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HuR is a post-transcriptional regulator of core metabolic enzymes in pancreatic cancer

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Cancer cell metabolism differs from normal cells, yet the regulatory mechanisms responsible for these differences are poorly understood. Mutations in cancer genes, like KRAS, have been implicated as drivers of the transformed metabolic phenotype. However, frequently found somatic mutations in cancer cells are most likely not selected for to accommodate for acute metabolic stress, such as nutrient deprivation, commonly encountered in the tumor microenvironment. HuR is an RNA-binding protein that acts under acute stress to regulate numerous core signaling pathways in cancer through post-transcriptional regulation of survival mRNA targets. We demonstrate that HuR regulates the metabolic phenotype in pancreatic cancer cells and is critical for survival under nutrient deprivation. We analyzed three different pancreatic cancer cell lines (MiaPaCa2, BxPC3, and Panc1) and found that HuR proficient cells were able to tolerate glucose deprivation better than isogenic cells after HuR expression silencing. Surprisingly, HuR proficient cells utilized less glucose, as indicated by glucose uptake from the media and metabolite analysis of cell lysate, than their isogenic counterparts, yet still produced more lactate. Glucose deprivation was validated as a strong inducer of HuR translocation (i.e., 'activation') from the nucleus to the cytoplasm, where it typically promotes translation of bound mRNA targets. We performed a focused Ribonucleoprotein-immunoprecipitation gene expression array and identified 11 novel mRNA targets of HuR which encode proteins that are central to glucose metabolism. We validated that HuR regulated targets GPI, IDH1, and PRPS2 on the mRNA and protein expression levels. These findings establish a role for HuR-directed gene regulation in cancer cell survival under acute glucose deprivation. Further insights into this HuR-dependent regulatory process should uncover novel therapeutic targets and a better understanding of how pancreatic cancer cells survive in a metabolically compromised tumor microenvironment.