A Novel Approach to Characterizing Pathogenicity of SLC25A13 Variants in Cancer

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A hallmark of cancer is the rewiring of cellular metabolism to meet proliferative needs. Citrin protein (transcribed from the human SLC25A13 gene) is a mitochondrial carrier involved in the malate aspartate shuttle, urea cycle, and pyrimidine synthesis-- multiple pathways contributing to tumorigenesis. Although Citrin variants have been well characterized in the context of inborn Citrin deficiency, a metabolic disease caused by its germline mutation, a limited amount of studies have examined Citrin in a cancer context. This study investigates Citrin's role in cancer patient prognosis and treatment. Analysis of publicly available cancer patient data revealed a striking correlation between Citrin mutations and increased cancer patient survival ($p=0.0112$). To analyze the functional impact of these mutations, deep-learning modeling was used to generate the first complete Citrin structural model which hasn't been resolved by conventional crystallographic methods. Substrate docking to and in silico mutagenesis of the model revealed Citrin's C-terminal domain's functional importance in substrate attraction and transmembrane passage regulation. The functional impact of mutations identified in cancer patients was analyzed with an evolutionary-conservation-based algorithm and physical analysis of variant residue interactions, stability, and movement, indicating a loss of Citrin function to correlate with increased patient survival. Docking of over 1600 ZINC20 ligands identified FDA-approved drugs capable of being repurposed as potent Citrin inhibitors. This study nominates Citrin as a novel therapeutic target for cancer treatment and also provides a basis for future Citrin-based pharmaceutical development through the creation of a comprehensive model and inhibitor identification.

Awards Won:
First Award of $5,000