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Targeting DNA Methylation Rewires Drug Responses of RB1-Deficient and Neuroendocrine Prostate Cancer

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Short commentary

A commentary on Targeting DNA methylation and B7-H3 in RB1-deficient and neuroendocrine prostate cancer by Yasutaka Yamada, Varadha Balaji Venkadakrishnan, Kei Mizuno, Martin Bakht, Sheng-Yu Ku, Maria Mica Garcia, Himisha Beltran (2023). Sci Transl Med. 15(722): eadf6732. doi: 10.1126/scitranslmed.adf6732.

As a prevalent and aggressive cancer in male population, prostate cancer is characterized by activation of androgen receptor (AR) signaling. However, up to 15~20% late-stage prostate cancers abolish their dependence on AR signaling by transforming into neuroendocrine prostate cancer (NEPC) so as to escape anti-androgen therapies [1]. Despite the AR independence and NEPC tumor phenotypes triggered by RB1 loss, aberrant epigenetic modifications also contribute to the progression of NEPC [2], thus making epigenetic modulators as a promising NEPC therapeutic option. In a recent issue of Science Translational Medicine, Himisha Beltran's lab evaluates the benefits from targeting DNA methyltransferases (DNMTs) in NEPC models, and intriguingly raised a rational and feasible drug combination of decitabine (a pan-DNMT inhibitor) and DS-7300a (antibody-drug conjugate (ADC) that targets B7-H3) for NEPC treatment. Considering that decitabine and DS-7300a are both clinically accessible, this impressive works may broaden the current therapeutic options in handling NEPC.

DNA methylation catalyzed by DNMTs is a major epigenetic mark at cytosine residues adjacent to guanine nucleotides (CpG sites) to silence tumor suppressor genes. Recent works have nominated the tight correlation between increased genome-wide DNA methylation and NEPC transformation [3]. Therefore, rectification of DNA methylation appears to yield potential therapeutic benefits for NEPC patients. To validate the benefits from DNA methylation rewiring, Yamada and colleagues firstly examined the expression levels of DNMTs across different stages of prostate cancer samples, and found that DNMT1, along with DNMT3A and DNMT3B, is significantly upregulated in NEPC specimens, compared with other less-progressive prostate cancer tissues. Accordantly, NEPC demonstrates increased levels of DNA methylation, compared with other non-NEPC subtypes. Besides, knockout of DNMT1 or DNMT3A by CRISPR-Cas9 significantly reduced cell proliferation and tumor growth of NEPC, but exhibits limited impact on non-NEPC prostate cancer models, indicating the specific reliance of NEPC on DNMTs-mediated global hypermethylation. In addition, deletion of DNMT1 or DNMT3A also decreased the expression of NEPC-associated genes, supporting a crucial role of DNMT1/3A in modulating the lineage of NEPC. However, more detailed dependence of NEPC on DNMTs and whether DNMT1/3A act as the switch of NEPC transformation awaits further experimental validation.

Based on the requirements of NEPC cell proliferation on DNMT1 and DNMT3A, a pan-DNMT inhibitor, decitabine was probed for efficacy evaluation on NEPC models. As expected, decitabine exhibits strikingly anti-proliferative effects on prostate cancer cells, with an astonishing over ten-fold selectivity on NEPC cell lines/ patient–derived organoid lines over cell lines from other prostate cancer subtypes. Such antitumor effects of decitabine were also validated in the PDX models, with the sustained growth repression and neuroendocrine marker expression blocking observed in the treatment group. Given that RB1 loss acts as an early driver for NEPC tumorigenesis (more than 70%), the authors further investigate the dependency of decitabine efficacy on RB1 deficiency. This experiment was carried out in castration-resistant prostate adenocarcinoma (CRPC) models. As another refractory prostate cancer types, CRPC also loss their dependence on AR signaling and shared RB1 loss in about 30% of the estimated specimens [4]. To this end, Yamada and colleagues evaluated the responses of RB1-proficient CRPCs and RB1-deficient CRPCs to decitabine compared to the RB1-proficient CRPCs, RB1-deficient CRPCs showed increased sensitivity to decitabine, which may be associated with their higher DNMT levels than CRPC without RB1 genomic alteration. Besides, artificially deletion of RB1 locus in RB1-proficient CRPC produced an enhanced antitumor effect in cellular and mouse

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models, thus highlighting the potential of DNMT as a possible synergistic lethal factor with RB1 loss in prostate cancer. Still, more experiments are required to validate this striking assumption. Overall, the data from RB1-deficient CRPC expands the potential therapeutic indications of decitabine to other RB1-loss prostate cancer subtypes beyond NEPC.

DNMT inhibition can globally induce gene expression by relieving transcriptional repression derived from CpG island hypermethylation, Yamada and colleagues carried out a combinative analysis of gene expression and methylation and identified B7-H3, also known as CD276, as a differentially hypomethylated gene which can be reactivated by decitabine. As a cell surface protein, B7-H3 is emerging therapeutic target in CRPC, with its antibody-drug conjugates (ADCs) being investigated for antitumor effects in clinical trials [5]. B7-H3 ADC's efficacy is tightly correlated to their protein levels in cellular membranes according to the data from Yamada and colleagues. Although B7-H3 is expressed in nearly all prostate cancers, unfortunately, a subpopulation of CRPC and NEPC exhibit minor or absent B7-H3 expression, which causes inherent drug resistance to B7-H3 targeting agents. Therefore, epigenetic reactivation of B7-H3 expression by DNMT inhibitors would be a promising routine to expand the application spectrums of B7-H3 ADCs to more CRPC and NEPC patients. To test this, decitabine plus DS-7300a (I-DXd, an ADC that targets B7-H3 under clinical trials for solid tumors (NCT04145622)) combinative strategy were evaluated in CRPC and NEPC models. Astonishingly, decitabine plus DS-7300a combinative strategy not only yields a synergistic antitumor effect, but also improves the drug response of the resistant prostate cancers to B7-H3 ADC therapy. Such effects were attributed to the reactivation of B7-H3 expression by DNMT inhibition, as cells harboring high B7-H3 endogenous expression fail to show improved DS-7300a response under decitabine stress. Given that DS-7300a are now under clinical trials, these findings by Yamada and colleagues provide a feasible drug combinative strategy to expand clinical applications of B7-H3 ADC agents. Still, more pre-clinical and clinical evaluation are required to further validate both the efficacy and the safety of the decitabine plus DS-7300a therapy. Additionally, more DNMT inhibitors and B7-H3 targeting agents should be included to screen the most beneficial drug combination in the near future.

Declarations

Author contributions: GJW conceived of and designed the commentary. GJW wrote and reviewed the draft, prepared the manuscript.

Conflict of interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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