“Role of Alternative Splicing in the Regulation of 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. Our recent finding that alternative pre-mRNA splicing of the glycolytic enzyme pyruvate kinase is sufficient to determine the fate of glucose in cells added to the growing body of evidence for key connections between alternative splicing and cancer. Likewise, we found that a factor that regulates alternative splicing, SF2/ASF, can act as an oncogene when misregulated, through effects on mTOR signaling, a key pathway in the regulation of cellular metabolism. We will continue our systematic studies to understand alternative splicing of the pyruvate kinase M pre-mRNA. We will additionally evaluate the effect of alternative splicing factors on a broader program of glucose metabolism, to gain new insights into the Warburg effect. Combining the expertise of the Krainer, Cantley, and Vander Heiden laboratories, we will pursue 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.