Stony Brook University
The Graduate School

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Abstract

Characterization of long non-coding RNAs in pluripotency and hepatocellular carcinoma

By

Allen Yu

Hepatocellular carcinoma (HCC), the most common type of liver malignancy, is one of the most lethal forms of cancer. HCC is not diagnosed until late stages and has a poor 5-year survival rate of less than 14%. The current standard of care for HCC is treatment with sorafenib, a multi-kinase inhibitor that targets Raf, receptor tyrosine kinases, and platelet-derived growth factor receptor, which extends median survival time from 7.9 months to 10.7 months. This modest gain emphasizes the urgent need to identify new and effective therapeutic targets for HCC. Genome wide analyses such as the ENCODE (ENCyclopedia Of DNA Elements) project have revealed that most of the human/mouse genomes are transcribed, even though less than 2% of each genome encodes for proteins. Thousands of transcripts greater than 200 nucleotides in length, called long non-coding RNAs (lncRNAs), are expressed in a tissue-specific manner, and have been implicated in numerous molecular functions including modulating transcriptional patterns, regulating protein activities, serving structural or organizational roles, altering RNA processing events, and serving as precursors to small RNAs. One lncRNA is of particular interest in that it is enriched in mouse hepatocellular carcinoma cell lines and it is conserved in human. It is up-regulated in HCC cells compared to normal mouse hepatocytes and is only expressed in hepatocytes in liver, and therefore, we named this lncRNA Pluripotency and Hepatocyte Associated RNA Overexpressed in HCC, or *PHAROH*. Knockdown and knockout of *PHAROH* impacts cell proliferation and migration, which can be rescued by ectopic expression of *PHAROH*. RNA-seq analysis of knockouts revealed that a large number of genes that were impacted contained a *c-Myc* motif in the promoter, and c-Myc is decreased at the protein level, but not the mRNA level. RNA-antisense pulldown assays identified nucleolysin TIAR, a translational repressor, to bind to a 71-nucleotide hairpin within *PHAROH*, which ultimately results in increased c-Myc translation. In summary, this data suggests that *PHAROH* may be a potential target as a therapy for HCC and/or have diagnostic potential in liver cancer.

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