Rapid adaptive translation in response to therapy-induced stress in prostate cancer

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The genetic landscape of patient samples has illustrated a vast array of potential diagnostic and clinical biomarkers through profiling of chromosomal rearrangements and examining subsequent alterations in RNA abundance. However, genome-wide analyses have also discovered that there are discrepancies between transcript expression levels and corresponding protein abundance, highlighting the limited predictive power of bulk RNA-based prognostic strategies to assist in therapy. Our findings have noted distinct mRNAs that are translationally increased, independent of their transcriptional regulation, in response to disease progression, and can be studied to create novel therapeutic avenues unique per disease phenotype. The mechanisms of RNA regulation and the discrepancies between intrinsic and extrinsic stressors leave much to discover for improved diagnostics and therapy.

Our previous research highlighted that the adaptive integrated stress response (ISR), a signaling pathway that rewires mRNA translation, is predictive of a poor prognosis for prostate cancer patients. The mechanism of ISR activation in these patients remains unknown, and we set out to evaluate clinically relevant therapies for activating the ISR. Here, we have mapped the post-transcriptional regulation of RNAs focusing on their modification status and translational regulation in response to hormonal and radiation therapy in prostate cancer. Our lab has identified that the ISR activation is an advantage to rapidly rewire translational signaling in response to clinically relevant therapy altering ribosome dynamics and select mRNA translation. Blocking this adaptive stress response in combination with various therapy decreases cell proliferation while enhancing cell death. We are actively identifying the *trans*- and *cis*- factors orchestrating the adaptive translatome in response to hormonal and radiation therapy to provide novel insights into targeting strategies for advanced prostate cancer.