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# KDM6A links genomic instability to immunometabolic rewiring: redefining the determinants of therapeutic response in bladder cancer

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## INTRODUCTION

Bladder cancer is one of the most common malignancies of the urinary tract and has a broad clinical spectrum, ranging from non-muscle-invasive disease to muscle-invasive and unresectable locally advanced or metastatic urothelial carcinoma. In advanced disease, platinum-based chemotherapy, immune checkpoint blockade (ICB), antibody-drug conjugates, and combination regimens have become central components of a rapidly evolving treatment landscape[1,2].

This clinical diversity is paralleled by molecular heterogeneity, with subtype-dependent immune and stromal features and differential treatment-associated outcomes, including benefit from PD-L1 blockade and cisplatin-based neoadjuvant chemotherapy[3,4]. This biological diversity partly explains the varied responses to chemotherapy and immunotherapy even among patients with similar clinicopathological features. PD-L1 immunohistochemistry and tumor mutational burden (TMB) are commonly used ICB-related biomarkers; however, their low specificity limits their utility for assessing the entirety of immune and stromal architecture or for determining overall microenvironmental suppression in bladder cancer[3]. Against this backdrop, Singh *et al.* showed that the consequences of KDM6A loss in bladder cancer are therapy-specific: extrachromosomal circular DNA (eccDNA)-driven amplification of chemoresistance loci promotes cisplatin resistance, while DNA repair defects and metabolic rewiring enhance tumor immunogenicity and relieve lactate-dependent regulatory T cell (Treg) suppression to favor response to PD-1/PD-L1 blockade[5].

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KDM6A is the most frequently mutated epigenetic regulator in bladder cancer to date, with loss-of-function mutations reported in about 26% of patients with muscle-invasive bladder cancer[6]. KDM6A is an established histone demethylase that removes the repressive histone mark H3 lysine 27 trimethylation (H3K27me3) and sustains chromatin accessibility and transcriptional activation[5]. It has been implicated in bladder tumorigenesis and the regulation of urothelial lineages by a proposed epigenetic switch that disables urothelial differentiation while driving cell proliferation[6], but the mechanistic basis for how it modulates sensitivity to therapy has remained insufficiently defined.

## KDM6A LOSS, ECCDNA FORMATION AND CISPLATIN RESISTANCE

To define how KDM6A loss modulates therapeutic responsiveness, Singh and coworkers combined retrospective clinical analysis with functional interrogation. The study showed significantly shorter overall survival in patients with KDM6A-mutant bladder cancer following cisplatin-based chemotherapy[5]. Using CRISPR-Cas9-mediated gene editing, the authors created KDM6A-deficient human and mouse models of bladder cancer, showing that loss of KDM6A markedly decreased cisplatin-induced cytotoxicity and, under these same culture conditions, enhanced cellular invasion, migration, and sphere formation[5]. Together, these data support the notion that loss of KDM6A is a functional driver of chemoresistance rather than merely an incidental passenger alteration.

The implications of this work go beyond identifying KDM6A as a potential biomarker, providing a mechanistic rationale to explain how an identical genomic alteration can impart dichotomous clinical consequences in different therapeutic contexts. Singh *et al.* therefore examined whether KDM6A loss could promote cisplatin resistance through eccDNA accumulation and amplification of cisplatin-resistance-associated loci[5]. In fact, several cisplatin-resistance-associated loci, including tumor protein p63 (*TP63*), claudin-4 (*CLDN4*), GLI family zinc finger 2 (*GLI2*), LUC7-like 3 pre-mRNA splicing factor (*LUC7L3*), ERCC excision repair 4, endonuclease catalytic subunit (*ERCC4*), and SHC SH2-domain binding protein 1 (*SHCBP1*), were enriched or amplified in KDM6A-deficient cells[5].

Importantly, these loci were identified through joint analyses of circular-amplicon and copy-number data, and the individual functional contribution of each locus to cisplatin resistance was not validated in the same report. Hence, these eccDNA-associated loci should still be regarded as candidates rather than established cisplatin-resistance drivers.

