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Epigenetic Alterations and Chromatin Landscape Remodeling in Urothelial Bladder Cancer: Molecular Drivers, Biomarker Potential, and Emerging Therapeutic Strategies

Amr Abd-Elraheem Abdo[1], Ahmed Mohamed Kamel[1]

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Abstract

Urothelial carcinoma of the bladder (UBC) is a heterogeneous disease from the clinicopathologic and molecular standpoint and presents clinical management problems for its range in progression, frequent recurrence and complicated genetic/epigenetic architecture. Not only traditional genetic changes, but also epigenetic dysregulation (e.g., alterations of chromatin remodeling, histone modification and DNA methylation) has been increasingly recognized to play a pivotal role in the process of tumor initiation, progression, metastasis and resistance to therapy. It is a dissapointing result that mutations of the chromatin remodeler such as ARID1A, KMT2C, KMT2D, and histone modifying enzymes (EP300, CREBBP and EZH2) not only cause loss-of-nucleosome positioning in addition lead to lack of enhancer function and perturbation ofT program contributing to shaping up intratumoral heterogeneity as well as transcriptional plasticity resulting in failure in immunoevasion. These changes sculpt the tumor microenvironment and impact the response to chemotherapy, immunotherapy, and targeted therapy.Epigenetic biomarkers based on mutation profiles, chromatin accessibility and DNA methylation signatures present new non-invasive strategies that can be followed for early detection, monitoring of disease and stratification of patients usage; which are all available in urine or plasma. Therapeutically, inhibitors of EZH2, HDACs, BET proteins, DNMTs and certain chromatin remodeling factors are currently being heavily investigated in preclinical studies or clinical trials as monotherapies or rational combinations with ICIs, chemotherapy or targeted therapies.Advances in tech nologies, such as single- and spatial genomics combined with AI-facilitated multi-omics integration make it possible to realize high-resolution maps of tumor heterogeneity, enhancer d namics, and epigenetic vulnerabilities. This review aims to present the current data on UBC epigenetic modifications and their mechanistic, biomarker and therapeutic implications. By combining mechanistic understanding with translational perspectives, we outline future directions to move precision oncology forward, optimize our treatment approach and improve clinical outcomes for UBC patients.

Key words urothelial bladder cancer, epigenetics, chromatin remodeling, DNA methylation, histone post-translational modification

1. College of Biotechnology, Misr University for Science and Technology (MUST), 6th of October City, Giza 12566, Egypt.

Correspondence: Amr Abd-Elraheem Abdo (College of Biotechnology, Misr University for Science and Technology (MUST), 6th of October City, Giza 12566, Egypt; Email: amrabdulraheem675@gmail.com).

Introduction

Urothelial bladder cancer (UBC) is one of the most common malignancies of the urinary system and results in substantial global morbidity and mortality [1]. Clinically, UBC shows a range from non-muscle invasive bladder cancer (NMIBC) with high rate of recurrence and good prognosis to muscle invasive bladder cancer (MIBC) with aggressive behavior, high metastasis propensity and poor overall survival [2]. Though there have been significant advances in surgery, intravesical therapy and systemic agents, five-year survival rate for invasive MIBC is still poor, emphasizing the requirement to better understand the molecular underpinnings of disease progression and therapeutic resistance [2].

Traditionally, the pathogenesis of UBC has been attributed mainly to classical genetic modifications such as activating mutations in FGFR3, PIK3CA and HRAS or loss-of-function mutations in tumor suppressors like TP53, RB1 and PTEN [3, 4]. Although such genetic alterations initiate and promote tumorigenesis, they do not fully explain the clinical heterogeneity among patients. Accumulating evidence is revealing that epigenetic deregulation plays a central role in determining UBC biology, including gene expression control, chromatin architecture regulation, transcriptional program control and metabolism adaptation, and tumor–immune interactions [5]. These epigenetic changes become especially relevant for tumor plasticity, intratumoral heterogeneity, treatment resistance, and relapse that still constitute important drawbacks in clinics [6].

