Editorial Commentary

Combination of PARP and DNA methylation inhibitors as a potential personalized therapy for SETD2-mutated clear-cell renal cancers

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Clear-cell renal cell carcinoma (ccRCC) arises from proximal tubules in the kidney cortex and is the most common kidney malignancy (1). Metastasis occurs in over one-third of cases and targeted therapies, primarily against angiogenesis, have been used in clinical practice over the past decade (1). The application of anti-angiogenesis therapies has been motivated by the inactivation of Von Hippel-Lindau (*VHL*) tumor suppressor gene, which is the most common genetic alteration in ccRCC. *VHL* deficiency leads to the aberrant activation of hypoxia signaling and downstream angiogenesis pathways (2,3). Furthermore, due to the immunogenic nature of ccRCC tumors, immune checkpoint inhibitors (ICIs) are used as the standard of care for advanced tumors, most recently in combination with tyrosine kinase inhibitors (TKIs) (3,4). While some patients benefit from these treatments, responses to anti-angiogenesis and ICI agents are transient and limited to a small subset of patients, emphasizing the critical need for prognostic and predictive biomarkers, which are currently lacking in clinical practice (5-7). Notably, the current therapies are directed against tumor microenvironment, highlighting the challenge of targeting cancer cells directly within ccRCC tumors.

Recent large-scale sequencing studies have advanced our knowledge about genomic drivers of ccRCC beyond *VHL* mutations and revealed significant heterogeneity in the genomic landscapes of tumors, which is linked to diverse clinical outcomes (8,9). The most commonly mutated genes in ccRCC include *VHL* (76%), *PBRM1* (39%), *SETD2* (18%), and *BAP1* (14%), all located on the short arm of chromosome 3 (8,10). Interestingly, *PBRM1* and *SETD2* encode two prominent epigenome modulators, highlighting the driving role of abnormal epigenome patterns in ccRCC development. In this context, previous studies have reported the anti-proliferative activity of DNA methyltransferase inhibitor 5-aza-20-deoxycytidine (DAC) against ccRCC cells (11). Notably, the combination of DAC with chemotherapeutic agents effectively demonstrates a synergistic impact in reducing the viability of renal cell carcinoma (RCC) cell lines (12). *SETD2* is the leading histone methyltransferase, responsible for catalyzing the methylation of histone-3 at lysine-36 (H3K36me3), and according to a previous study, *SETD2* deficiency can increase DNA double-strand breaks (DSB) damage by impairing homologous recombination (HR) (13). These observations have inspired Zhou and colleagues to examine the potential impacts of combination therapy with DNA hypomethylating agents (HMAs) and DNA repair inhibitors in ccRCC. Specifically, they evaluated the effects of combining DAC with an inhibitor of poly (ADP-ribose)

polymerase (PARP) (talazoparib; BMN-673) on the viability and growth of *SETD2*-deficient human ccRCC (14).

PARP inhibitors (PARPi) interrupt the ability of malignant cells to tolerate DNA damage, leading to cell cycle arrest and apoptosis, and have shown significant efficacy in different tumor types (15).

Zhou and colleagues investigated the effects of treatment with BMN-673 and DAC on different RCC cell lines, categorized into three groups as follows: (I) ACHN (*SETD2* wild-type) and A498 (*SETD2* mutant); (II) Caki-2 (*SETD2* wild-type) and 769-P (*SETD2* down-regulated); (III) 786-O *SETD2* wild-type (*SETD2*-WT) and 786-O *SETD2* knock-out (*SETD2*-KO). First, the authors observed a synergetic inhibition of cell growth by inducing apoptosis in *SETD2*-mutated cells upon a combination therapy with DAC and BMN-673. Moreover, they showed a relationship between increased cell cycle inhibition and apoptosis induction and higher rates of DNA damage, inefficient DNA repair systems for DNA DSBs, and loss of genomic stability in *SETD2*-altered cells.