## DNA REPAIR DEFECTS AND IMMUNOTHERAPY-ASSOCIATED VULNERABILITY

In contrast to eccDNA-mediated chemoresistance, KDM6A loss additionally induces an immunotherapy-sensitizing state by disrupting DNA repair programs. Singh *et al.* demonstrated that, in bladder cancer, KDM6A regulates genes involved in DNA repair, such as MutS homolog 2 (*MSH2*), MutS homolog 6 (*MSH6*), and exonuclease 1 (*EXO1*), via changes in H3K27me3 and H3 lysine 4 trimethylation (H3K4me3) at their promoters[5]. KDM6A depletion increased repressive H3K27me3 and reduced the activating H3K4me3 mark at these promoter regions, which may limit the function of mismatch repair (MMR) and double-strand break repair[5].

Functionally, these repair defects resulted in increased tumor mutational burden and DNA damage[5]. Deficient DNA repair and a high TMB may increase the likelihood of responsiveness to ICB, but these features do not appear to be sufficiently specific as sole determinants of sensitivity, since TMB only partially captures the larger cumulative immune, stromal and transcriptional programs that determine checkpoint blockade success in bladder cancer[3]. KDM6A loss gives rise to two opposing phenomena relevant to therapeutic response: eccDNA-associated oncogene and copy-number amplification driving cisplatin

resistance, versus defective DNA repair, which could promote mutational and neoantigen load, potentially enhancing the immunogenicity of tumors and ICB sensitization[5]. Taken together, these findings indicate that TMB-associated signals alone cannot be regarded as stand-alone predictors of bladder cancer response to ICB, but rather should be considered in combination with DNA repair status, immune and stromal contexture, and KDM6A-linked metabolic rewiring for clinically oriented stratification[3,5].

Although the KDM6A mutation was associated with poor outcomes after cisplatin treatment, PD-1/PD-L1 blockade enhanced survival[5]. This bidirectional association illustrates how identical molecular changes can have completely different biological effects, as determined by the selection pressure exerted by therapy. Chemotherapy may select for resistant clones with increased genomic plasticity, whereas DNA repair defects can increase neoantigen burden and thereby enhance the immunogenic potential of these tumors[5].

## IMMUNOMETABOLIC REWIRING OF THE TUMOR MICROENVIRONMENT

In addition to DNA repair defects, this immunotherapy-sensitizing arm was also associated with metabolic alterations, since KDM6A loss was related to reduced glucose catabolism and lactate production in bladder cancer cells and tumors[5]. Importantly, recent findings have shown that lactate is not only an end product of glycolysis but can also enter Tregs via monocarboxylate transporter 1 (MCT1). More generally, lactate may regulate chromatin-level transcriptional programs in the immune system, including through histone lactylation[7-9]. This pathway facilitates PD-1 induction in Tregs and further enhances the immunosuppressive properties of Tregs in lactate-enriched glycolytic tumor microenvironments[8,9].

In line with this lactate-uptake and chromatin-regulatory axis, Singh *et al.* found that KDM6A depletion led to reduced levels of H3 lysine 9 lactylation (H3K9la) and H3 lysine 18 lactylation (H3K18la) in Tregs, downregulating the expression of immunoregulatory genes including *Foxp3*, *Tgfb*, and *Pdcd1*. PD-1 blockade enhanced the $CD8^+$ effector T cell/Treg cell ratio while limiting the induction of $PD\text{-}1^{hi}$ Tregs[5]. Together, the results provide evidence that KDM6A affects immunotherapy responsiveness not only through mutational burden, but also in a lactate-dependent manner through immunoepigenetic regulation. Loss of KDM6A thus provides a mechanistic connection among genetic deregulation, genome instability and immunometabolic remodeling in bladder cancer. Figure 1 summarizes this integrated framework linking KDM6A-dependent chromatin regulation, genomic instability, immunometabolic remodeling and therapy-specific response patterns.

