Serican Journal of Medicine
2026, VOL. 3, NO. 3, 25998
https://doi.org/10.17161/sjm.v3i3.2598

Dual DNMT-EZH2 Inhibition as a Stroma-Directed Strategy in Castration-Resistant Prostate Cancer: A Commentary

Rongxin Chang and Guodong Liu*

School of Life Sciences, Anhui Medical University, Hefei Anhui 230032, China.

Corresponding Author: Guodong Liu, PhD, email address: lgd1274@163.com

ABSTRACT

Background: Castration-resistant prostate cancer (CRPC) remains a lethal progression state despite androgen-deprivation therapy, driven by epigenetic plasticity and a fibrotic tumour microenvironment. Single-agent epigenetic inhibitors have limited activity in solid tumors, partly because compensatory H3K27me3-mediated silencing may preserve gene repression after DNMT inhibition.

Objective: To comment on a recent PNAS study and evaluate the mechanistic and translational rationale for dual DNMT–EZH2 inhibition as a stroma-directed strategy in CRPC.

Discussion: The study shows that DNMT inhibitor monotherapy induces compensatory EZH2-dependent H3K27me3 deposition at the *ADAMTS1* locus, maintaining silencing of this collagenase. Dual DNMT–EZH2 targeting reactivates *ADAMTS1*, promotes collagenolysis, and disrupts FAK/MAPK/EMT mechanotransduction, thereby counteracting androgen-independent survival. In immunocompetent preclinical models, the combination achieves over 90% tumour suppression, increases $CD8^+$ T-cell infiltration by 11.4-fold, reduces immunosuppressive cells, and activates interferon-driven innate immune pathways with limited systemic toxicity.

Conclusion: Dual DNMT–EZH2 inhibition is a mechanistically justified preclinical strategy that links epigenetic reprogramming, ECM remodelling, and anti-tumour immunity. Clinical validation, biomarker development, and assessment of immune-checkpoint combinations are needed before translation.

ARTICLE HISTORY
Received: Aug. 17, 2026
Revised: Aug. 25, 2026
Accepted: Aug. 30, 2026

KEYWORDS
Dual DNMT-EZH2 inhibition, castration-resistant prostate cancer, epigenetic compensation, ADAMTS1/ECM remodeling, tumor immune microenvironment

Introduction

Progress in oncology frequently emerges from discoveries that bridge epigenetic biology and tumour-microenvironment research. Androgen-deprivation therapy (ADT) remains standard care for advanced prostate cancer, yet many patients progress to lethal castration-resistant prostate cancer (CRPC). Resistance arises through multiple routes, including androgen receptor alterations, neuroendocrine trans-differentiation, and epigenetic dysregulation. Although DNMT and EZH2 inhibitors have shown clinical activity in hematological malignancies, single-agent epigenetic inhibition generally produces unsatisfactory responses in solid tumors such as CRPC.

A key unresolved question concerns the compensatory crosstalk between two repressive chromatin marks: DNA methylation and H3K27me3. After DNMT inhibition, H3K27me3 can act as a secondary silencer that preserves gene repression and limits therapeutic benefit. CRPC is also characterized by a dense fibrotic extracellular matrix (ECM). Stiff, collagen-rich stroma activates androgen-independent survival signaling and forms a physical barrier that restricts cytotoxic T-cell infiltration, contributing to local immunosuppression. Although these components have been studied separately, how epigenetic plasticity cooperates with ECM biomechanical remodelling has remained under-appreciated. A recent PNAS study addresses this gap and raises important translational questions for advanced prostate cancer [1].

Epigenetic Compensation in a Tumour–Stromal Context

Earlier work documented compensatory H3K27-

me3 accumulation following DNMT inhibition [2], mainly in hematological models [3-5]. Whether this epigenetic switch regulates ECM-remodelling genes in stroma-rich CRPC was previously unclear.