Encompassing epigenetic regulation includes modifications that are inheritable but do not involve changes to the nucleotide sequence. The principal mechanisms involve DNA methylation, histone modifications (e.g. acetylation, methylation and ubiquitination), chromatin remodelling and enhancer–promoter looping [7]. In UBC, these processes are often dysregulated by chromatin regulating mutations such as ARID1A, KMT2C/D, EP300 and CREBBP or abnormal functions of epigenetic enzymes including EZH2, DNMTs and HDACs [8]. These changes collaborate with genetic abnormalities to reshape chromatin architecture into permissive or repressive transcriptional landscapes, which affect the ability of tumor cells to escape growth suppression, survive genotoxic stress and acclimate to the tumor microenvironment [8].

A signature feature of UBC is the rewiring of enhancer and super-enhancer networks promoting oncogenic transcriptional programs that sustain aspects of proliferation, invasion, and metastases [9]. Defects in chromatin-modifying enzymes in concert with metabolic reprogramming and hypoxia signaling hijack these regulatory regions to enhance the activity of known potent oncogenes such as MYC, FGFR3 and angiogenic factors. This enhancer reprogramming results in enhanced aggressive tumor phenotypes that drives therapeutic resistance through maintenance of transcriptional plasticity and cellular heterogeneity [10].

Additionally, epigenetic changes are relevant for tumor–immune crosstalk. Impaired antigen presentation, cytokine signaling, and interferon responses by dysregulated chromatin accessibility and histone modifications can shape an immunosuppressive tumor microenvironment [11, 12]. For instance, ARID1A or KDM6A loss is associated with impaired MHC class I expression, and EZH2 overactivity drives T-cell exclusion and inflammatory gene suppression [13]. A knowledge of these epigenetic mechanisms leads to the rational combining of epigenetic modulators with immune checkpoint inhibitors (ICIs) to increase antitumor immunity in certain patient subsets [14].

The reversibility of epigenetic modifications renders them as ideal therapeutic targets. Agents including EZH2 inhibitors, HDAC inhibitors, BET inhibitors and DNMT inhibtiors are being studied in UBC as single agent or combined with immune therapy, targeted therapy or chemotherapy [15, 16]. Furthermore, epigenetic tumor and non-invasive markers such as circulating tumor DNA and urine can be used to early detection, disease monitoring as well as patient stratification [17]. By integrating epigenomic characterization of UBC with genome-wide maps of genomic, transcriptomic and proteomic features, the scope of classification of UBC into biologically and clinically relevant subtypes to enable precision oncology becomes apparent [18].

However, there are a number of requirements and challenges to address. Intratumoral heterogeneity in UBC makes it difficult to establish strong biomarkers and treatment regimens. Epigenetic changes are frequently dynamic and context-specific, with function determined by co-option with the tumour microenvironment (TME), hypoxia, and metabolic programming [19, 20]. Further, off-target activities and the reversible nature of many epigenetic marks represent challenges to achieving efficient and permanent treatments. Tackling these challenges calls for mechanistic and systems level studies, high resolution epigenomic mapping, and translational investigations integrating molecular biology with the clinical dimension.

The objective of this review is to fine-tune the current knowledge on epigenetic reprogramming in UBC. We analyse chromatin-remodelling, histone-modifying and DNA-methylation mechanisms, and explore how they dynamically interact to establish tumour transcriptional outputs, enhancer landscapes and immune-immunomankinductive processes. We also address major regulators of chromatin, their contribution to the definition of molecular subtypes, as well as translational implications for biomarker discovery and therapeutic intervention. Last, we spotlight frontier technologies including single-cell and spatial epigenomics as well as AI-powered multi-omics integration, which are revolutionizing research and precision medicine in UBC. Through unifying the concepts of mechanisms and clinic, this review focuses to direct future research, therapeutic design and stratification in patients suffering from urothelial bladder cancer.

Core epigenetic mechanisms in UBC

The regulation of epigenetic mechanisms in urothelial bladder cancer (UBC) is multidimensional and controls tumor behaviour through interconnected pathways, such as chromatin remodelling, histone modification and DNA methylation [21]. Together these processes impact transcriptional and enhancer landscapes as well as the tumor-immune environment. Dysfunctions in these process are involved in tumor initiation, progression and metastasis as well as resistance to therapy [22]. There is growing evidence that epigenetic changes co-operate with genetic mutations to establish transcriptional flexibility and hence contribute to the intra tumoral heterogeneity of UBC which underpins their clinical presentation [18]. Moreover, as epigenetic alterations are reversible they provide potential opportunities for therapy and development of biomarkers [23].

