatty acids and methyl-group donors.

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