Defining ABI1-driven mechanism of enzalutamide resistance.

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Background: Prostate cancer remains a significant global health challenge. Advances in anti-androgen therapies have evolved from inhibiting androgen production to targeting the androgen receptor (AR) pathway. However, blocking AR's transcriptional function often leads to short-term effects, treatment resistance, and progression to lethal disease. We previously identified ABI1 as an AR-dependent gene regulated by hormone-directed therapies. While ABI1 is known to bind DNA in vitro and in ChIP assays, its role in directing transcription and its regulation under treatment remain unclear. Understanding the transcriptional regulation of ABI1 could lead to novel breakthroughs in prostate cancer treatment.

Methods: We analyzed the correlation between ABI1 expression in retrospective prostate cancer biopsy samples from patients undergoing neoadjuvant androgen deprivation therapy (ADT) (goserelin plus enzalutamide). The impact of ABI1 on gene transcription was assessed by comparing RNA-seq data from ABI1 CRISPR knockout (KO) DU145 cell lines with those from naïve and ABI1-rescued lines, specifically focusing on the presence or absence of Exon 4. We further investigated ABI1's role in DNA binding and chromatin stability using ChIP-seq and ATAC-seq.

Results: Our analysis of patient samples showed altered ABI1 expression in prostate tumors treated with neoadjuvant ADT. RNA-seq splicing data from 37 patients revealed increased selection for ABI1 Exon 4 in post-treatment samples (after 24 weeks of therapy) compared to paired untreated biopsies, alongside a decrease in the isoform lacking Exon 4. To explore the role of ABI1 Exon 4 in treatment-resistant prostate cancer, we conducted experiments examining ABI1's role in transcriptional regulation. Since ABI1 binds DNA, we hypothesized that Exon 4 influences chromatin function. In androgen-independent DU145 cells engineered with CRISPR to knockout ABI1, we re-expressed either wild-type ABI1 or ABI1 lacking Exon 4. ChIP-seq data showed that ABI1 with Exon 4 exhibited significantly enhanced DNA binding compared to the variant lacking Exon 4 (48,928 vs. 2,248 peaks) and displayed distinct gene-binding profiles. RNA-seq results further demonstrated that ABI1 Exon 4 drives a specific transcriptional program, while the variant lacking Exon 4 exhibited transcription patterns similar to ABI1 KO cells. ATAC-seq analysis confirmed that ABI1 re-expression altered chromatin accessibility, with cells expressing ABI1 with Exon 4 showing the highest nucleosome-free peak scores compared to those lacking Exon 4 or ABI1 KO cells. This suggests that ABI1 modulates chromatin activity through DNA binding, with Exon 4 playing a crucial role.

Conclusions: Our findings suggest that ABI1 contributes to treatment resistance in prostate cancer by regulating transcription and gene expression through DNA binding, which is modulated by specific ABI1 transcripts. Validating this mechanism in clinical samples could lead to new therapeutic strategies that transform the treatment of prostate cancer.

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

Funding Acknowledgements. DoD Award No. HT94252410044, R21CA260381, Joyce Curry Pancreatic Cancer Fund, Upstate Foundation and Upstate Cancer Pilot Grant (LK).