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Implications of Chromatin Modifier Mutations in Epigenetic Regulation of Bladder Cancer

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Abstract: Chromatin deregulation is an emerging theme in cancer pathogenesis, and bladder cancer stands out among many other cancer types with frequent mutations of genes involved in epigenetic regulation. Defects in chromatin-level regulation can be manifested at multiple levels such as changes in DNA methylation, histone methylation patterns, and non-coding RNAs. Chromatin modifiers mutated in bladder cancer, such as *KDM6A*, *KMT2D*, *KMT2C*, *ARID1A*, *EP300*, have been studied in bladder cell line models. Also, there are studies that mapped the active regulatory landscape of bladder cancer and histone modification profiles. Collectively, existing literature emphasizes the importance of a thorough understanding of epigenetic deregulation in bladder cancer. The epigenetic signatures of bladder cancer can be targeted via epigenetic drugs or other genome editing tools, ultimately bringing specific treatment options for this cancer.

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This chapter provides an overview of the epigenetic modifications in bladder cancer, and the potential of epidrugs for the treatment of bladder cancer.

Keywords: chromatin modifiers in bladder cancer; epidrugs for bladder cancer; epigenetics in bladder cancer; histone methylation in bladder cancer; mutations in bladder cancer

INTRODUCTION

Cancer is a complex disease with many hallmarks (1). During the last decade, there has been a tremendous effort to characterize the genomic landscape and to identify molecular subgroups of diverse cancer types (2–4). All these molecular studies made it clear that epigenetic deregulation was a common theme implicated in tumorigenesis. It became apparent that proper epigenetic regulation is essential for normal cellular homeostasis and any deviation from this tightly regulated balance disrupts the cellular states and may result in tumor formation (5, 6). Among all the other cancers, bladder cancer has an exceptionally high rate of chromatin modifier mutations (7), and thus considered as a disease where epigenetic deregulatory mechanisms play a fundamental role. Bladder cancer mostly originates from the urothelium and causes over 200,000 deaths each year (8). Its main classification is done based on histopathology as non-muscle invasive bladder cancer (NMIBC) and muscle invasive bladder cancer (MIBC). Recent studies characterized the mutational landscape of both MIBC and NMIBC and further identified the consensus molecular subgroups, providing fundamental insights about the pathogenesis of bladder cancer (9–12). However, there is still need for further studies to characterize the epigenetic deregulation of bladder cancer in detail and use this information for specific diagnosis and treatment of bladder cancer. This chapter mainly focuses on the chromatin modifiers frequently mutated in bladder cancer, the major regulatory mechanisms disrupted, and the potential use of epigenetic therapies in bladder cancer.

EPIGENETIC REGULATION AND CANCER

To understand and explain the origin and characteristics of the cancer, several theories have been proposed throughout the years. “Hallmarks of cancer” proposed by Hanahan and Weinberg conceptualizes and organizes the principles in a logical framework (1). All hallmarks and characteristics define functional properties acquired by normal cells in the way of progressive transformation from normal state to neoplastic state (6, 13). Acquisition of hallmarks depends on alterations in the genome, epigenetic reprogramming, and microenvironmental remodeling. In addition to genetic alterations, epigenetic modifications contribute to gene expression deregulation in cancer. Aberrations in epigenetic mechanisms, such as DNA methylation, histone modifications, deregulation in non-coding RNAs (miRNA, lncRNA), play an important role in tumorigenesis

contributing to the different hallmarks of cancer (14, 15). These epigenetic deregulations may result in inappropriate activation or inhibition of gene expression.

DNA methylation occurs at cytosine residues at CpG dinucleotides. While CpG dinucleotides spread throughout the genome, CpG islands (CGIs) are located at 5' regulatory regions, such as promoter of genes. Promoter DNA methylation is associated with repression of transcription (16, 17). In human cells, 3 different DNA methyltransferases (DNMT1, DNMT3A, and DMT3B) catalyze the transfer of methyl group to cytosine residue (18). Aberrations in the maintenance of the DNA methylation are critical for tumorigenesis. Global hypomethylation and the promoter hypermethylation are the characteristics of the cancer epigenome and contribute to the overexpression of protooncogenes and the silencing of tumor suppressor genes, respectively (19, 20). Oncogenic signaling pathways also direct the activity of global methyltransferases which contributes to the shift from normal to cancer-specific methylation profile (15). Alterations in the DNA methylation have been known as early event in bladder cancer development and are considered as a hallmark of cancer (21).

In a eukaryotic nucleus, DNA is wrapped around the histone octamers forming nucleosome structure. N-terminal tails of core histone protein (H2A, H2B, H3, and H4) are largely targeted for the posttranslational modifications (PTMs), such as methylation, acetylation, and phosphorylation (16). Modifications in histone tails affect the chromatin structure which is critical for the gene regulation (22). Chromatin structure is highly dynamic, and orchestrated by chromatin remodeling complexes, and histone modifying enzymes. Aberrations in histone modification caused by defects in activity of histone modifying enzymes and chromatin remodeling complexes may contribute to the neoplastic transformation (23). Mutations in histone genes or chromatin modifier proteins are frequently detected in many cancer types, resulting in impairments in gene expression programs and genomic integrity (24) (Figure 1).

CHROMATIN MODIFIERS FREQUENTLY MUTATED IN BLADDER CANCER

To advance our understanding on the molecular landscape of cancer, large-scale genome wide studies, especially the TCGA project, collected data on gene expression, transcript splice variation, protein expression, DNA copy number alterations, somatic mutation, DNA methylation, and gene fusion, and also clinicopathological data from many cancer types, including bladder cancer (11, 25). Integrated omics studies have revealed that, with five or more mutations per megabase, bladder cancer has a higher mutational burden compared to the other cancer types (10, 11, 25, 26). The most common mutations in bladder cancer occur in genes functioning in histone modification and chromatin remodeling genes. These include *ARID1A* (25%), *KDM6A* (24%), *KMT2D* (27%), *EP300* (15%) (27). Globally, almost 80% of all bladder cancer patients have mutations in genes involved in epigenetic regulation, demonstrating the high degree of epigenetic dysregulation in this cancer (28). It is also important to the notice that chromatin modifiers