## THERAPEUTIC STRATIFICATION AND CLINICAL PERSPECTIVES

The findings described above emphasize that metabolic rewiring and epigenetic regulation are not independent processes but work together to rewire the immune microenvironment in tumors[7,9]. Metabolites are considered not only intermediates of cellular energetics but also epigenetic substrates that can directly influence immune-cell fate. The enhancer-regulatory function of KDM6A and its impact on lactate-dependent Treg suppression place it at the center of this regulatory axis, in which chromatin dynamics, metabolic circuitry, and immune signaling jointly shape tumor behavior across therapeutic contexts[5,6].

This concept may have implications for precision medicine in bladder cancer. ICB, antibody-drug conjugates, and combination regimens are now being used in earlier lines of treatment for advanced urothelial carcinoma after a rapid evolution of the treatment landscape in recent years[1,2]. More generally, this transition also resonates with broader efforts to move beyond single-marker decision-making in cancer research and management, including new checkpoint targets and therapeutic combinations, migrasome-associated lncRNA risk stratification and immune-landscape assessment in bladder cancer, and physical-property-based approaches to cancer diagnosis and treatment design[10-12]. PD-L1 immunohistochemistry

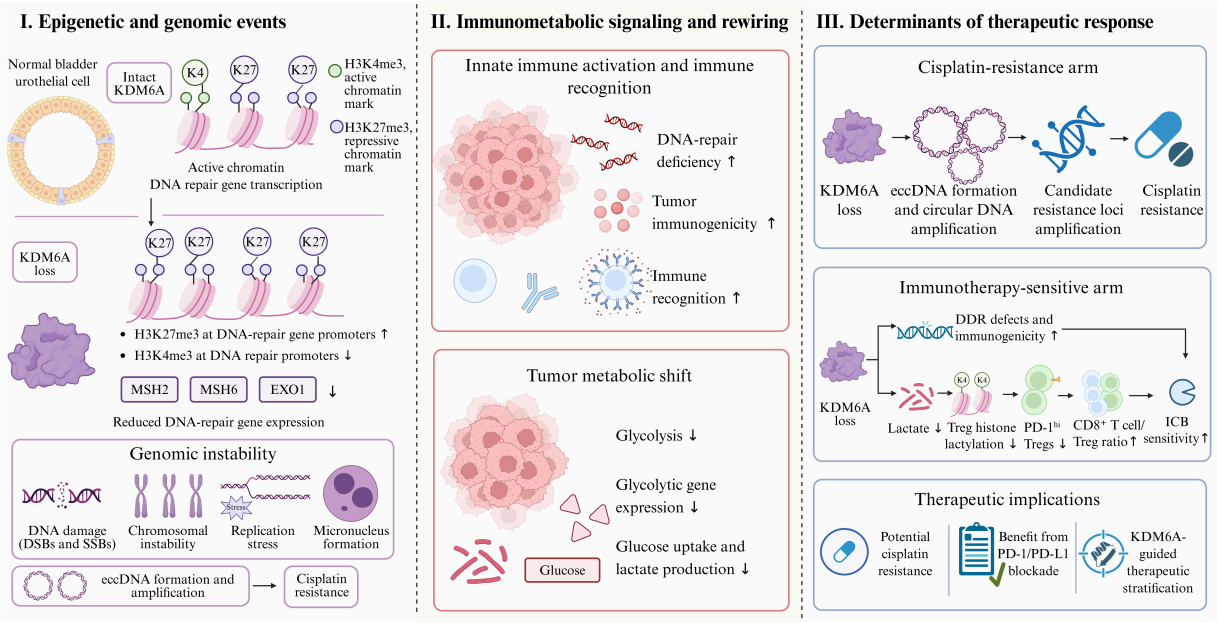


**Figure 1.** KDM6A loss links genomic instability, immunometabolic remodeling and therapeutic response in bladder cancer. (I) KDM6A promotes chromatin accessibility by inhibiting repressive H3K27me3 and increasing the transcription of DNA repair genes. Increased deposition of H3K27me3 and decreased deposition of H3K4me3 at DNA repair gene promoters due to KDM6A loss downregulate the expression of *MSH2*, *MSH6,* and *EXO1*. These alterations contribute to DNA repair deficiency, DNA damage, chromosomal instability, replication stress, as well as the formation of micronuclei and eccDNA; (II) Genomic instability might enhance the immunogenicity and immune detection of tumors, whereas KDM6A loss is also associated with reduced glycolysis, glycolytic gene expression, glucose uptake, and lactate production; (III) These changes distinguish two separable therapeutic consequences of KDM6A loss. The genomic-instability arm associated with eccDNA may favour amplification of candidate