

Epigenetically Informed Therapeutic Strategies for DNA-Hypomethylated Prostate Cancer

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Background

DNA methylation is a fundamental regulator of chromatin architecture and transcriptional control. While numerous studies have focused on the role of hypermethylation in disease progression, the biological and therapeutic consequences of widespread DNA methylation loss remain poorly defined. We identified a distinct subset of prostate cancers (PC), termed DNA Hypomethylated Prostate Cancers (DHMPCs), which are characterized by profound reductions in global DNA methylation levels. These tumors display aggressive clinical behavior, highlighting the urgent need to define effective therapeutic strategies tailored to this epigenetically defined cancer state.

Objective

We hypothesized that the global loss of DNA methylation observed in DHMPCs disrupts epigenome homeostasis and creates specific molecular dependencies that can be exploited therapeutically. Our goal was to systematically define these vulnerabilities and to rationally design combination treatment strategies for effective targeting of DHMPCs, with a focus on advanced PC.

Study Design

To delineate the biology of DHMPCs, we measured changes in global methylation pattern using validated orthogonal methods in large representative cohorts of localized and metastatic prostate cancer. We determined tumor cell intrinsic therapeutic vulnerabilities in broad pharmacologic screens and further assessed the patterns of epigenetic and transcriptomic alterations induced upon targeting these vulnerabilities in DHMPCs.

Results

Drug screens revealed that DHMPCs are highly sensitive to pharmacological AKT inhibition (AKTi). We show that the degree of global hypomethylation correlated strongly with response to AKTi across a broad panel of cancers, independent of canonical PI3K pathway alterations, including *PTEN* loss. Moreover, pharmacological induction of global DNA hypermethylation increased AKTi sensitivity, providing functional evidence for a methylation-dependent mechanism of response. Mechanistic studies demonstrated that AKTi triggers widespread epigenomic perturbations in DHMPCs, including global depletion of core histones and compensatory enrichment of the polycomb repressive complex 2 (PRC2)-associated histone mark H3K27me3. Building on this dependency, combined inhibition of AKT with EZH2 or EED inhibitors resulted in highly synergistic therapeutic effects, producing robust tumor growth suppression in preclinical models.

Conclusions

Together, these findings uncover an unanticipated mechanistic link between AKT signaling and DNA methylation state in PC. They establish global hypomethylation as a predictive biomarker for therapeutic vulnerability and provide a strong rationale for biomarker-guided development of combination therapies that co-target AKT and PRC2. More broadly, this work demonstrates how integrating epigenomic context with signaling pathway biology can enable the design of rational, effective treatment strategies for epigenetically defined cancer subtypes.

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Conflict of Interest Statement

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