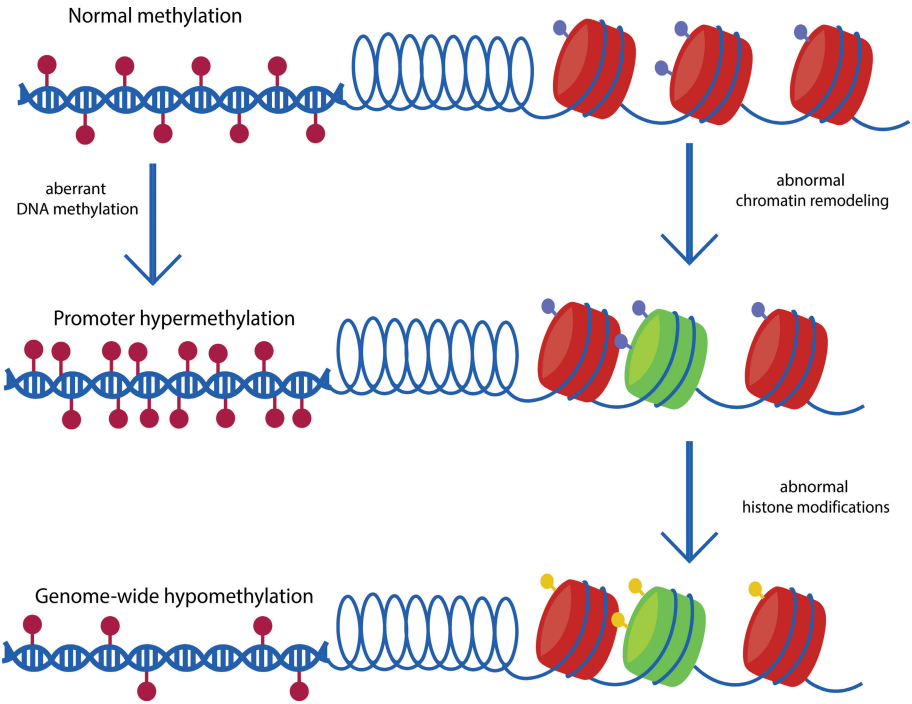

Figure 1. The landscape of epigenetic deregulations in cancer. During the tumorigenesis, DNA methylation in promoter regions is induced, while genome-wide DNA methylation is downregulated. Cancer cells exhibit disrupted histone tail modifications and chromatin organization.

mutated in bladder cancer mostly function in active chromatin organization and activation of gene expression. In this context, it might be speculated that chromatin modifier mutations in bladder cancer results in a closed chromatin configuration, likely prohibiting the expression of genes required for urothelial differentiation while resulting in gene expression programs supporting proliferation and tumorigenesis (Figure 2).

EPIGENETIC LANDSCAPE OF BLADDER CANCER

As already mentioned, aberrations in the epigenetic landscape are one of the hallmarks of cancer and abnormalities in DNA methylation, chromatin modifier mutations, and altered gene expression of chromatin modifiers and non-coding RNAs result in changes in cellular characteristics and promote the unfavorable prognosis. The association between epigenetic landscape and gene expression in bladder cancer has been addressed in several studies (10, 11, 29). One study defined the genome-wide chromatin accessibility profiles and cancer-specific DNA regulatory elements across 23 cancer types from TCGA (including bladder cancer) and

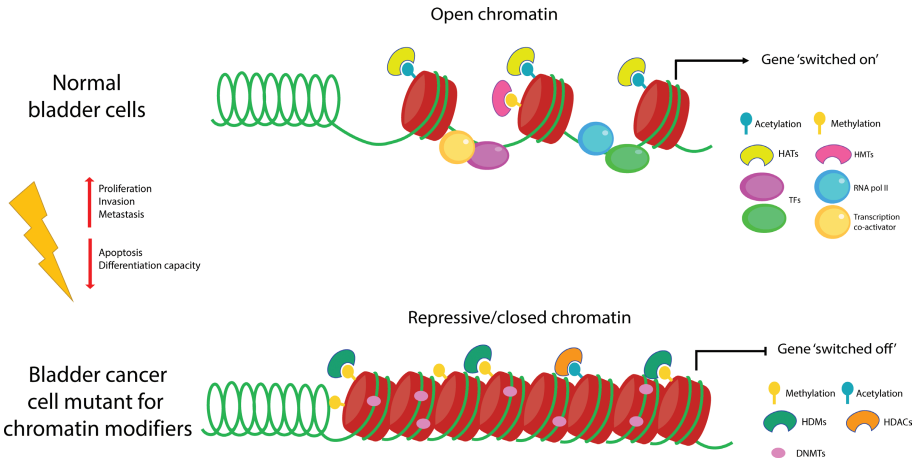

Figure 2. Chromatin modifier mutations contribute to neoplastic transformation of bladder cells. Mutations in chromatin modifying genes direct the shift from active chromatin organization to repressive state. DNMT, DNA methyltransferase; HAT, histone acetyltransferase; HDAC, histone deacetylase; HDM, histone demethylase; HMT, histone methyltransferase; RNA pol II, RNA polymerase II; TF, transcription factor.

identified significant correlations between gene expression and chromatin accessibility, integrating transcriptomics data and ATAC-seq (the assay for transposase-accessible chromatin using sequencing). Besides, this study demonstrated impressive similarity between ATAC-seq based clustering and previously established mRNA, miRNA, DNA methylation or copy number variation (CNV) profile-based classifications. In this study, it has been also revealed that a somatic mutation observed in one regulatory region of bladder cancer increases chromatin accessibility and changes gene expression in mutant bladder cancer (29).

To further extend the knowledge on epigenomic landscape of bladder cancer, van der Vos et al. (10) conducted a study on genome-wide histone methylation profiling of MIBC (10). Integrated analysis of the H3K27me3, a repressive histone mark, and H3K4me1 and H3K4me3 (gene-activating histone marks) ChIP-seq and RNA-seq data indicated that different enhancer regions play critical role in the characterization of luminal and basal subtypes of MIBC.

Non-coding RNAs, such as microRNAs (miRNA), long non-coding RNAs (lncRNA), circular RNAs (circRNA), piwi-interacting RNAs (piRNA), small nuclear RNA (snRNA), and small nucleolar RNAs (snoRNA), are not translated into proteins, but they have still significant functions in every cellular process. NcRNAs also contribute to the epigenetic alterations that promote bladder cancer development and progression (30).

Prognostic biomarker potential of DNA hypermethylation has been widely investigated in bladder cancer (31, 32). Yet, further investigation is necessary to obtain more sensitive and specific biomarkers. It has been identified that CpG-rich transposons, such as LINE1, are hypomethylated in bladder cancer types. This leads to retrotranspositions inducing genomic instability (33). A recent study investigated global histone acetylation levels and its prognostic value in bladder

cancer patients and reported decreased H3 acetylation level in both NMIBC and MIBC patients compared to normal urothelial control group (34).

Histone deacetylases (HDACs) are divided into different classes based on their similarity to yeast HDACs (35). Another study reported that HDAC-1, HDAC-2, and HDAC-3 expression levels are elevated in urothelial carcinoma. Notably, increased HDAC-1 and HDAC-2 levels were associated with high grade tumors. Moreover, high grade tumors with high HDAC-1 expression correlated with worse prognosis compared to low grade tumors (36). This finding supports the therapeutic target potential of HDACs. Another study identified the chromatin interactions by Hi-C, integrating it with transcriptome and enhancer profiles in luminal and basal types of bladder cancer. Even though the study implicated the association between epigenomic landscape and 3D genome structure in a subtype-specific manner, further studies are needed to comprehensively unveil the molecular basis and involved factors (37).