Second, they employed RNA-sequencing to examine alterations in transcriptional profiles of 786-O *SETD2*-WT and 786-O *SETD2*-KO cells before and after treatments. The Gene Set Enrichment Analysis (GSEA) revealed that main pathways upregulated following treatments with DAC alone or in combination with BMN-673 were related to innate and adaptive immune responses. The activation of immune response pathways correlated with an increased expression of transposable elements (TEs), particularly following the combination therapy. However, these pathways were not significantly affected following PARPi monotherapy, indicating a noticeable effect of the dual treatment on the activation of immune-related pathways. Additionally, the study revealed a significant increase in STING1 protein levels, particularly in *SETD2*-KO cells, following treatment with DAC or the combination of DAC and BMN-673. These findings suggest that activation of TEs, resembling viral mimicry, and the STING1 pathway are potentially involved in immune response activation and may contribute to the therapeutic impacts observed after treatment with DAC or the combination of DAC and BMN-673.

Lastly, to validate *in vitro* findings, Zhou *et al.* examined the effects of therapies *in vivo* on xenografts developed by implanting *SETD2*-WT and *SETD2*-KO 786-O cells in immune-deficient nude mice. The *in vivo* results confirmed that the *SETD2*-deficient xenografts were more sensitive to the combination therapy, consistent with the *in vitro* results (14).

The results of this study are novel and interesting in terms of proposing a new therapeutic strategy that targets cancer cells directly in ccRCC tumor milieu. However, the translational potential of the findings cannot be assessed thoroughly due to the limitations of the study, as discussed below. First, the results are generated using a limited number of cell lines *in vitro* and only one cell line (786-O) *in vivo*. Given the diverse histological subtypes of RCC, the *in vivo* observations are only limited to the ccRCC subtype (represented by 786-O) and may not be valid for other *SETD2*-mutant subtypes of RCC. Second, the cell line models do not capture the complex environment of tumors faithfully, and patient-derived organoid (PDO) or patient-derived xenograft (PDX) models have emerged as more appropriate tools for the evaluation and pre-clinical studies of novel treatment approaches (16). Lastly, the use of immune-deficient animals did not allow to verify possible involvement of immune responses.

Genome-based therapeutic approaches in RCC have a long-standing history. An eminent example is the application of anti-angiogenesis TKIs in ccRCCs, characterized by inactivating mutations of *VHL*. While the use of anti-angiogenic agents was the first-line treatment in ccRCC for many years, the landscape of ccRCC management is consistently changing, owing to the emergence of new links between genomic alterations and targeted therapies. For example, it has been proposed that *PBRM1* mutations may be associated with better response to ICI treatments (17,18). Furthermore, recent research has shown that RCC cells carrying *SETD2* mutations or exhibiting reduced expression of *SETD2* are sensitive to HMAs both *in vitro* and *in vivo* (19). In addition, it has been shown that combination therapy with an HMA and PARPi has the potential to inhibit cell growth in some cancers (20,21). In this context, the study by Zhou *et al.* is the first report proposing a dual therapy with DAC and PARPi against *SETD2*-mutant ccRCC (14). The results of this study can complement those of preclinical studies that have indicated the potential use of PARPi in ccRCC management (22,23), and a current phase Ib/II clinical trial that is evaluating the outcomes of the talazoparib and axitinib combination in patients with previously treated metastatic RCC (24). In sum, the study by Zhou *et al.* may open new avenues for personalizing PARPi-therapies for *SETD2*-mutated metastatic ccRCCs, addressing the limitations of existing approaches (25). However, additional studies are needed to validate these observations and elucidate the involved pathways.

