CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP140800

Project Title:
The Role of Alternative Polyadenylation in Glioblastoma Tumor Progression

Award Mechanism:
Individual Investigator

Principal Investigator:
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Entity:
The University of Texas Medical Branch at Galveston

Lay Summary:

Glioblastoma (GBM) is the most prevalent and malignant primary brain tumor. The unfortunate combination of its infiltrative growth and aggressive phenotype prevents virtually any positive clinical outcome. The Cancer Genome Atlas project has devoted significant efforts to characterize mutations associated with GBM but due to the bias towards exome sequencing, correlations between survival and changes in epigenetics, intergenic regions, and UTRs have not been thoroughly investigated. At the heart of this proposal are these examples of so-called “dark matter” present within the cancer genomics landscape. Alternative polyadenylation (APA) represents an exciting paradigm in gene expression regulation and is an illustrative case of genomic dark matter. In this context, APA adds a new dimension to how we think of gene expression, as mRNAs with shorter 3’ UTRs due to APA will no longer be regulated by microRNA. Through our continuing research on APA, we have definitively determined that the Cleavage Factor I 25kDa (CFIm25) is a “Master Regulator” of this process. Using a novel bioinformatic algorithm we developed to identify APA events in cancer, we identified many of the genes under CFIm25 regulation. Importantly, we have discovered that levels of CFIm25 correlate with human GBM survival and that expression of CFIm25 can directly impact GBM tumor growth. Based upon these results, we hypothesize that downregulation of CFIm25 in GBM tumors leads to broad 3’UTR shortening causing increased tumor aggressiveness and growth. This proposal will use a multi-disciplinary approach to address this hypothesis. We will first define a CFIm25 APA “Atlas” in GBM cells, then we will use a mouse model to investigate the role of CFIm25 in GBM tumor progression, finally we will determine how CFIm25 expression is reduced in GBM. These experiments have the potential of defining a new layer of gene expression within GBM and may lead to additional tools for diagnosis and treatment.