resistance loci and contribute to cisplatin resistance. Conversely, DNA repair defects and lactate-dependent immunometabolic rewiring may confer sensitivity to immune checkpoint blockade (ICB), especially PD-1/PD-L1 blockade, due to decreased Treg-cell histone lactylation, which limits the expansion of PD-1$^{hi}$ Tregs and increases the CD8$^{+}$ T-cell/Treg ratio. Created in BioRender. Zhang H (2026) https://BioRender.com/fnuhatw.

(IHC) and TMB remain poor stand-alone predictive markers in bladder cancer, as they do not accurately capture the relevant immune, stromal, and metabolic programs dictating the tumor microenvironment[3]. In this context, the biological significance of KDM6A loss might extend beyond its role as a predictive marker of immunotherapy sensitivity towards defining a biologically distinct tumor state characterised by enhanced genomic plasticity and a diminished lactate-driven Treg-suppressive microenvironment surrounding these tumors[5].

Thus, a translational pathway would be to evaluate KDM6A mutation status using targeted sequencing, including truncating mutations, missense mutations, and copy-number loss, as well as IHC for low or absent KDM6A protein expression, since sequence-level alterations may not be concordant with protein-level loss, which has potential therapeutic implications[5,13]. Although IHC may be a practical screen at the protein level, next-generation sequencing (NGS) is important for detecting genomic signatures that can be relevant to DNA repair deficiency, microsatellite instability (MSI)/TMB status and broader biomarker stratification[14]. Finally, since biomarker discovery, subtype-related interpretation and treatment-response modelling in cancer research using bulk transcriptomic datasets can be affected by technical biases and biological confounders, conclusions derived from such datasets should be interpreted cautiously[15]. Accordingly, KDM6A-guided stratification should be performed along with both genomic and protein-level assessment, integrating TMB, PD-L1 expression, and immunometabolic features, and should be validated in prospective biomarker-stratified cohorts prior to routine clinical application. Cisplatin-first strategies may require careful consideration in KDM6A-deficient tumors, whereas earlier PD-1/PD-L1 blockade or rational combination strategies may merit prospective testing in biomarker-stratified cohorts[1,2,5].