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Footnote

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References

1. Ljungberg B, Albiges L, Abu-Ghanem Y, et al. European Association of Urology Guidelines on Renal Cell Carcinoma: The 2022 Update. Eur Urol 2022;82:399-410.
2. Gossage L, Eisen T, Maher ER. VHL, the story of a tumour suppressor gene. Nat Rev Cancer 2015;15:55-64.
3. Schiavoni V, Campagna R, Pozzi V, et al. Recent Advances in the Management of Clear Cell Renal Cell Carcinoma: Novel Biomarkers and Targeted Therapies. Cancers (Basel) 2023;15:3207.
4. Yang J, Wang K, Yang Z. Treatment strategies for clear cell renal cell carcinoma: Past, present and future. Front Oncol 2023;13:1133832.
5. McKay RR, Bossé D, Choueiri TK. Evolving Systemic Treatment Landscape for Patients With Advanced Renal Cell Carcinoma. J Clin Oncol 2018. [Epub ahead of print]. doi: 10.1200/JCO.2018.79.0253.
6. Rebuzzi SE, Perrone F, Bersanelli M, et al. Prognostic and predictive molecular biomarkers in metastatic renal cell carcinoma patients treated with immune checkpoint inhibitors: a systematic review. Expert Rev Mol Diagn 2020;20:169-85.
7. Lemelin A, Takemura K, Heng DYC, et al. Prognostic Models in Metastatic Renal Cell Carcinoma. Hematol Oncol Clin North Am 2023;37:925-35.
8. Vasudev NS, Scelo G, Glennon KI, et al. Application of Genomic Sequencing to Refine Patient Stratification for Adjuvant Therapy in Renal Cell Carcinoma. Clin Cancer Res 2023;29:1220-31.
9. Linehan WM, Ricketts CJ. The Cancer Genome Atlas of renal cell carcinoma: findings and clinical implications. Nat Rev Urol 2019;16:539-52.
10. Scelo G, Riazalhosseini Y, Greger L, et al. Variation in genomic landscape of clear cell renal cell carcinoma across Europe. Nat Commun 2014;5:5135.
11. Shang D, Ito N, Kamoto T, et al. Demethylating agent 5-aza-2'-deoxycytidine enhances susceptibility of renal cell carcinoma to paclitaxel. Urology 2007;69:1007-12.
12. Shang D, Xian S, Han T, et al. VHL-TGFBI signaling is involved in the synergy between 5-aza-2'-deoxycytidine and paclitaxel against human renal cell carcinoma. J BUON 2017;22:500-7.
13. Yu M, Qian K, Wang G, et al. Histone methyltransferase SETD2: An epigenetic driver in clear cell renal cell carcinoma. Front Oncol 2023;13:1114461.
14. Zhou X, Sekino Y, Li HT, et al. SETD2 Deficiency Confers Sensitivity to Dual Inhibition of DNA Methylation and PARP in Kidney Cancer. Cancer Res 2023;83:3813-26.
15. Lord CJ, Ashworth A. PARP inhibitors: Synthetic lethality in the clinic. Science 2017;355:1152-8.
16. Tuveson D, Clevers H. Cancer modeling meets human organoid technology. Science 2019;364:952-5.
17. Miao D, Margolis CA, Gao W, et al. Genomic correlates of response to immune checkpoint therapies in clear cell renal cell carcinoma. Science 2018;359:801-6.
18. Nayak AP, Villalba D, Deshpande DA. Bitter Taste Receptors: an Answer to Comprehensive Asthma Control? Curr Allergy Asthma Rep 2019;19:48.
19. Li HT, Jang HJ, Rohena-Rivera K, et al. RNA mis-splicing drives viral mimicry response after DNMTi therapy in SETD2-mutant kidney cancer. Cell Rep 2023;42:112016.

20. Baer MR, Kogan AA, Bentzen SM, et al. Phase I Clinical Trial of DNA Methyltransferase Inhibitor Decitabine and PARP Inhibitor Talazoparib Combination Therapy in Relapsed/Refractory Acute Myeloid Leukemia. Clin Cancer Res 2022;28:1313-22.
21. Muvarak NE, Chowdhury K, Xia L, et al. Enhancing the Cytotoxic Effects of PARP Inhibitors with DNA Demethylating Agents - A Potential Therapy for Cancer. Cancer Cell 2016;30:637-50.
22. Scanlon SE, Hegan DC, Sulkowski PL, et al. Suppression of homology-dependent DNA double-strand break repair induces PARP inhibitor sensitivity in VHL-deficient human renal cell carcinoma. Oncotarget 2017;9:4647-60.
23. Chabanon RM, Morel D, Eychenne T, et al. PBRM1 Deficiency Confers Synthetic Lethality to DNA Repair Inhibitors in Cancer. Cancer Res 2021;81:2888-902.
24. Iacovelli R, Ciccarese C, Procopio G, et al. Current evidence for second-line treatment in metastatic renal cell carcinoma after progression to immune-based combinations. Cancer Treat Rev 2022;105:102379.
25. Riazalhosseini Y, Lathrop M. Precision medicine from the renal cancer genome. Nat Rev Nephrol 2016;12:655-66.

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