SPEN mutations as a biomarker for androgen receptor signaling inhibitor therapy resistance in metastatic prostate cancer

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Background:

Treatment intensification with androgen-targeted therapies has become the standard of care for patients with metastatic prostate cancer (mPC). However, there remains an unmet need to identify biomarkers for androgen receptor signaling inhibitor (ARSI) resistance, especially given the high prevalence of mPC. Here, we conducted an unbiased genome-wide screen and identified SPEN as a novel driver of ARSI resistance. SPEN is a nuclear hormone receptor scaffolding protein and has been shown to function as a transcriptional repressor via recruitment of NCoR/SMRT/HDAC3. We hypothesize that patients with mPC harboring genomic alterations in SPEN, experience early resistance to ARSIs and worse clinical outcomes including overall survival (OS). Accordingly, we expect patients with castration-resistant disease will be significantly enriched for SPEN genomic alterations.

Methods:

Pre-clinical studies were performed in LNCaP and VCaP prostate cancer cell lines including CRISPR/Cas9 screen (Brunello library) and competition assays. Puromycin incorporation and polysome profiling assays were used to assess for changes in translation. Patient-level data from the deidentified Foundation Medicine (FM) clinico-genomic database was extracted. The log-rank test and Cox proportional hazards models were used to compare time to next treatment (TTNT) and OS in ARSI treated patients with/without SPEN mutations. SPEN IHC was performed using the University of Washington rapid autopsy metastatic tissue microarray.

Results:

SPEN was identified as a top enzalutamide resistance hit in a genome-wide loss-of-function screen in LNCaP cells. We validated rapid resistance to enzalutamide in SPEN complete knock-out (KO) LNCaP and VCaP cells by competition assays and showed increased S and G2/M compared to SPEN WT cells. mRNA-Seq analysis revealed increased cell cycle proliferation (CCP) pathways with upregulation of E2F target genes in enzalutamide resistant SPEN KO LNCaP cells. mRNA signature analysis demonstrated increased CCP and basal-like PAM50 activity in the setting of low AR signaling. Additional mechanisms of resistance were identified including increased global protein synthesis and translation of mRNAs involved in WNT and NOTCH signaling. In the FM patient cohort (6101 patients), SPEN mutations are enriched following treatment with ARSI (1.9% to 3.4%, p=0.002) and patients with pathologic variants have shorter TTNT on ARSI in hormone-sensitive prostate cancer (median 6.4 vs 26.4 months, HR 2.61, p=0.022) and decreased OS (median 19.6 vs 50.8 months, HR 1.83, p=0.302). In an independent metastatic rapid autopsy cohort, low SPEN H-score is associated with shorter time on abiraterone in mCRPC (median 5.0 vs 7.9 months, p = 0.023) and the AR-/NE+ phenotype.

Conclusions:

In pre-clinical and real-world settings, loss of SPEN function results in decreased time to ARSI resistance. This may serve as a predictive biomarker to guide treatment selection in patients with metastatic hormone-sensitive prostate cancer. Moreover, we identify potentially targetable pathways downstream of SPEN including CCP and increased protein synthesis.

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Conflict of Interest Disclosure Statement:

The authors report no conflicts of interest associated with this study.