Current clinical oncology does not regard DNMT or EZH2 monotherapy as sufficient for CRPC. CRPC resistance is multifactorial, shaped by genetic alterations, androgen-receptor plasticity [6], epigenetic rewiring [7], and stromal signals [8]. Nevertheless, clinical cohorts show that higher EZH2 and DNMT expression correlates with poorer survival, and prostate cancer specimens display a reciprocal negative correlation between H3K27me3 and DNA methylation. These observations suggest that this epigenetic switch is associated with aggressive disease features.

They also give rise to a testable hypothesis: compensatory epigenetic silencing of ECM-regulatory genes such as *ADAMTS1* may represent an important bottleneck limiting epigenetic therapy efficacy. Definitive clinical evidence is lacking, but this mechanistic model warrants objective experimental evaluation.

Fibrotic Stroma as a Driver of Resistance

CRPC remains a major cause of cancer-related mortality among men. Despite modern androgen-receptor-targeted therapies, stroma-driven resistance frequently emerges. Fibrotic ECM increases tumor stiffness and activates FAK/MAPK/EMT mechanotransduction, and sustains androgen-independent tumour-cell survival. Such resistance cannot be fully overcome by agents that target only tumour-cell-intrinsic pathways.

Dense collagen also contributes to immunotherapy failure. Immunologically "cold" CRPC shows scarce $CD8^+$ T-cell infiltration together with abundant immunosuppressive macrophages and regulatory T cells. Although cancer-cell-intrinsic defects contribute to immune escape, the fibrotic matrix physically restricts T-cell access to tumour sites. This creates a major clinical obstacle: even effective tumour-cell killing may fail if stromal exclusion persists.

Linking Epigenetic Reprogramming, ECM Remodelling, and Immunity

The featured PNAS study supports an interconnected model in which epigenetic state, ECM architecture, and anti-tumour immunity are functionally linked. Key observations include:

- DNMT-inhibitor monotherapy triggers compensatory EZH2-dependent H3K27me3 deposition at the *ADAMTS1* locus, maintaining silencing of this collagenase despite partial DNA hypomethylation.
- Dual DNMT–EZH2 targeting disrupts this epigenetic switch and synergistically reactivates *ADAMTS1*; restored *ADAMTS1* drives collagenolysis and degrades fibrotic tumour stroma.
- *ADAMTS1*-mediated ECM breakdown inactivates FAK/MAPK/EMT mechanotransduction and counteracts castration resistance; *ADAMTS1* knockdown largely abrogates the anti-tumour benefit of dual epigenetic therapy.
- In immunocompetent preclinical models, combined DNMT–EZH2 inhibition achieves over 90% tumour suppression, increases $CD8^+$ T-cell infiltration by 11.4-fold, reduces immunosuppressive cell populations, and stimulates interferon-driven innate immune pathways.
- *In vivo* studies suggest limited systemic toxicity, supporting further translational exploration.

These findings underscore the value of co-targeting chromatin plasticity and the stromal biomechanical niche to overcome solid-tumour resistance.

Translational Considerations

Although durable tumour control with DNMT–EZH2 dual inhibition has not yet been demonstrated in patients with CRPC, the combination represents a biologically plausible therapeutic concept. Dual epigenetic targeting relieves silencing of ECM-remodelling genes while remodelling the immunosuppressive microenvironment, and clinically available DNMT and EZH2 inhibitors could be repurposed.

Several practical considerations should be addressed before clinical implementation:

- Profile human CRPC biopsies to determine how frequently *ADAMTS1* undergoes dual silencing by DNA methylation and H3K27me3 across clinical subtypes.
- Validate therapeutic responses in patient-derived xenografts or organoids, which were not used in the original study.
- Prioritize selective DNMT1 inhibitors or EZH2 degraders to reduce off-target epigenetic perturbation in normal tissues.
- Explore whether dual epigenetic therapy synergises with immune-checkpoint blockade.

- Develop epigenetic biomarkers to select patients most likely to benefit from this combination.