Chromatin remodeling abnormalities

Chromatin Remodelers (SWI/SNF [ARID1A, SMARCA4] and NuRD [CHD4]) chromatin remodeling complexes that play a central role in the regulation of nucleosome positions and DNA accessibility to transcription factors [24]. In UBC, mutations in ARID1A, which are found in about 20%–25% of MIBCs, alter chromatin structure and loosen transcriptional fidelity along with aberrant regulation of pathways that mediate DNA damage response, cell cycle checkpoint control and apoptosis [13]. Biologically, depletion of ARID1A has been associated

with tumor cell plasticity and an immunosuppressive immune microenvironment, as well as chemotherapy resistance, underscoring its role in both tumorigenesis and treatment response [13, 25].

Mutation of H3K4 methyltransferases KMT2C and KMT2D, which mediate enhancer-associated chromatin accessibility and function, are also seen [26, 27]. These changes contribute to pathological activation of oncogenic transcriptional programs, such as those controlling proliferation, invasion and angiogenesis [28]. Perturbation of these enhancer landscapes by mutations in chromatin remodelers is also a strong driver of intratumoral heterogeneity, leading to the generation of subclones with different transcriptional and metabolic properties that can have varying therapeutic responses, including immune checkpoint inhibitors [29].

Beside mutations, defective function of chromatin remodelers can be caused by aberrant post-translational modifications or altered associated cofactors [30]. For instance, uncontrolled recruitment of SWI/SNF complexes to enhancers or promoters can enhance oncogenic signals or repress tumor suppressor genes in a manner that is mutation independent [31]. Collectively, these mechanisms of action support the importance of chromatin remodeling in UBC pathogenesis and identify it as a promising target for epigenetic therapy to re-establish appropriate chromatin accessibility and transcriptional regulation.

Histone modification dysregulation

Modifications of histones such as methylation, acetylation and ubiquitination are important for chromatin structure maintenance and gene expression regulation [32]. In UBC, histone-modifying enzyme alterations are frequent and induce transcriptional reprogramming. Both acquired and germline loss-of-function mutations in EP300 and CREBBP, two master histone acetyltransferases (HATs), lead to decreased promoter and enhancer histone acetylation of tumor suppressor genes, compromising transcriptional activation [24, 26]. This epigenetic silencing promotes unhindered proliferation, evasion of apoptosis, and increased survival against tumor killing leading to progression and resistance of the disease. Elevated levels or gain-of-function mutations in the catalytic subunit of PRC2, EZH2, has been shown to induce H3K27 trimethyl (H3K27me3) and silence expression of differentiation and immune response genes [33]. EZH2-induced silencing plays a role in promoting a dedifferentiated tumor phenotype and enabling evasion of the immune system via suppression of chemokines and tools for antigen presentation [34]. Concomitantly, mutations in histone demethylases such as KDM6A compromise H3K27me3 erasure at enhancers, thus additionally increasing transcriptional flexibility and oncogenic signaling [32].

Histone modifications do not function alone and work together with chromatin remodelers and DNA methylation to sculpt enhancer landscapes and affect TF binding [24]. The combination patterns of histone acetylation and methylation are super-enhancer features determining the expression levels of or key oncogenes HIV-1 Tat and Angiogenin [35]. Aberrant regulation of these marks predisposes to EMT (epithelial-mesenchymal transition), angiogenesis, and resistance to both chemotherapy and immunotherapy [36]. It is of note that a great impetus exists for the pharmacologic inhibition of histone-modifying enzymes with the aim to reestablish normal transcriptional programs and enhance tumor susceptibility to conventional antineoplastic agents [37].

