Histone-Modifying Enzymes in Androgen-Deprived Prostate Cancer: EZH1 as a Synergistic Therapeutic Target

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Background: Androgen deprivation therapy (ADT) is the cornerstone of treatment for advanced prostate cancer (PC). While ADT induces apoptosis and senescence, residual tumor cells frequently persist and drive castration resistance. The initiation of ADT may create vulnerabilities that can be therapeutically exploited. We investigated the role of histone-modifying enzymes (HMEs) in supporting tumor cell survival after ADT, hypothesizing that their upregulation contributes to persistence and represents a target for synergistic therapy.

Methods: High-risk prostatectomy samples treated with 3 months of ADT were compared to untreated controls using RNA sequencing (n=10 vs. 26). Publicly available datasets (Wyatt GSE55016; Sowalsky GSE183100) were interrogated for validation. Functional assays were performed with EZH1 shRNAs in 2-D and 3-D cultures of hormone-sensitive LNCaP, LAPC4, and VCaP cells under ADT. Flow sorting of treated populations for stem cell markers CD44 and others was performed. Patient-derived organoids and cell lines were further tested with the EZH1 inhibitor valemetostat in combination with ADT.

Results: High-risk prostatectomy samples identified four consistently upregulated HMEs: EZH1, MECOM, SIRT1, and GCN5 after ADT. Among these, EZH1 and MECOM showed increased protein expression in a validation tissue microarray of 61 patients with EZH1 correlated with adverse clinical features including positive surgical margins and PSA recurrence. In LNCaP and VCaP cell lines EZH1 expression rose or persisted after early ADT, while EZH2 declined with increased H3K27 levels. Total H3k27m3 levels increased. EZH1 expression was enriched in stem populations. EZH1 knockdown reduced survival of ADT-treated cells, and organoid models showed synergistic cell death with combined darolutamide and EZH1 inhibition (valemetostat).

Conclusions: ADT induces EZH1 upregulation, which promotes prostate cancer cell persistence through regulation of stemness and epithelial-to-mesenchymal transition. These findings establish EZH1 as a mediator of survival after ADT and a promising target for synergistic therapeutic inhibition.

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