FUNCTIONAL OUTCOMES OF CHROMATIN MODIFIER MUTATIONS IN BLADDER CANCER

Given the high rate of chromatin modifier mutations in bladder cancer, there have been many studies investigating the functional impact of the mutations in different model systems (Table 1) (38–46). Polycomb repressive complex 2 (PRC2)-dependent epigenetic regulation is critical for cell differentiation and proliferation in bladder urothelium (47). SWI/SNF complex acts as an antagonist of PRC2 complex promoting the expression of genes which are silenced by PRC2 (48).

TABLE 1 **Key functional outcomes associated with the chromatin modifier mutations in bladder cancer**

Mutation/loss of function	Functional outcome	Reference
ARID1A	Impairments in cell cycle Genomic stability Induced cell proliferation	(38, 39)
KDM6A	Induced tumor immune escape Activation of proinflammatory pathways Induced proliferation Deregulation in the expression of cell identity related genes	(40–43)
KMT2C	Increased chromatin instability Impairments in DNA replication and repair Misregulation of apoptosis, and cell cycle control	(44)
KMT2D	Impairments in DNA replication and cell cycle Induced invasion, migration, and viability	(45, 68)
CBP/EP300	Impairments in histone acetylation Increased anti-tumor immunity	(46)

ARID1A belongs to SWI/SNF complex proteins (49), and it is frequently mutated in primary human bladder carcinoma (25). ARID1A has role in the tumor suppressor mechanisms regulating cell cycle progression and maintaining genomic stability (38).

ARID1A protein loss is predominantly observed in high grade and high stages of bladder tumors that indicates association with poorer prognosis (39, 50). The potential functions of ARID1A have been investigated in urothelial cells of ARID1A knockout mice. It has been shown that loss-of-function mutation in ARID1A upregulates urothelial cell proliferation, emphasizing the tumor suppressor role of ARID1A in bladder cancer development (39). Additionally, findings implicated an antagonistic relationship between ARID1A and PRC2 complex in bladder (51). However, function of ARID1A might be context-dependent since different studies addressed opposing roles for ARID1A in different cellular processes and cancer types (52).

KDM6A (UTX), lysine histone demethylase, physically interacts with chromatin modifying enzymes, such as KMT2C (MLL3) and KMT2D (MLL4) (53). KDM6A protein contains tetratricopeptide repeat (TPR) domains and Jumonji C (JmjC) domain. JmjC domain catalyzes the removal of the methyl group from H3K27me2 and H3K27me3 (53, 54). TPR domain conducts interaction with components of MLL3 and MLL4 complexes (55). The function of KDM6A has been the subject of numerous studies. These studies reported that KDM6A regulates gene expression and cellular processes. As a component of the COMPASS complex, KDM6A is involved in regulation of gene activation (56–58). Loss-of-function and inactivating mutations frequently occur in several neoplasms, including bladder tumors (59–62). Reduced KDM6A expression and KDM6A mutations is correlated with poor prognosis in bladder cancer (40). Furthermore, potential roles of KDM6A in immune response have been shown via TIMER and CIBERSORT algorithms. Gene set enrichment analyses have indicated that the signaling pathways involved in immunity have been repressed in patients with mutated KDM6A. These findings imply the relationship between KDM6A mutations and anti-tumor immunity (40). In another study, Kobatake et al. showed that decreased expression of KDM6A is associated with the activation of proinflammatory pathways (41). Increased proliferation has been observed in two different KDM6A knock-out bladder cell lines (42). Notably, KDM6A has a role in safeguarding luminal gene expression program in bladder cancer cell lines (43).

Studies focused on the function of KMT2C (MLL3, histone lysine methyltransferase 2C) in normal cells defined its role in regulation of enhancer activity, focusing on the profile of H3K4me1 mark (63, 64). Independent from its H3K4me activity, the roles of KMT2C in transcription regulation have been shown in recent reports (65, 66). Tumor suppressor role of KMT2C has been reported for urothelial carcinoma. KMT2C silencing in 2 different bladder cancer cell lines has been shown to directly or indirectly affect the expression of genes involved in cell cycle control, DNA repair, DNA replication, and apoptosis (44). To investigate its further effects, genome-wide binding profile of KMT2C has been mapped via ChIP-seq (44). To evaluate the effects of KMT2C on epigenetic landscape of bladder cancer, Rampias et al. (44) also studied the changes in H3K4me3, H3K27ac, and H3K9ac histone modifications upon KMT2C silencing. Knockdown of KMT2C influences the enhancer activity in bladder cancer cell lines. In parallel with its well-established role in deposition of H3K4me1, co-localization of KMT2C with

active enhancer mark H3K27ac points out the increased enhancer activity (44). Additionally, KMT2C loss affects expression of genes critical for cell adherence, extracellular organization, and epithelial differentiation (44).

KMT2D (also known as MLL4) is one of the histone methyltransferases that may play a critical role in tumorigenesis and progression of bladder cancer (63). KMT2D regulates the activity of H3K4 methylation (67). KMT2D has high mutation rates in bladder cancer. Low levels of KMT2D are associated with lymph node metastasis (68). KMT2D mRNA and protein expression is decreased in 4 bladder cancer cell lines (T24, J82, UM-UC-3, and HTB-9) compared to normal bladder cell line. Silencing of KMT2D induces invasion in T24, and HTB-9 cell lines, while its overexpression suppresses. It has been demonstrated that KMT2D regulates level of H3K4me1 in bladder cell lines (68). Interestingly, while Sun et al (68) showed association between higher KMT2D expression and higher survival rate, Ding et al (45) implied that KMT2D mutations are associated with better prognosis in bladder tumors. Gene set enrichment analysis has indicated that KMT2D mutations are also significantly associated with cell cycle and DNA replication processes (45).

CREB-binding protein (CREBBP or CBP) and E1A binding protein (EP300 or P300) are transcriptional coactivators which also have ubiquitin ligase activity and histone acetyltransferase activity (69). CBP and EP300 are frequently mutated in a variety of human tumors (70). These inactivating alterations resulting in deregulation of acetylation and neoplastic transformation have been investigated in tumor models and bladder cancer lines (71, 72). Duex et al. (71) defined that those mutations are largely enriched at histone acetyltransferase domains of EP300 and CBP, implying potential significance of the domain activity on tumorigenesis. They also postulated that impairments in histone acetyltransferase activity are more likely to be linked with aggressive, MIBC cases (71). It was also identified that mutations in *EP300* promote the signaling pathways involved in anti-tumor response in bladder cancer (46).

MANIPULATING CHROMATIN MODIFIER MUTATIONS FOR TREATMENT OF BLADDER CANCER

New strategies and options for diagnosis and treatment of bladder cancer are needed to augment pharmacological outcome. The utilization of epigenetics for diagnostic markers and therapy targets is a rapidly developing and promising area. The reversibility of epigenetic changes serves a great potential as a therapeutic target in bladder cancer. Improvement of epidrugs has great advantage for cancers or disease in which epigenetic dysregulation plays a key role (Figure 3) (73).

