

MicroRNA Drivers of Resistance to Androgen Deprivation Therapy in Prostate Cancer

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Abstract : INTRODUCTION: Prostate cancer is the most prevalent malignancy affecting Western males. It is initially an androgen-dependent disease: androgens bind to the androgen receptor and drive the expression of genes that promote proliferation and evasion of apoptosis. Despite reduced androgen dependence in advanced prostate cancer, androgen receptor signaling remains a key driver of growth. Androgen deprivation therapy (ADT) is, therefore, a first-line treatment approach and works well initially, but resistance inevitably develops. Abiraterone and Enzalutamide are drugs widely used in ADT and are androgen synthesis and androgen receptor signaling inhibitors, respectively. The shortage of other treatment options means acquired resistance to these drugs is a major clinical problem. MicroRNAs (miRs) are important mediators of post-transcriptional gene regulation and show altered expression in cancer. Several have been linked to the development of resistance to ADT. Manipulation of such miRs may be a pathway to breakthrough treatments for advanced prostate cancer. This study aimed to validate ADT resistance-implicated miRs and their clinically relevant targets. MATERIAL AND METHOD: Small RNA-sequencing of Abiraterone- and Enzalutamide-resistant C42 prostate cancer cells identified subsets of miRs dysregulated as compared to parental cells. Real-Time Quantitative Reverse Transcription PCR (qRT-PCR) was used to validate altered expression of candidate ADT resistance-implicated miRs 195-5p, 497-5p and 29a-5p in ADT-resistant and -responsive prostate cancer cell lines, patient-derived xenografts (PDXs) and primary prostate cancer explants. RESULTS AND DISCUSSION: This study suggests a possible role for miR-497-5p in the development of ADT resistance in prostate cancer. MiR-497-5p expression was increased in ADT-resistant versus ADT-responsive prostate cancer cells. Importantly, miR-497-5p expression was also increased in Enzalutamide-treated, castrated (ADT-mimicking) PDXs versus intact PDXs. MiR-195-5p was also elevated in ADT-resistant versus -responsive prostate cancer cells, while there was a drop in miR-29a-5p expression. Candidate clinically relevant targets of miR-497-5p in prostate cancer were identified by mining AGO-PAR-CLIP-seq data sets and may include AVL9 and FZD6. CONCLUSION: In summary, this study identified microRNAs that are implicated in prostate cancer resistance to androgen deprivation therapy and could represent novel therapeutic targets for advanced disease.

Keywords : microRNA, androgen deprivation therapy, Enzalutamide, abiraterone, patient-derived xenograft

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