DNA methylation deregulation

DNA methylation, the modification of cytosine residue by adding a methyl group in CpG dinucleotides, was a vital epigenetic mechanism in controlling gene expression in UBC [16]. Histone modification and promoter aberrant hypermethylation of tumor suppressor genes like CDKN2A and RASSF1A contributes to transcriptional silencing, eventually inducing the dysregulation of cell cycle control with apoptosis resistance or tumor proliferation [38]. Hypermethylated regions are commonly over-represented in networks regulating DNA repair, cell adhesion and immune surveillance, which can lead to a more aggressive tumour phenotype with enhanced metastatic capacity [39]. In contrast, loss of global DNA methylation induces chromosome instability and activation of proto-oncogenic pathways involved in proliferation, angiogenesis and metabolic adaptation [40]. Hypomethylation can also lead to the reexpression of transposable elements and endogeneous retroviral sequences, which could mediate genomic instability or immune evasion [41]. These alterations often crosstalk with histone modification and chromatin remodeling to affect enhancer accessibility, as well as TF binding, thereby serving to promote the oncogenic transcriptional program [24]. Notably, DNA methylation is being explored as a non-invasive biomarker for UBC [42]. As urine or plasma are easy to collect, detection of the methylated DNA fragments would facilitate early diagnosis and monitoring recurrence of disease as well as follow-up after treatment [17]. Methylation-based tests may support other diagnostic tools, lead to better patient stratification and tailor patients' treatment in a more individualised manner [43]. In total, DNA methylation dysregulation is a major cause of transcriptional plasticity and a worthy direction for translational studies in UBC (**Table 1**) [44].

Enhancer and super-enhancer reprogramming

Urothelial bladder cancer (UBC) is associated with a massive degree of enhancer rewiring which activates pathological transcriptional programs to onset, drive and promote metastasis of the tumor [9]. Enhancers are a class of cis-regulatory DNA elements that mediate the assembly of transcription factors and coactivators at target gene promoters, whereas super-enhancers represent large complexes of enhancers that drive cell identity-specific and oncogenic gene expression [10, 45]. Enhancer remodeling during carcinogenesis has been reported in UBC, including muscle-invasive bladder cancer (MIBC), through which they drive expression of oncogenes like MYC, FGFR3 and VEGFA to accelerate proliferation, angiogenesis and metabolic reprogramming [46]. Genomic mutations that occur in chromatin remodelers (such as ARID1A, KMT2C, KMT2D) affect enhancer structure to a large extent [26]. Loss of ARID1A, or impairment of KMT2C/D-regulated H3K4 methylation, perturbs nucleosome positioning to cause erroneous enhancer accessibility and activation of oncogenic transcriptional programs [47]. These modifications enable transcriptional flexibility permitting tumor cells to adjust to their microcenvironment, hypoxia and therapeutic stress [48]. Hypoxia signaling, most commonly associated with metabolic reprogramming in UBC, additionally alters enhancer landscapes through the stabilization of HIF TFs that occupy enhancers of glycolytic and angiogenic genes [22]. Super-enhancers are especially over-represented in aggressive MIBC subsets and promote excessive expression of an array of oncogenes and invasion- and immune-modulating genes [49]. These enhancer hubs serve as important nodes of transcriptional addiction, inasmuch as continuing function of these regulatory sites is necessary for tumor cell survival. Accordingly, inhibition of super-enhancer-associated transcription by chromatin remodelers or BET proteins has become an attractive avenue for therapeutic intervention to blunt oncogene-directed transcription networks and circumvent therapy resistance (**Figure 1**) [45].

Table 1. Key chromatin and epigenetic regulators in urothelial bladder cancer.

Gene	Mutation frequency	Epigenetic function	Impact on tumor biology	Therapeutic implication
ARID1A	20-25%	SWI/SNF chromatin remodeler; regulates nucleosome positioning	Alters chromatin accessibility, transcriptional programs, DNA damage response; promotes immune evasion	Potential target for chromatin-directed therapies; may influence immunotherapy response
KMT2C/D	15-20%	Histone methyltransferases (H3K4) affecting enhancer landscapes	Aberrant enhancer activation; promotes oncogenic transcriptional programs and tumor plasticity	Investigational enhancer-targeted therapies; combination with BET or HDAC inhibitors
EP300	10-15%	Histone acetyltransferase; regulates transcriptional activation	Loss impairs tumor suppressor gene expression; contributes to therapy resistance	HDAC or BET inhibitor combinations may restore transcriptional control
CREBBP	5-10%	Histone acetyltransferase; modulates chromatin accessibility	Disruption leads to transcriptional dysregulation and enhanced proliferation	Combination with epigenetic modulators or immunotherapy
EZH2	10-15% (overexpression)	Histone methyltransferase (H3K27); mediates gene repression	Silences differentiation and immune genes; promotes proliferation and immune evasion	EZH2 inhibitors; synergistic with immunotherapy and chemotherapy
KDM6A	20-25%	Histone demethylase (H3K27); regulates enhancer activity	Alters transcriptional plasticity; facilitates tumor progression and immune escape	Potential target for combination epigenetic therapy