Inhibiting the DNMT enzymes, gene silencing can be reversed, and in turn expression of tumor suppressor genes is recovered. It has been revealed that 5-Aza-2′-Deoxycytidine (DAC), DNMT inhibitor, induces cell cycle arrest, and increases the susceptibility to chemotherapy in bladder tumors (74). 5-aza-2′-deoxycytidine and 5-azacytidine are approved for treatment of myelodysplastic syndrome and myeloid leukemia by the FDA. There are ongoing clinical trials for use in bladder cancer therapy (75).

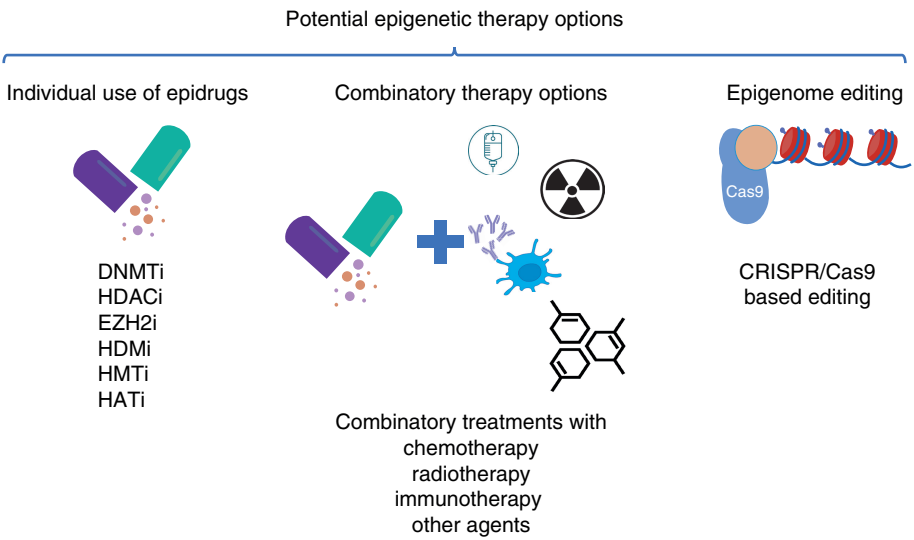

Figure 3. Epigenetic therapy options for cancer treatment. Epidrugs can be used alone or in combination with the other treatments. Epigenome editing technologies are also emerging alternatives for cancer therapy. DNMTi, DNA methyltransferase inhibitors; EZH2i, EZH2 inhibitors; HATi, histone acetyltransferase inhibitors; HDACi, histone deacetylase inhibitors; HDMi, histone demethylase inhibitors; HMTi, histone methyltransferase inhibitors.

Several HDAC inhibitors show promise in urological cancers (76). It has been demonstrated that cellular growth and proliferation is inhibited upon the treatment of bladder cancer cells with HDAC inhibitors Vorinostat, Romidepsin, and Trichostatin A (77, 78). Further analyses showed that changes in the protein expression are mostly associated with apoptosis, regulation of cell cycle, and DNA damage repair mechanisms in response to treatment with these HDAC inhibitors (78). HDAC inhibitors Romidepsin, have been approved by FDA for treatment of cutaneous T cell lymphoma (CTCL), while Belinostat and Panobinostat approved for the treatment of T cell lymphoma (79). In combination with the other chemotherapy agents, HDAC inhibitors synergistically affect the cell cycle arrest, apoptosis, and differentiation of malignant cells (30, 80). It has been shown that combination of DNMT inhibitor and HDAC inhibitors has also synergistic effect on cancer cells (76).

Increased expression levels of G9a, H3K9 methyltransferase, have been detected in bladder cancer. Inhibition of G9a in bladder cancer suppresses the proliferation inducing autophagic cell death in bladder cancer cells (81). Treatment of bladder cancer cell lines with small molecule UNC064, G9a inhibitor, decreases the cell viability, while inducing the apoptosis (82).

As a catalytic subunit of PRC2 complex, histone methyltransferase EZH2 regulates trimethylation of H3K27 (H3K27me3) (83). This histone mark is critical for repression of gene expression. An increasing number of evidence demonstrated that EZH2 dictates both development and progression of different types of tumors.

Dysregulation in EZH2 expression has been associated with increased cell proliferation, invasion, and metastasis (84). Notably, it has been reported that EZH2 is also linked with the chemotherapy resistance (85). Upregulated expression of EZH2 plays oncogenic roles in bladder cancer. Since it affects the gene expression and regulates the several cellular mechanisms, EZH2 serves a great potential as target for treatment (86). Currently, EZH2 inhibitor Tazemetostat is being investigated in ongoing clinical trials for treatment of urothelial carcinoma, in addition to lymphomas, and other solid tumors (87–89).

Therapeutic targeting of epigenetic modifiers which are currently in clinical trials (https://www.clinicaltrials.gov/) is summarized in Table 2. In a review, Ozgun et al. (28) evaluated the combination of EZH2 inhibitors or HDAC inhibitors with retinoids in bladder carcinoma. They pointed out the potential therapeutic options with retinoic acid and its derivatives and emphasized the clinical trials investigating combinatorial use of retinoids with epidrugs (28).

Another type of epigenetic therapy is based on miRNA manipulation. Strategies basically focus on regulation of the miRNA expression and activity in cancer cells (75, 90). This manipulation is managed via mimicking the specific miRNAs (91) or administration of epidrugs, such as EZH inhibitors (92, 93).

CRISPR/Cas9 system has become widely used technology for genome targeting. Due to the technical improvements, targeted epigenome editing can be achieved using CRISPR platform (94). The fusion of dCas to chromatin-modifying domains represents a powerful tool for chromatin editing (95). Epigenome editing is achieved in human cells through CRISPR activation and inhibition systems (CRISPRa/CRISPRi). These approaches can be applied for epigenetic reprogramming both in vivo and ex vivo, disease modeling, therapeutic targeting, and cellular therapies (94). Recent clinical studies have been performed CRISPR-based epigenome editing in human hematopoietic progenitor and stem cells for the treatment of an immune disease (96). Yet, there is a need for more effort to establish routine clinical use.

TABLE 2 Potential epidrugs for bladder cancer

Epidrug	Biological effect	Clinical trial	Combinatory therapies
5-Aza-2′-Deoxycytidine	DNMT inhibitor	Yes (Phase 2)	
5-azacytidine	DNMT inhibitor	Yes (Phase 1)	• Carboplatin • Paclitaxel
Vorinostat	HDAC inhibitor	Yes (Phase 2)	• Pembrolizumab • Docetaxel
Romidepsin	HDAC inhibitor	Yes (Phase 1, 2)	
Belinostat	HDAC inhibitor	Yes (Phase 2)	• Carboplatin • Paclitaxel • 5-Fluorouracil (5-FU)
Tazemetostat	EZH2 inhibitor	Yes (Phase 1, 2)	• Pembrolizumab

CONCLUSION

Mutations in chromatin modifying genes are highly frequent in bladder cancer (11). There have been plenty of studies which emphasize that epigenetic deregulations are critical for understanding of bladder cancer pathogenesis, characterization of phenotype, determination of disease outcome, and also for directing the treatment options. Clinical adoption of bladder cancer epigenetics is still in a developmental phase. Expanding our limited knowledge on epigenetics of urothelial malignancies will contribute to the improvements in diagnosis, and development of more precise targeted therapies. Drugs targeting epigenetic machinery, epigenetic biomarkers for diagnosis, and tailoring the epigenome state of cancer cells are the emerging fields in personalized medicine. Yet, implementation of epidrugs and epigenome editing to clinic still needs to overcome many challenges.