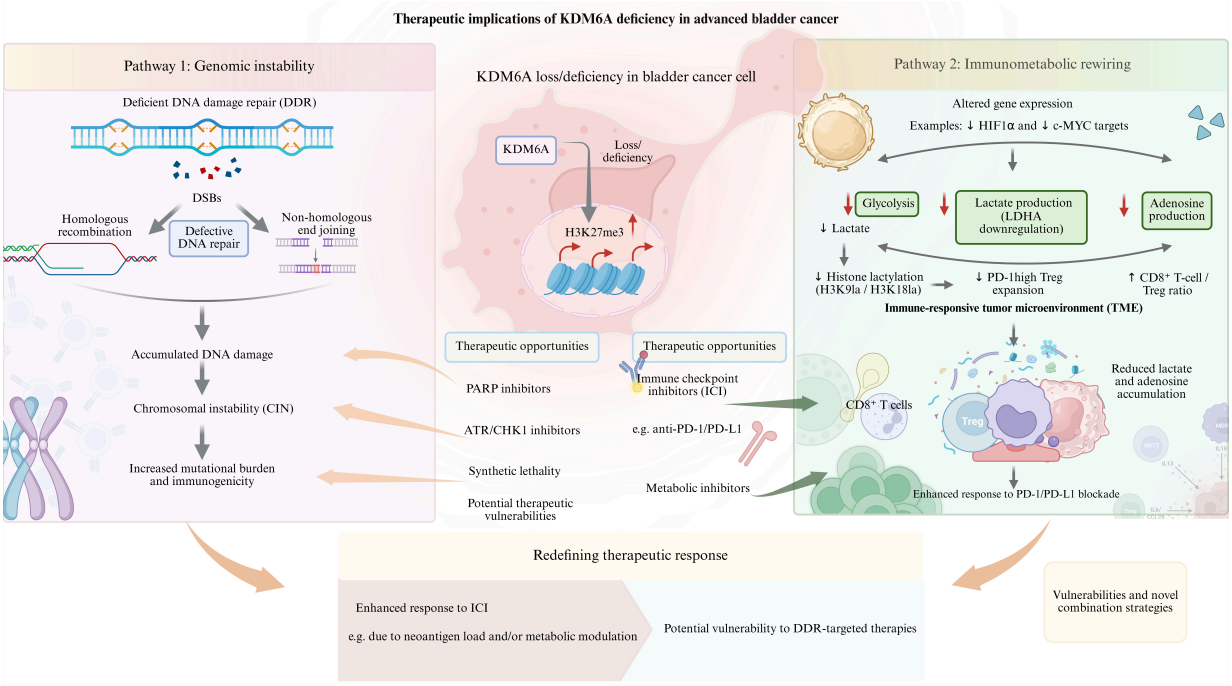


**Figure 2.** Therapeutic implications of KDM6A deficiency in advanced bladder cancer. Two biologically relevant disease trajectories occur with KDM6A deficiency. First, impaired DNA damage repair results in accumulated DNA damage, chromosomal instability, and an increased mutational burden; this may promote tumor immunogenicity but also renders tumors susceptible to DDR-targeted strategies, including poly(ADP-ribose) polymerase (PARP) inhibition, ataxia telangiectasia and Rad3-related protein/checkpoint kinase 1 (ATR/CHK1) inhibition, and synthetic lethal approaches. Second, KDM6A loss elicits immunometabolic rewiring characterized by reduced glycolysis, reduced lactate production, decreased histone lactylation in Tregs, reduced expansion of PD-1$^{hi}$ Tregs, and an elevated CD8$^+$ T-cell/Treg ratio. These alterations could help explain enhanced responses to PD-1/PD-L1 blockade. KDM6A status, in combination, may further refine therapeutic stratification across chemotherapy, immunotherapy, and rational combination strategies in advanced bladder cancer. Created in BioRender. Zhang H. (2026) https://BioRender.com/79m73os. DSBs: DNA double-strand breaks; DDR: DNA damage repair; HIFα: hypoxia-inducible factor 1 alpha; c-MYC: cellular myelocytomatosis oncogene.

## CONCLUSION AND PERSPECTIVES

Although the study by Singh *et al.* provided an important basis for connecting KDM6A to genome stability, metabolic rewiring, and immuno-oncology response, its clinical relevance still needs to be confirmed because current evidence is largely retrospective and the functional heterogeneity of different KDM6A alterations remains unexplored[5]. Whether these mechanisms are conserved across molecular subtypes of muscle-invasive bladder cancer remains unclear. KDM6A alteration enrichment, immune and stromal contexture, and treatment-associated vulnerabilities may differ among molecularly defined urothelial tumors with luminal-, basal- and neuroendocrine-like properties[3,4]; thus, KDM6A-guided stratification should be validated in subtype-defined bladder cancer cohorts rather than in bladder cancer as a single entity.

These results support the concept that therapeutic response in bladder cancer cannot be explained solely by a single biomarker or therapeutic context but instead reflects an interplay among chromatin state, DNA repair capacity, metabolic architecture and the tumor immune microenvironment[5]. KDM6A could therefore be a crucial junction in this interaction network, providing a biological basis for precision therapy stratification. KDM6A status may function not only as a prognostic biomarker but also as a potential indicator for therapy stratification; however, the significance of KDM6A alterations may differ across chemotherapy, immunotherapy, and rational combination strategies. These therapeutic implications are summarized in Figure 2.

## DECLARATIONS

### Author contributions

Contributed to the manuscript writing and figure preparation: Guo Y, Song L

Designed and supervised the work: Zhang H, Zhang W
All authors read and approved the final manuscript.

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Not applicable.

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All authors declared that there are no conflicts of interest.

## Ethics approval and consent to participate

Not applicable.

## Consent for publication

Not applicable.



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