Conclusion

The crosstalk between epigenetic plasticity and fibrotic tumour microenvironments is an active research frontier in prostate cancer biology. Current data are largely confined to preclinical systems, and human trial outcomes are not yet available. Nevertheless, dual DNMT–EZH2 targeting disrupts a critical compensatory epigenetic switch, restores *ADAMTS1*-driven ECM remodeling, blunts mechanotransduction-mediated resistance, and relieves local immunosuppression.

The concept of epigenetic–ECM co-evolution expands our understanding of CRPC beyond tumor-cell-centered perspectives. Future work should define the prevalence of this silencing signature across human CRPC subgroups, improve drug selectivity, and assess rational combinatorial regimens. Until clinical data emerge, dual DNMT–EZH2 inhibition remains a promising, mechanistically justified preclinical strategy for overcoming stroma-driven resistance in CRPC and potentially other ECM-rich solid malignancies.

References

1. Wu X, Song X, Li B, Yang Y, Li K, Zhu J, Li Y, Yang X, Dai Y, Zhang Z: **Targeting the DNA methylation-H3K27me3 switch reverses castration resistance and immunosuppression via ADAMTS1-driven collagenolysis**. *Proc Natl Acad Sci U S A* 2026, **123**(25):e2525431123. doi:10.1073/pnas.2525431123: PMC13291630.
2. Chomiak AA, Tiedemann RL, Liu Y, Kong X, Cui Y, Wiseman AK, Thurlow KE, Cornett EM, Topper MJ, Baylin SB *et al*: **Select EZH2 inhibitors enhance viral mimicry effects of DNMT inhibition through a mechanism involving NFAT:AP-1 signaling**. *Sci Adv* 2024, **10**(13):eadk4423. doi:10.1126/sciadv.adk4423: PMC10971413.
3. Peng D, Kryczek I, Nagarsheth N, Zhao L, Wei S, Wang W, Sun Y, Zhao E, Vatan L, Szeliga W *et al*: **Epigenetic silencing of TH1-type chemokines shapes tumour immunity and immunotherapy**. *Nature* 2015, **527**(7577):249–253. doi:10.1038/nature15520: PMC4779053.
4. Zhang L, Li HT, Shereda R, Lu Q, Weisenberger DJ, O'Connell C, Machida K, An W, Lenz HJ, El-Khoueiry A *et al*: **DNMT and EZH2 inhibitors synergize to activate therapeutic targets in hepatocellular carcinoma**. *Cancer Lett* 2022, **548**:215899. doi:10.1016/j.canlet.2022.215899: PMC9563073.
5. Kurahashi Y, Watanabe T, Yamamoto Y, Ureshino H, Kamachi K, Yoshida-Sakai N, Fukuda-Kurahashi Y, Yamashita S, Hattori N, Nakamura H *et al*: **Dual targeting of aberrant DNA and histone methylation synergistically suppresses tumor cell growth in ATL**. *Blood Adv* 2023, **7**(8):1545–1559. doi:10.1182/bloodadvances.2022008362: PMC10130614.
6. Watson PA, Arora VK, Sawyers CL: **Emerging mechanisms of resistance to androgen receptor inhibitors in prostate cancer**. *Nat Rev Cancer* 2015, **15**(12):701–711. doi:10.1038/nrc4016: PMC4771416.
7. Ge R, Wang Z, Montironi R, Jiang Z, Cheng M, Santoni M, Huang K, Massari F, Lu X, Cimadamore A *et al*: **Epigenetic modulations and lineage plasticity in advanced prostate cancer**. *Ann Oncol* 2020, **31**(4):470–479. doi:10.1016/j.annonc.2020.02.002:
8. Luthold C, Hallal T, Labbé DP, Bordeleau F: **The Extracellular Matrix Stiffening: A Trigger of Prostate Cancer Progression and Castration Resistance?** *Cancers (Basel)* 2022, **14**(12). doi:10.3390/cancers14122887: PMC9221142.