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REFERENCES

1. Hanahan D, Weinberg RA. The Hallmarks of Cancer. Vol. 100, Cell. 2000. https://doi.org/10.1016/S0092-8674(00)81683-9
2. Vogelstein B, Papadopoulos N, Velculescu VE, Zhou S, Diaz LA, Kinzler KW. Cancer Genome Landscapes [Internet]. Available from: www.sciencemag.org
3. Rheinbay E. The genomic landscape of advanced cancer. Nature Cancer. 2020 Apr;1(4):372–3. https://doi.org/10.1038/s43018-020-0057-z
4. Zhao L, Lee VHF, Ng MK, Yan H, Bijlsma MF. Molecular subtyping of cancer: Current status and moving toward clinical applications. Briefings in Bioinformatics. 2019 Mar 22;20(2):572–84. https://doi.org/10.1093/bib/bby026
5. Flavahan WA, Gaskell E, Bernstein BE. Epigenetic plasticity and the hallmarks of cancer. Vol. 357, Science. American Association for the Advancement of Science; 2017. https://doi.org/10.1126/science.aal2380
6. Hanahan D, Weinberg RA. Hallmarks of cancer: The next generation. Vol. 144, Cell. 2011. p. 646–74. https://doi.org/10.1016/j.cell.2011.02.013
7. Hoffmann MJ, Schulz WA. Alterations of chromatin regulators in the pathogenesis of urinary bladder urothelial carcinoma. Vol. 13, Cancers. MDPI; 2021. https://doi.org/10.3390/cancers13236040
8. Richters A, Aben KKH, Kiemeney LALM. The global burden of urinary bladder cancer: an update. Vol. 38, World Journal of Urology. Springer; 2020. p. 1895–904. https://doi.org/10.1007/s00345-019-02984-4

9. Lindskrog SV, Prip FF, Lamy P, Taber A, Clarice S. An integrated multi-omics analysis identifies clinically relevant molecular subtypes of non-muscle-invasive bladder cancer. 2020;
10. van der Vos KE, Vis DJ, Nevedomskaya E, Kim Y, Choi W, McConkey D, et al. Epigenetic profiling demarcates molecular subtypes of muscle-invasive bladder cancer. Scientific Reports. 2020 Dec 1;10(1). https://doi.org/10.1038/s41598-020-67850-5
11. Weinstein JN, Akbani R, Broom BM, Wang W, Verhaak RGW, McConkey D, et al. Comprehensive molecular characterization of urothelial bladder carcinoma. Nature. 2014;507(7492):315–22. https://doi.org/10.1038/nature12965
12. Kamoun A, de Reyniès A, Allory Y, Sjödahl G, Robertson AG, Seiler R, et al. A Consensus Molecular Classification of Muscle-invasive Bladder Cancer[Formula presented]. European Urology. 2020 Apr 1;77(4):420–33. https://doi.org/10.1016/j.eururo.2019.11.011
13. Hanahan D. Hallmarks of Cancer: New Dimensions. Vol. 12, Cancer Discovery. American Association for Cancer Research Inc.; 2022. p. 31–46. https://doi.org/10.1158/2159-8290.CD-21-1059
14. Ilango S, Paital B, Jayachandran P, Raghunathan Padma P, Nirmaladevi R. Epigenetic alterations in cancer. Vol. 25, Frontiers in Bioscience. 2020. https://doi.org/10.2741/4847
15. Darwiche N. Epigenetic mechanisms and the hallmarks of cancer: an intimate affair [Internet]. Vol. 10, Am J Cancer Res. 2020. Available from: www.ajcr.us/
16. Lu Y, Chan YT, Tan HY, Li S, Wang N, Feng Y. Epigenetic regulation in human cancer: The potential role of epi-drug in cancer therapy. Vol. 19, Molecular Cancer. BioMed Central Ltd.; 2020. https://doi.org/10.1186/s12943-020-01197-3
17. Greenberg MVC, Bourc'his D. The diverse roles of DNA methylation in mammalian development and disease. Vol. 20, Nature Reviews Molecular Cell Biology. Nature Publishing Group; 2019. p. 590–607. https://doi.org/10.1038/s41580-019-0159-6
18. Mohammad HP, Barbash O, Creasy CL. Targeting epigenetic modifications in cancer therapy: erasing the roadmap to cancer. Vol. 25, Nature Medicine. Nature Publishing Group; 2019. p. 403–18. https://doi.org/10.1038/s41591-019-0376-8
19. Baxter E, Windloch K, Gannon F, Lee JS. Epigenetic regulation in cancer progression. Vol. 4, Cell and Bioscience. BioMed Central Ltd.; 2014. https://doi.org/10.1186/2045-3701-4-45
20. Feinberg AP, Koldobskiy MA, Göndör A. Epigenetic modulators, modifiers and mediators in cancer aetiology and progression. Vol. 17, Nature Reviews Genetics. Nature Publishing Group; 2016. p. 284–99. https://doi.org/10.1038/nrg.2016.13
21. Jones PA, Issa JPJ, Baylin S. Targeting the cancer epigenome for therapy. Vol. 17, Nature Reviews Genetics. Nature Publishing Group; 2016. p. 630–41. https://doi.org/10.1038/nrg.2016.93
22. Kagohara LT, Stein-O'Brien GL, Kelley D, Flam E, Wick HC, Danilova L v., et al. Epigenetic regulation of gene expression in cancer: Techniques, resources and analysis. Vol. 17, Briefings in Functional Genomics. Oxford University Press; 2018. p. 49–63. https://doi.org/10.1093/bfgp/elx018
23. Zhao Z, Shilatifard A. Epigenetic modifications of histones in cancer. Vol. 20, Genome Biology. BioMed Central Ltd.; 2019. https://doi.org/10.1186/s13059-019-1870-5
24. Guo CC, Czerniak B. Bladder cancer in the genomic era. Archives of Pathology and Laboratory Medicine. 2019;143(6):695–704. https://doi.org/10.5858/arpa.2018-0329-RA
25. Robertson AG, Kim J, Al-ahmadie H, Weinstein JN, Kwiatkowski DJ, Lerner SP. Comprehensive Molecular Characterization of Muscle-Invasive Bladder Cancer Article Comprehensive Molecular Characterization of Muscle-Invasive Bladder Cancer. 2017;
26. Giannopoulou AF, Velentzas AD, Konstantakou EG, Avgeris M, Katarachia SA, Papandreou NC, et al. Revisiting histone deacetylases in human tumorigenesis: The paradigm of urothelial bladder cancer. Vol. 20, International Journal of Molecular Sciences. MDPI AG; 2019. https://doi.org/10.3390/ijms20061291
27. Knowles MA, Hurst CD. Molecular biology of bladder cancer: New insights into pathogenesis and clinical diversity. Vol. 15, Nature Reviews Cancer. Nature Publishing Group; 2015. p. 25–41. https://doi.org/10.1038/nrc3817
28. Ozgun G, Senturk S, Erkek-Ozhan S. Retinoic acid signaling and bladder cancer: Epigenetic deregulation, therapy and beyond. Vol. 148, International Journal of Cancer. John Wiley and Sons Inc; 2021. p. 2364–74. https://doi.org/10.1002/ijc.33374

