Modulation of Translation Regulation by N^6-methyladenosine in Prostate Cancer

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Recent evidence has highlighted the role of N^6-methyladenosine (m^6A) in post-transcriptional control of mRNA, in particular, in altering translation efficiency. The N^6-adenosine-methyltransferase (METTL3) is up-regulated in prostate adenocarcinoma (PCa). This leads to the hypothesis that PCa exhibits alterations in m^6A, and by extension changes in the translation efficiency of those transcripts. In this study we sought to produce an epitranscriptome map of m^6A in PCa using single-nucleotide m^6A mapping (miCLIP) of benign (RWPE) and PCa (LNCaP) cell lines. Further, in order to assess the role of m^6A methylation in altering translation efficiency we combined ribosome footprint profiling with paired total RNA-seq in cell lines with and without METTL3 knock-down. Distribution of m^6A marks within transcripts mimics those seen in previous datasets: most peaks map to regions in cds or 3' UTR, and show enrichment surrounding the TSS and stop codon. Overall miCLIP identified over 10,000 transcripts with at least one m^6A in the two cell lines, with many important genes for prostate cancer exhibiting a high number of m^6A sites. Ribosome footprint analysis identified many genes as targets for translational regulation by METTL3. Gene set enrichment analysis identified multiple genes related to cell migration and metastasis that have enrichment in m^6A, and demonstrated translational regulation by METTL3. These results validate m^6A as a potentially important additional mechanism of gene regulation at the level of translation in PCa. Further, by allowing for the identification of changes in expression at the protein level previously undetectable by gene expression analysis alone, these findings may lead to the discovery of novel biomarkers or pathways as potential targets for treatment.

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