ARID1A: AT-Rich interaction domain 1A; KMT2C/D: lysine methyltransferase 2C/2D; EP300: E1A binding protein P300; CREBBP: CREB binding protein; EZH2: enhancer of zeste homolog 2; KDM6A: lysine demethylase 6A; SWI/SNF: SWItch/sucrose non-fermentable (chromatin remodeling complex); HDACs: histone deacetylases.

Epigenetic regulation of tumor immunity

Epigenetic alterations massively impact immune surveillance and therapeutics efficacy in UBC. Loss of function mutations in chromatin remodeling genes, such as ARID1A or histone demethylases like KDM6A, decrease antigen presentation by decreasing MHC-I expression and inhibiting interferon signaling pathway [25]. EZH2 overactivity promotes tumor immune evasion by increasing H3K27me3-mediated silencing of immune-related genes, a process that has been shown in several cancers to reduce cytotoxic T-cell infiltration and contribute to an immunologically "cold" tumor microenvironment (**Figure 2)** [50, 51]. In contrast, some epigenetic alterations may help sensitize a tumor to immune therapy [51]. For instance, inhibition of EZH2 or HDACs can reprogram expression of chemokines, cytokines and antigen presenting machinery, recruiting T cells to tumours and improving response to immune checkpoint blockade [52]. Epigenetic modifications also modulate the expression of immune checkpoint ligands (PD-L1, PD-L2) and co-stimulatory molecules, with further consequences for therapy response [12]. These data lend strong support to combination approaches in UBC using epigenetic therapies and immunotherapies to make immune-unresponsive tumors responsive.

Therapeutic exploitation of epigenetic vulnerabilities

The reversibility of epigenetic changes offers the potential for effective therapeutic targeting in urothelial bladder cancer (UBC) [37]. Several classes of epigenetic modulatory agents are currently being investigated preclinically and clinically to disrupt these suppressive chromatin states, which alter gene expression programs by targeting chromatin remodelers, histone-modifying enzymes, or DNA methyltransferases in an attempt to normalize transcriptional programs and bolster a response by the antitumor immune system **(Table 2)** [15]. EZH2 inhibitors inhibit transcriptional repression mediated by H3K27me3, especially in tumors that have EZH2 overexpression or defective SWI/SNF complex elements like ARID1A [53, 54]. By reprogramming silenced tumor suppressor and immune-related genes, inhibition of EZH2 is able to restore differentiation programs, elevate the immunogenicity of tumors and sensitize tumors to immune checkpoint blockade. Early phase clinical trials have shown encouraging activity, especially when combined with immunotherapy or chemotherapy [53].

HDAC inhibitors change histone acetylation pattern in order to restore transcription of tumor supressor genes and their accessiblity to chromatin [16]. This form of epigenetic reprogramming could also potentiate the effectivity of classic therapy (chemotherapy, immune checkpoint inhibitor) [32]. Preclinical and early-phase clinical translation studies demonstrate a potential synergy between HDAC inhibition and other epigenetic modalities or immunotherapy, supporting rational combination strategies [55].