29. Corces MR, Granja JM, Shams S, Louie BH, Seoane JA, Zhou W, et al. The chromatin accessibility landscape of primary human cancers. Science (1979). 2018 Oct 26;362(6413). https://doi.org/10.1126/science.362.6413.415-k
30. Porten SP. Epigenetic Alterations in Bladder Cancer. Vol. 19, Current Urology Reports. Current Medicine Group LLC 1; 2018. https://doi.org/10.1007/s11934-018-0861-5
31. Casadevall D, Kilian AY, Bellmunt J. The prognostic role of epigenetic dysregulation in bladder cancer: A systematic review. Vol. 61, Cancer Treatment Reviews. W.B. Saunders Ltd; 2017. p. 82–93. https://doi.org/10.1016/j.ctrv.2017.10.004
32. Bosschieter J, Lutz C, Segerink LI, Vis AN, Zwarthoff EC, van Moorselaar RJA, et al. The diagnostic accuracy of methylation markers in urine for the detection of bladder cancer: A systematic review. Vol. 10, Epigenomics. Future Medicine Ltd.; 2018. p. 673–87. https://doi.org/10.2217/epi-2017-0156
33. Kreimer U, Schulz WA, Koch A, Niegisch G, Goering W. HERV-K and LINE-1 DNA methylation and reexpression in urothelial carcinoma. Frontiers in Oncology. 2013;3 SEP. https://doi.org/10.3389/fonc.2013.00255
34. HDACs BC Ellinger et al, 2016.
35. Park SY, Kim JS. A short guide to histone deacetylases including recent progress on class II enzymes. Vol. 52, Experimental and Molecular Medicine. Springer Nature; 2020. p. 204–12. https://doi.org/10.1038/s12276-020-0382-4
36. Poyet C, Jentsch B, Hermanns T, Schweckendiek D, Seifert HH, Schmidtpeter M, et al. Expression of histone deacetylases 1, 2 and 3 in urothelial bladder cancer. BMC Clinical Pathology. 2014 Mar 13;14(1). https://doi.org/10.1186/1472-6890-14-10
37. Iyyanki T, Zhang B, Jin Q, Yang H, Liu T, Wang X, et al. Subtype-specific epigenomic landscape and 3D genome structure in bladder cancer. 2020;1–20. https://doi.org/10.1101/2020.02.26.966697
38. Wu RC, Wang TL, Shih IM. The emerging roles of ARID1A in tumor suppression. Vol. 15, Cancer Biology and Therapy. Landes Bioscience; 2014. p. 655–64. https://doi.org/10.4161/cbt.28411
39. Balbás-Martínez C, Rodríguez-Pinilla M, Casanova A, Domínguez O, Pisano DG, Gómez G, et al. ARID1A Alterations Are Associated with FGFR3-Wild Type, Poor-Prognosis, Urothelial Bladder Tumors. PLoS ONE. 2013 May 1;8(5). https://doi.org/10.1371/journal.pone.0062483
40. Chen X, Lin X, Pang G, Deng J, Xie Q, Zhang Z. Significance of KDM6A mutation in bladder cancer immune escape. BMC Cancer. 2021 Dec 1;21(1). https://doi.org/10.1186/s12885-021-08372-9
41. Kobatake K, Ikeda KI, Nakata Y, Yamasaki N, Ueda T, Kanai A, et al. Kdm6a deficiency activates inflammatory pathways, promotes M2 macrophage polarization, and causes bladder cancer in cooperation with p53 dysfunction. Clinical Cancer Research. 2020 Apr 15;26(8):2065–79. https://doi.org/10.1158/1078-0432.CCR-19-2230
42. Ahn J, Kim KH, Park S, Ahn YH, Kim HY, Yoon H, et al. Target sequencing and CRISPR/Cas editing reveal simultaneous loss of UTX and UTY in urothelial bladder cancer [Internet]. Vol. 7. 2016. Available from: www.impactjournals.com/oncotarget https://doi.org/10.18632/oncotarget.11207
43. Barrows D, Feng L, Carroll TS, David Allis C, Baylin SB, Ge K, et al. Loss of UTX/KDM6A and the activation of FGFR3 converge to regulate differentiation gene-expression programs in bladder cancer. Available from: https://www.pnas.org/lookup/suppl/
44. Rampias T, Karagiannis D, Avgeris M, Polyzos A, Kokkalis A, Kanaki Z, et al. The lysine-specific methyltransferase KMT 2C/ MLL 3 regulates DNA repair components in cancer . EMBO Rep. 2019 Mar;20(3). https://doi.org/10.15252/embr.201846821
45. Ding B, Yan L, Zhang Y, Wang Z, Zhang Y, Xia D, et al. Analysis of the role of mutations in the KMT2D histone lysine methyltransferase in bladder cancer. FEBS Open Bio. 2019 Apr 1;9(4):693–706. https://doi.org/10.1002/2211-5463.12600
46. Zhu G, Pei L, Li Y, Gou X. EP300 mutation is associated with tumor mutation burden and promotes antitumor immunity in bladder cancer patients. Aging. 2020;12(3):2132–41. https://doi.org/10.18632/aging.102728
47. Guo C, Balsara ZR, Hill WG, Li X. Stage- and subunit-specific functions of polycomb repressive complex 2 in bladder urothelial formation and regeneration. Development (Cambridge). 2017 Feb 1;144(3):400–8. https://doi.org/10.1242/dev.143958

