A miR-194-regulated transcriptional network is associated with progression to androgen receptor-independent prostate cancer

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MicroRNAs (miRNAs) are small, non-coding RNAs that regulate gene expression programs and have a critical role in both normal biology and disease. We previously identified microRNA-194 (miR-194) as an important driver of prostate cancer metastasis, although the molecular mechanisms by which it mediates these effects are not fully understood. This study aimed to identify target genes and pathways that are responsible for miR-194's oncogenic activity. By integrating transcriptomics with a cutting-edge molecular technique that delineates miRNA:mRNA interaction sites, HITS-CLIP (high-throughput sequencing of RNA isolated by crosslinking immunoprecipitation), we characterised the complete set of miR-194 target genes (its "targetome") in prostate cancer cells. MiR-194 targets approximately 160 genes in prostate cancer - predominantly through canonical binding to 3'UTR regions - many of which are involved in key metastatic pathways. Interestingly, miR-194 activity was inversely correlated with androgen receptor (AR) activity in clinical metastatic cohorts, an observation explained mechanistically by AR-mediated repression of miR-194 expression. In concordance with these findings, miR-194 activity is significantly elevated in aggressive AR-independent metastatic prostate cancer subtypes, including neuroendocrine prostate cancer (NEPC) and double-negative prostate cancer (DNPC). Importantly, miR-194 can promote the expression of genes associated with NEPC and DNPC, and targeting miR-194 in aggressive models of these subtypes effectively inhibits cell growth. Overall, our study provides new insights into miR-194 function in prostate cancer progression and the emergence of aggressive AR-independent disease subtypes.

Conflict of Interest
The authors declare no conflict of interest.

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