UQCRH Downregulation Promotes Warburg Effect in Renal Cell Carcinoma Cells

Yanting Luo[1,2], Louise Medina Bengtsson[1,2], Xuechun Wang[1,2], Tianhe Huang[1,2], Guoqiang Liu[1,2,3], Sean Murphy[1,2], Caiqin Wang[1,2], John Koren III[4], Zachary Schafer[1,2], **Xin Lu**[1,2,3,5]

[1] Department of Biological Sciences, Boler-Parseghian Center for Rare and Neglected Diseases, University of Notre Dame, Notre Dame, IN, USA; [2] Harper Cancer Research Institute, University of Notre Dame, IN, USA; [3] Integrated Biomedical Sciences Graduate Program, Warren Family Research Center for Drug Discovery and Development, University of Notre Dame, Notre Dame, IN, USA; [4] Department of Chemistry and Biochemistry, University of Notre Dame, Notre Dame, IN, USA;[5] Tumor Microenvironment and Metastasis Program, Indiana University Melvin and Bren Simon Cancer Center, Indianapolis, IN, USA

Ubiquinol-cytochrome c reductase hinge protein (UQCRH) is the hinge protein for the multi-subunit complex III of the mitochondrial electron transport chain and is involved in the electron transfer reaction between cytochrome c1 and c. Recent genome-wide transcriptomic and epigenomic profiling of clear cell renal cell carcinoma (ccRCC) by The Cancer Genome Atlas (TCGA) identified UQCRH as the top-ranked gene showing inverse correlation between DNA hypermethylation and mRNA downregulation. The function and underlying mechanism of UQCRH in the Warburg effect metabolism of ccRCC have not been characterized. Here, we verified the clinical association of low UQCRH expression and shorter survival of ccRCC patients through *in silico* analysis and identified KMRC2 as a highly relevant ccRCC cell line that displays hypermethylation-induced UQCRH extinction. Ectopic overexpression of UQCRH in KMRC2 restored mitochondrial membrane potential, increased oxygen consumption, and attenuated the Warburg effect at the cellular level. UQCRH overexpression in KMRC2 induced higher apoptosis and slowed down *in vitro* and *in vivo* tumor growth. UQCRH knockout by CRISPR/cas9 had little impact on the metabolism and proliferation of 786O ccRCC cell line, suggesting the dispensable role of UQCRH in cells that have entered a Warburg-like state through other mechanisms. Together, our study suggests that loss of UQCRH expression by hypermethylation may promote kidney carcinogenesis through exacerbating the functional decline of mitochondria thus reinforcing the Warburg effect.