48. Ho L, Miller EL, Ronan JL, Ho WQ, Jothi R, Crabtree GR. EsBAF facilitates pluripotency by conditioning the genome for LIF/STAT3 signalling and by regulating polycomb function. Nature Cell Biology. 2011 Aug;13(8):903–13. https://doi.org/10.1038/ncb2285
49. Gao X, Tate P, Hu P, Tjian R, Skarnes WC, Wang Z. ES cell pluripotency and germ-layer formation require the SWI/SNF chromatin remodeling component BAF250a [Internet]. 2008. Available from: www.pnas.org/cgi/content/full/ https://doi.org/10.1073/pnas.0801802105
50. Garczyk S, Schneider U, Lurje I, Becker K, Vögeli TA, Gaisa NT, et al. ARID1A-deficiency in urothelial bladder cancer: No predictive biomarker for EZH2-inhibitor treatment response? PLoS ONE. 2018 Aug 1;13(8). https://doi.org/10.1371/journal.pone.0202965
51. Guo C, Zhang Y, Tan R, Tang Z, Lam CM, Ye X, et al. Arid1a regulates bladder urothelium formation and maintenance. Developmental Biology. 2022 May 1;485:61–9. https://doi.org/10.1016/j.ydbio.2022.02.008
52. Li W, Yang L, He Q, Hu C, Zhu L, Ma X, et al. A Homeostatic Arid1a-Dependent Permissive Chromatin State Licenses Hepatocyte Responsiveness to Liver-Injury-Associated YAP Signaling. Cell Stem Cell. 2019 Jul 3;25(1):54–68.e5. https://doi.org/10.1016/j.stem.2019.06.008
53. Tran N, Broun A, Ge K. Lysine Demethylase KDM6A in Differentiation, Development, and Cancer. 2020; Available from: https://doi.org/10.1128/MCB.00341-20
54. Hong S, Cho YW, Yu LR, Yu H, Veenstra TD, Ge K, et al. Identification of JmjC domain-containing UTX and JMJD3 as histone H3 lysine 27 demethylases [Internet]. Available from: www.pnas.orgcgidoi10.1073pnas.0707292104
55. Kato H, Asamitsu K, Sun W, Kitajima S, Yoshizawa-Sugata N, Okamoto T, et al. Cancer-derived UTX TPR mutations G137V and D336G impair interaction with MLL3/4 complexes and affect UTX subcellular localization. Oncogene. 2020 Apr 16;39(16):3322–35. https://doi.org/10.1038/s41388-020-1218-3
56. Revia S, Seretny A, Wendler L, Banito A, Eckert C, Breuer K, et al. Histone H3K27 demethylase KDM6A is an epigenetic gatekeeper of mTORC1 signalling in cancer. Gut. 2021 Sep 11;gutjnl-2021-325405. https://doi.org/10.1136/gutjnl-2021-325405
57. Andricovich J, Perkail S, Kai Y, Casasanta N, Peng W, Tzatsos A. Loss of KDM6A Activates Super-Enhancers to Induce Gender-Specific Squamous-like Pancreatic Cancer and Confers Sensitivity to BET Inhibitors. Cancer Cell. 2018 Mar 12;33(3):512–526.e8. https://doi.org/10.1016/j.ccell.2018.02.003
58. Schulz WA, Lang A, Koch J, Greife A. The histone demethylase UTX/KDM6A in cancer: Progress and puzzles. Vol. 145, International Journal of Cancer. Wiley-Liss Inc.; 2019. p. 614–20. https://doi.org/10.1002/ijc.32116
59. Chen X, Chen H, He D, Cheng Y, Zhu Y, Xiao M, et al. Analysis of Tumor Microenvironment Characteristics in Bladder Cancer: Implications for Immune Checkpoint Inhibitor Therapy. Frontiers in Immunology. 2021;12(April):1–16. https://doi.org/10.3389/fimmu.2021.672158
60. Liu J, Lee W, Jiang Z, Chen Z, Jhunjhunwala S, Haverty PM, et al. Genome and transcriptome sequencing of lung cancers reveal diverse mutational and splicing events. Genome Research. 2012 Dec;22(12):2315–27. https://doi.org/10.1101/gr.140988.112
61. Kandoth C, McLellan MD, Vandin F, Ye K, Niu B, Lu C, et al. Mutational landscape and significance across 12 major cancer types. Nature. 2013;502(7471):333–9. https://doi.org/10.1038/nature12634
62. Li X, Zhang Y, Zheng L, Liu M, Chen CD, Jiang H. UTX is an escape from X-inactivation tumor-suppressor in B cell lymphoma. Nature Communications. 2018 Dec 1;9(1). https://doi.org/10.1038/s41467-018-05084-w
63. Wang Chaochen, Lee Ji-Eun, Lai Binbin, Macfarlan Todd S., Xu Shiliyang, Zhuang Lenan, et al. Enhancer priming by H3K4 methyltransferase MLL4 controls cell fate transition. Proc Natl Acad Sci U S A. 2016 Oct 18;113(42):11871–6. https://doi.org/10.1073/pnas.1606857113
64. Herz HM, Mohan M, Garruss AS, Liang K, Takahashi Y hei, Mickey K, et al. Enhancer-associated H3K4 monomethylation by trithorax-related, the drosophila homolog of mammalian MLL3/MLL4. Genes and Development. 2012 Dec;26(23):2604–20. https://doi.org/10.1101/gad.201327.112
65. Dorighi KM, Swigut T, Henriques T, Bhanu N v., Scruggs BS, Nady N, et al. Mll3 and Mll4 Facilitate Enhancer RNA Synthesis and Transcription from Promoters Independently of H3K4 Monomethylation. Molecular Cell. 2017 May 18;66(4):568–576.e4. https://doi.org/10.1016/j.molcel.2017.04.018

