

Defining biology of ABI1-driven mechanism of treatment resistance to dual ADT/ARPI therapy

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Background: Prostate cancer (PCa) remains a major health challenge. While anti-androgen therapies have improved outcomes for initial androgen receptor (AR)-driven stages of disease, resistance inevitably develops through tumor plasticity, leading to therapy failure and mortality. We previously identified ABI1 as an AR-regulated gene, and analysis of paired tumor biopsies before and after enzalutamide treatment revealed selective upregulation of ABI1 Exon 4. Furthermore, we established association of high Exon 4 inclusion in neuroendocrine prostate cancer (NEPC) models. Because Exon 4 critically regulates ABI1's transcriptional function, we hypothesize that it plays a central role in mediating resistance to AR-targeted therapies by promoting lineage plasticity.

Methods: ABI1 Exon 4 expression was assessed across prostate cancer models, including tumors, patient-derived xenografts (PDXs), organoids (PDOs), and established prostate cancer cell lines representing CRPC and NEPC (RNA-seq). LuCaP tissue microarrays (TMA) were also stained for ABI1 Exon 4 using new Exon 4-containing and -lacking specific antibodies. Functional studies compared transcriptional activity in ABI1 CRISPR knockout (KO) lines versus ABI1-rescued lines expressing or lacking Exon 4, with additional evaluation under anti-AR inhibitor treatment.

Results: Among 125 PDXs/PDOs, ABI1 Exon 4 expression was significantly elevated in AR-independent phenotypes, including treatment-induced NEPC, double-negative PCa, and amphotericin prostate cancer. In these models, high Exon 4 expression correlated with SRRM4, the NEPC associated splicing factor. In accordance with its transcription regulatory ability, Exon 4 expression showed high nuclear staining, while Exon 4-lacking ABI1 expression was entirely cytoplasmic. ABI1 Exon 4 was universally upregulated after treatment with anti-AR therapies (enzalutamide, apalutamide, and darolutamide) while knockdown of SRRM4 decreased Exon 4 expression. Transcriptomic analyses revealed that ABI1 Exon 4 deregulation reshaped cell phenotype specifically after AR-inhibition, and promoted pathways associated with neuronal development, alternative growth drivers and cell-cell signaling. Disruption of Exon 4 also impacted cell viability, demonstrating its importance to cancer cell survival. ABI1 Exon 4 transcripts were readily detectable in saliva and blood, demonstrating feasibility for a non-invasive liquid biopsy assay to track emergence of resistance.

Conclusions: ABI1 Exon 4's upregulation after anti-AR treatment, combined with its transcriptomic signature, demonstrates a key mechanism for the development of treatment-induced resistance in prostate cancer. Exon 4 thus may serve as an effective biomarker of disease progression, and a potential target for future treatment.

Conflicts of Interest Disclosure Statement. Authors declare no conflict of interest.

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