CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP150292

Project Title:
Broad Shortening of 3' UTRs in Human Cancers: Methods, Target Genes and Functional Consequences

Award Mechanism:
Individual Investigator

Principal Investigator:
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Entity:
Baylor College of Medicine

Lay Summary:

For more than 70% of human genes, their three prime untranslated regions (3? UTR) can be shortened under diverse physiological conditions. Since 3' UTRs contain many important cis-regulatory elements, such as miRNA binding sites, gene with shorter 3' UTRs will no longer be repressed by miRNA, leading to higher expression. The role of 3' UTR in human cancers is only beginning to be appreciated. Both proliferating and transformed cells have been shown to favor shortened 3? UTRs, leading to activation of proto-oncogenes. In addition, our recent study (Nature in press) identified CFIm25, a master 3' UTR regulator, as a glioblastoma (GBM) tumor suppressor, further underscoring the importance of 3' UTR in cancer development. However, the critical target genes subject to 3' UTR shortening and the cause-and-effect relationship between 3' UTR shortening and disease phenotype remain poorly understood. This is mainly because traditional 3' UTR profiling methods (3P-seq) have not been widely adopted. In contrast, RNA-seq has been widely used for gene expression analysis, yet there is no bioinformatics tool for the de novo identification of 3' UTR shortening events directly from RNA-seq. In this proposal, we hypothesize that with a powerful and dedicated bioinformatics method, RNA-seq can be used to study 3' UTR regulation in most cancer models and tumor samples. The objective of this proposal is to develop such a novel bioinformatics method, and apply this method to detect and functionally characterize 3' UTR shortening target genes from public tumor RNA-seq data. As a case study, we will focus on 3' UTR shortening of GLS, a key enzyme in glutaminolysis and cancer metabolic phenotype, in lung cancer development. Together, these 3' UTR shortening events that can potentially activate proto-oncogenes represent an illustrative case of genomic "dark matter" beyond coding regions, and thus may provide new directions for novel cancer driver gene discovery.