

## **“Role of Alternative Splicing in Regulating Cancer-Cell Metabolism”**

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**Abstract:** Cancer cells, unlike their normal counterparts, metabolize glucose by aerobic glycolysis. This phenomenon, known as the Warburg effect, is characterized by increased glycolysis with lactate production and decreased oxidative phosphorylation. Although this observation was made over 75 years ago, how cancer cells establish this altered metabolic phenotype remains elusive. Recently, we found that alternative pre-mRNA splicing of the glycolytic enzyme pyruvate kinase is sufficient to determine the fate of glucose in cells. This finding adds to the growing body of evidence for key connections between alternative splicing and cancer. In this regard, we also recently demonstrated that a factor that regulates alternative splicing can act as an oncogene when misregulated, through effects on mTOR signaling, a key pathway in the regulation of cellular metabolism. Here we propose systematic studies to understand alternative splicing of metabolic genes. We aim to evaluate the effect of oncogenic alternative splicing factors on cell metabolism, and to understand the mechanism of pyruvate kinase alternative splicing. Combining the expertise of the Krainer and Cantley laboratories, we will use a combination of genetic and biochemical techniques to address the impact of alternative splicing on cancer-cell metabolism. Despite extensive data addressing the importance of both alternative splicing and metabolic changes to cancer-cell survival, neither pathway has yet been targeted for cancer therapy. This project has the potential to significantly alter our understanding of tumor biology, and will ultimately allow us to target both alternative splicing and the unique tumor-cell metabolism to develop novel therapies for malignancy.