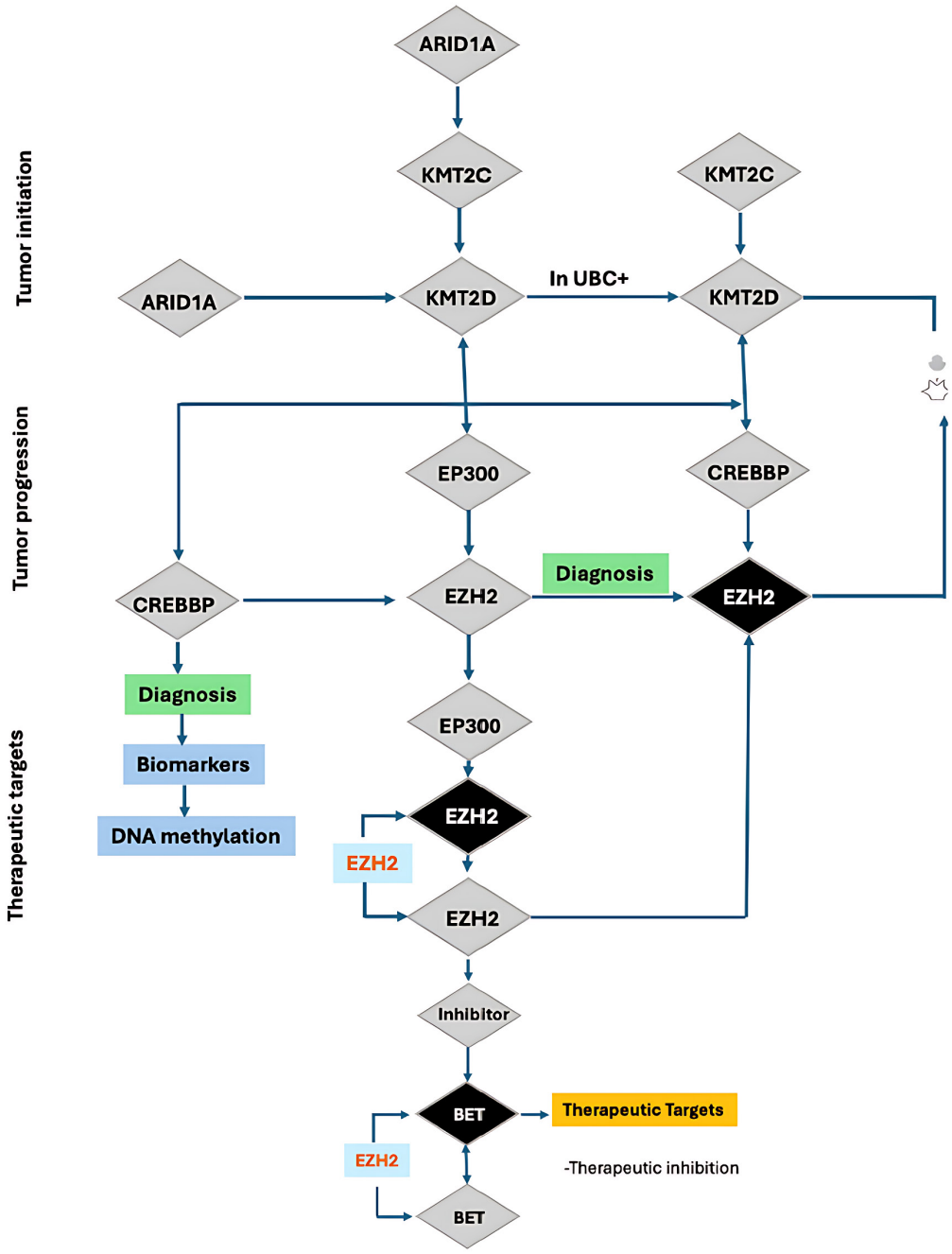

Figure 1. Schematic illustration of tumor initiation, progression, and therapeutic targeting involving chromatin-modifying genes in urothelial bladder cancer (UBC). This schematic outlines the stepwise genetic modification and epigenetic deregulation in the induction of tumorigenesis. Early in tumorigenesis, ARID1A inactivation results in loss of function alteration downregulating KMT2C and KMT2D which are master regulators of histone methylation. In UBC+, KMT2C/KMT2D changes contribute to EP300 (histone acetyltransferase p300) and CREBBP-(CREB-binding protein) pathways in the context of an epigenetic rewiring that fosters tumor evolution. Progressive dysregulation increases the activity or expression of the catalytic subunit of the PRC2 (Polycomb Repressive Complex 2) EZH2 (enhancer of zeste homolog 2), which mediates trimethylation of histone H3K27. EZH2 overexpression is considered a key event associated with diagnostic biomarkers and DNA methylation alterations. Treatment modalities are directed towards abnormal epigenome modifiers. EZH2 inhibitors and subsequent inhibition of BET proteins (bromodomain and extra-terminal domain proteins) are highlighted as prospective therapeutic strategies, mainly because of their involvement in gene regulation and dependency mechanisms in EZH2-mediated cancers. The screen depicts a hierarchy of genetic mutations to epigenetically driven therapeutic targets, with decision points for diagnostic and therapy intervention.

