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Presentation Abstract

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Presentation Title:	Fumarate hydratase and deuterium depletion control oncogenesis via NADPH-dependent reductive synthesis: mitochondrial matrix water, DNA deuteration and epigenetic events
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Abstract Body:	Clear cell kidney tumors become exclusively oxidative pentose cycle, hence cytoplasmic free water dependent by fumarate hydratase mutations, which disrupts the use of low deuterium containing metabolic water of the mitochondrial matrix and consumes pentose cycle-derived NADPH for reductive carboxylation [Yang Y., et al. PLoS One 8: e72179 (2013); Mullen AR, et al. Nature 481: 385-8, (2011)]. Metabolic water by complete fat oxidation, coupled with cytochrome-c, contains low average ~115 ppm (parts per million) deuterium due to deuterium discrimination by plant lipogenic enzymes during photosynthesis. We herein report that mono-deuterated, 100 ppm, 50 ppm and 25 ppm extracellular (free) water treatment significantly decrease nucleotide and nuclear membrane behenic- and lignoceric acid synthesis in comparison with natural 150 ppm deuterium containing water via the oxidative branch of the pentose cycle in breast (MCF7) and lung (H441) cancer cell cultures, which recapitulates metabolism after genetically restored mitochondrial fumarate hydratase function in clear cell kidney tumors. Targeted [1,2-13C2]-D-glucose to [1-13C1]-D-ribose and 13C-glutamate fate associations indicate that the serine synthesis, one-carbon (folate) metabolism and the glycine cleavage (SOGC) pathway [Tedeschi PM, et al. Cell Death Dis 4: e877, (2013)] also mediates the metabolic control of deuterium depletion in MIA-PaCa pancreatic adenocarcinoma cells. We conclude that impaired mitochondria are involved in cell transformation by limiting the low natural deuterium containing complete fatty acid oxidation product, metabolic water, to enter nuclear membranes and nucleotides via reductive synthesis. In turn, “heavy” natural water and sugar dependent NADPH production taken over by the oxidative branch of the pentose cycle, as well as the SOGC-pathway, are deuterium loading “ticking time bombs” with a strong isotope effect and thus oncogenic epigenetic events that include unstable hydrogen bonds, aneuploidy in DNA structures and chemically altered methylation sites with severely disrupted gene expression patterns. Nevertheless, extra-mitochondrial NADPH synthesis opens a therapeutic window for deuterium depleted water to maintain and/or restore normal cellular functions. Our study provides a novel mechanism regarding lipid based ketogenic diets in the presence of hyperbaric oxygen treatment to decrease metastasis formation by producing low deuterium metabolic water via complete oxidation to prevent DNA, histone and nuclear membrane deuteration during NADPH dependent reductive synthesis.

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