ABI1 as liquid biopsy biomarker of ARPI resistance

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Background: Prostate cancer remains a major global health challenge. While next-generation anti-androgen therapies targeting the androgen receptor (AR) pathway have improved outcomes, resistance inevitably develops, driving progression to lethal disease. 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. Because Exon 4 critically regulates ABI1's transcriptional function, we hypothesize that it plays a central role in mediating resistance to AR-targeted therapies. Importantly, we detected ABI1 Exon 4 in both saliva and blood, highlighting its potential as a novel liquid biopsy biomarker for real-time, non-invasive monitoring of treatment resistance.

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). 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: ABI1 Exon 4 was consistently enriched in tumors treated with enzalutamide, a finding recapitulated in vitro following enzalutamide and apalutamide exposure. Among 125 PDXs/PDOs derived from patients receiving neoadjuvant therapy (goserelin plus enzalutamide), ABI1 Exon 4 expression was significantly elevated in AR-independent phenotypes, including treatment-induced NEPC, double-negative PCa, and AMPC. Increased Exon 4 expression correlated with SRRM4, the splicing factor driving ABI1 alternative splicing. Transcriptomic analyses revealed that ABI1 Exon 4 deregulation reshaped diverse cancer-related pathways, including stress response (FOS, NME1, FUS, NEAT1), tumor growth, angiogenesis, and cell–cell communication. Notably, ABI1 Exon 4 regulated KLK3/PSA expression—even under AR blockade—underscoring the limitations of PSA as a treatment response marker. Crucially, 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 functions as a critical driver of transcriptional reprogramming and AR-independent resistance in prostate cancer. Its detection in saliva and blood establishes the foundation for a liquid biopsy assay with the potential to revolutionize monitoring of treatment resistance and guide precision therapy.

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

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