

Mitochondrial dysfunction in human cancers mutant in isocitrate dehydrogenase, succinate dehydrogenase and fumarate hydratase.

1. Abstract:

Three enzymes active in the tricarboxylic acid (TCA) cycle, which is central to cellular energy homeostasis, are mutated in a number of different human cancers. Mutation of each of these genes (isocitrate dehydrogenase, succinate dehydrogenase or fumarate hydratase) results in accumulation of metabolites that alter the epigenetic profile of the tumor, through inhibition of enzymes that modify histones and DNA. My laboratory studies the role of mitochondrial epigenetics in cancer, and the relationship between this epigenetic mtDNA modification and the metabolic switch to aerobic glycolysis that is common in cancer cells. We propose here to investigate the consequences of mutation in each of these metabolic enzymes on mitochondrial function and on the epigenetic regulation of mitochondrial gene expression from both nuclear and mitochondrial genomes.