66. Rickels R, Herz HM, Sze CC, Cao K, Morgan MA, Collings CK, et al. Histone H3K4 monomethylation catalyzed by Trr and mammalian COMPASS-like proteins at enhancers is dispensable for development and viability. Nature Genetics. 2017 Nov 1;49(11):1647–53. https://doi.org/10.1038/ng.3965
67. Ford DJ, Dingwall AK. The cancer COMPASS: Navigating the functions of MLL complexes in cancer. Cancer Genetics. 2015 May 1;208(5):178–91. https://doi.org/10.1016/j.cancergen.2015.01.005
68. Sun P, Wu T, Sun X, Cui Z, Zhang H, Xia Q, et al. KMT2D inhibits the growth and metastasis of bladder Cancer cells by maintaining the tumor suppressor genes. Biomedicine and Pharmacotherapy. 2019 Jul 1;115. https://doi.org/10.1016/j.biopha.2019.108924
69. Attar N, Kurdistani SK. Exploitation of EP300 and CREBBP lysine acetyltransferases by cancer. Cold Spring Harbor Perspectives in Medicine. 2017 Mar 1;7(3). https://doi.org/10.1101/cshperspect.a026534
70. Gui Y, Guo G, Huang Y, Hu X, Tang A, Gao S, et al. Frequent mutations of chromatin remodeling genes in transitional cell carcinoma of the bladder. Nature Genetics. 2011 Sep;43(9):875–8. https://doi.org/10.1038/ng.907
71. Duex JE, Swain KE, Dancik GM, Paucek RD, Owens C, Churchill MEA, et al. Functional impact of chromatin remodeling gene mutations and predictive signature for therapeutic response in bladder cancer. Molecular Cancer Research. 2018 Jan 1;16(1):69–77. https://doi.org/10.1158/1541-7786.MCR-17-0260
72. Li J, Huang C, Xiong T, Zhuang C, Zhuang C, Li Y, et al. A CRISPR interference of CBP and p300 selectively induced synthetic lethality in bladder cancer cells in vitro. International Journal of Biological Sciences. 2019;15(6):757–67. https://doi.org/10.7150/ijbs.32332
73. Ghorbaninejad M, Khademi-Shirvan M, Hosseini S, Baghaban Eslaminejad M. Epidrugs: novel epigenetic regulators that open a new window for targeting osteoblast differentiation. Vol. 11, Stem Cell Research and Therapy. BioMed Central Ltd; 2020. https://doi.org/10.1186/s13287-020-01966-3
74. Shang D, Liu Y, Matsui Y, Ito N, Nishiyama H, Kamoto T, et al. Demethylating Agent 5-Aza-2′-Deoxycytidine Enhances Susceptibility of Bladder Transitional Cell Carcinoma to Cisplatin. Urology. 2008 Jun;71(6):1220–5. https://doi.org/10.1016/j.urology.2007.11.029
75. Martinez VG, Munera-Maravilla E, Bernardini A, Rubio C, Suarez-Cabrera C, Segovia C, et al. Epigenetics of Bladder Cancer: Where Biomarkers and Therapeutic Targets Meet. Vol. 10, Frontiers in Genetics. Frontiers Media S.A.; 2019. https://doi.org/10.3389/fgene.2019.01125
76. Harb-De La Rosa A, Acker M, Kumar RA, Manoharan M. Epigenetics application in the diagnosis and treatment of bladder cancer. Vol. 22, The Canadian Journal of UrologyTM. 2015.
77. Faleiro I, Leão R, Binnie A, Andrade De Mello R, Maia AT, Castelo-Branco P. Epigenetic therapy in urologic cancers: an update on clinical trials [Internet]. Vol. 8, Oncotarget. 2017. Available from: www.impactjournals.com/oncotarget/https://doi.org/10.18632/oncotarget.14226
78. Li QQ, Hao JJ, Zhang Z, Hsu I, Liu Y, Tao Z, et al. Histone deacetylase inhibitor-induced cell death in bladder cancer is associated with chromatin modification and modifying protein expression: A proteomic approach. International Journal of Oncology. 2016;48(6):2591–607. https://doi.org/10.3892/ijo.2016.3478
79. Park JW, Han JW. Targeting epigenetics for cancer therapy. Vol. 42, Archives of Pharmacal Research. Pharmaceutical Society of Korea; 2019. p. 159–70. https://doi.org/10.1007/s12272-019-01126-z
80. Adam RM. Histone Deacetylase Inhibitors and Bladder Cancer. Vol. 183, Journal of Urology. 2010. p. 2120–1. https://doi.org/10.1016/j.juro.2010.03.047
81. Li F, Zeng J, Gao Y, Guan Z, Ma Z, Shi Q, et al. G9a inhibition induces autophagic cell death via AMPK/mTOR pathway in bladder transitional cell carcinoma. PLoS ONE. 2015 Sep 23;10(9). https://doi.org/10.1371/journal.pone.0138390
82. Cao Y peng, Sun J ya, Li M qian, Dong Y, Zhang Y heng, Yan J, et al. Inhibition of G9a by a small molecule inhibitor, UNC0642, induces apoptosis of human bladder cancer cells. Acta Pharmacologica Sinica. 2019 Aug 1;40(8):1076–84. https://doi.org/10.1038/s41401-018-0205-5
83. Duan R, Du W, Guo W. EZH2: A novel target for cancer treatment. Vol. 13, Journal of Hematology and Oncology. BioMed Central Ltd; 2020. https://doi.org/10.1186/s13045-020-00937-8
84. Kim KH, Roberts CWM. Targeting EZH2 in cancer. Vol. 22, Nature Medicine. Nature Publishing Group; 2016. p. 128–34. https://doi.org/10.1038/nm.4036

85. Gan L, Yang Y, Li Q, Feng Y, Liu T, Guo W. Epigenetic regulation of cancer progression by EZH2: From biological insights to therapeutic potential. Vol. 6, Biomarker Research. BioMed Central Ltd.; 2018. https://doi.org/10.1186/s40364-018-0122-2
86. Martínez-Fernández M, Rubio C, Segovia C, López-Calderón FF, Dueñas M, Paramio JM. EZH2 in bladder cancer, a promising therapeutic target. Vol. 16, International Journal of Molecular Sciences. MDPI AG; 2015. p. 27107–32. https://doi.org/10.3390/ijms161126000
87. Cheng Y, He C, Wang M, Ma X, Mo F, Yang S, et al. Targeting epigenetic regulators for cancer therapy: Mechanisms and advances in clinical trials. Signal Transduction and Targeted Therapy. 2019;4(1). https://doi.org/10.1038/s41392-019-0095-0
88. Morel D, Jeffery D, Aspeslagh S, Almouzni G, Postel-Vinay S. Combining epigenetic drugs with other therapies for solid tumours - past lessons and future promise. Vol. 17, Nature Reviews Clinical Oncology. Nature Research; 2020. p. 91–107. https://doi.org/10.1038/s41571-019-0267-4
89. Pfister SX, Ashworth A. Marked for death: Targeting epigenetic changes in cancer. Vol. 16, Nature Reviews Drug Discovery. Nature Publishing Group; 2017. p. 241–63. https://doi.org/10.1038/nrd.2016.256
90. Ghasemi S. Cancer's epigenetic drugs: where are they in the cancer medicines? Vol. 20, Pharmacogenomics Journal. Springer Nature; 2020. p. 367–79. https://doi.org/10.1038/s41397-019-0138-5
91. Misso G, di Martino MT, de Rosa G, Farooqi AA, Lombardi A, Campani V, et al. Mir-34: A new weapon against cancer? Vol. 3, Molecular Therapy - Nucleic Acids. Nature Publishing Group; 2014. p. e195. https://doi.org/10.1038/mtna.2014.47
92. Zhang Q, Zhao W, Ye C, Zhuang J, Chang C, Li Y, et al. Honokiol inhibits bladder tumor growth by suppressing EZH2/ miR-143 axis [Internet]. Vol. 6. Available from: www.impactjournals.com/oncotarget https://doi.org/10.18632/oncotarget.6135
93. Wang Y, Xiang W, Wang M, Huang T, Xiao X, Wang L, et al. Methyl jasmonate sensitizes human bladder cancer cells to gambogic acid-induced apoptosis through down-regulation of EZH2 expression by miR-101. British Journal of Pharmacology. 2014 Feb;171(3):618–35. https://doi.org/10.1111/bph.12501
94. Goell JH, Hilton IB. CRISPR/Cas-Based Epigenome Editing: Advances, Applications, and Clinical Utility. Vol. 39, Trends in Biotechnology. Elsevier Ltd; 2021. p. 678–91. https://doi.org/10.1016/j.tibtech.2020.10.012
95. Nakamura K, Smyth MJ. Immunoediting of cancer metastasis by NK cells. Nature Cancer [Internet]. 2020;1(7):670–1. Available from: https://doi.org/10.1038/s43018-020-0081-z
96. Xu L, Wang J, Liu Y, Xie L, Su B, Mou D, et al. CRISPR-Edited Stem Cells in a Patient with HIV and Acute Lymphocytic Leukemia. New England Journal of Medicine. 2019 Sep 26;381(13):1240–7. https://doi.org/10.1056/NEJMoa1817426