Respiratory Extremes in Kidney Cancer: Exploration of Mitochondrial Ultrastructure and Metabolism in Human Hereditary Renal Cancer Syndromes

D.R. Crooks[1], Y. Yang[1], R.C. Hsia[1], W.M. Linehan[1]

[1] National Cancer Institute, Bethesda, MD.

Abstract

Kidney cancer is not a single disease but is rather distinguished by multiple distinct types of cancer that happen to occur in the kidney. Renal tumors have defining histologies and genotypes that are associated with distinct clinical courses and different responses to therapy. In this presentation, we will examine two metabolic extremes of human renal tumors. Fumarate hydratase (FH)-deficient renal tumors are associated with Hereditary Leiomyomatosis and Renal Cell Cancer (HLRCC) syndrome and can have an early onset and a propensity to metastasize when the primary tumor is small. These atypical papillary tumors exhibit a strong phenotype of aerobic glycolysis that is associated with elevated fumarate levels, pseudohypoxia, and fumarate-mediated loss and mutation of mitochondrial DNA. Ultrastructural analysis of these tumors reveals swollen mitochondria containing few cristae structures that were frequently fragmented and breach sites where the integrity of the inner and outer mitochondrial membranes appear to be disrupted. These alterations are associated with a profound loss of assembly and activity of the mitochondrial respiratory chain complexes in FH-deficient tumors. In contrast, hybrid oncocytic renal tumors that arise in patients carrying germline alterations in the folliculin (FLCN) gene exhibit numerous mitochondria with abundant cristae structures. Ex vivo tissue slice experiments reveal that the abundant mitochondria in FLCN-deficient renal tumors are associated with an enhanced propensity for more complete oxidation of glucose in the Krebs cycle relative to renal cortex tissue. These data demonstrate that tumor ultrastructural features match closely with metabolic phenotypes in these genetically defined examples of human renal tumors.