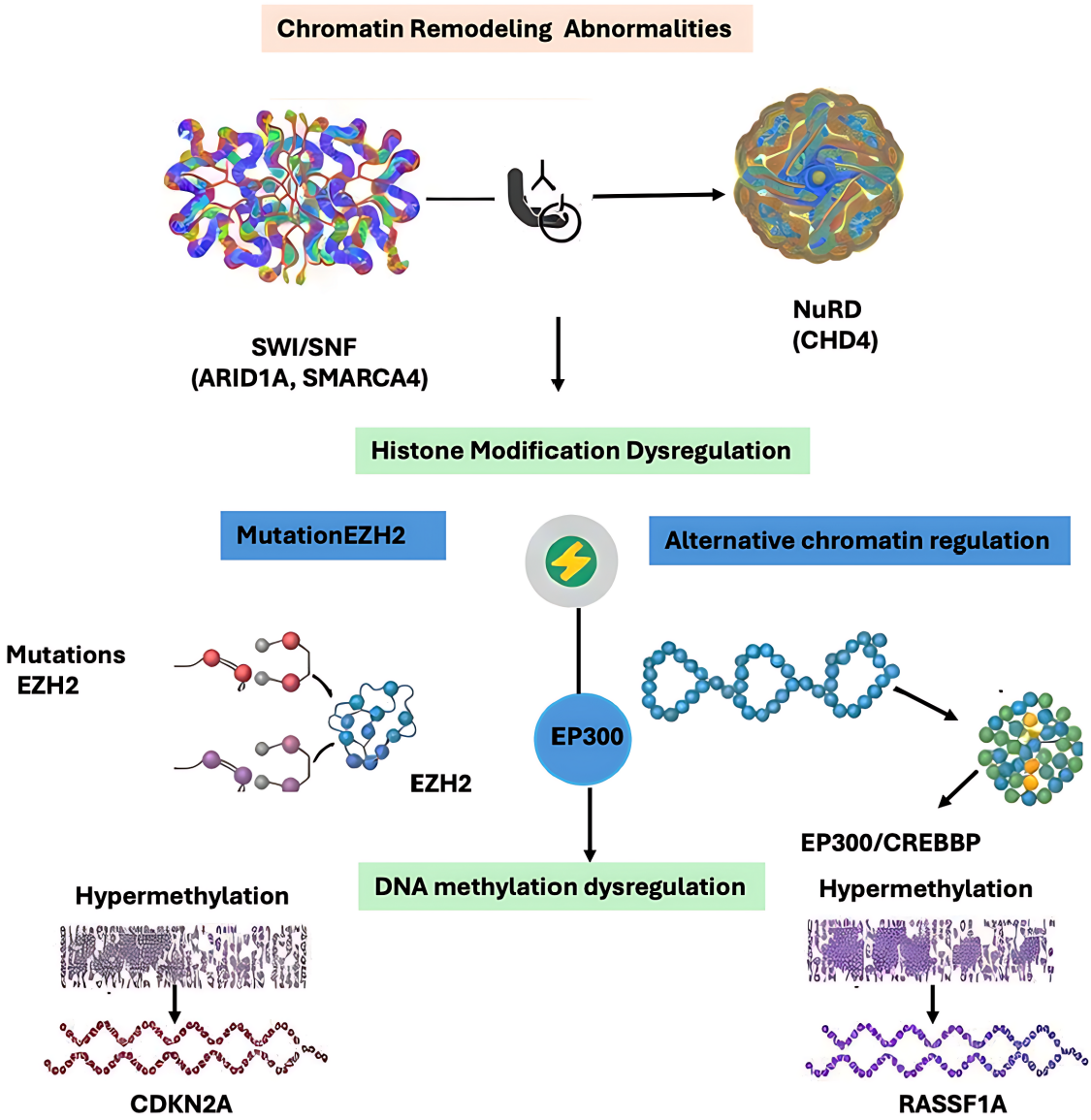

Figure 2. Chromatin remodeling abnormalities and downstream epigenetic dysregulation contributing to tumorigenesis. This diagram shows how malfunctioning chromatin-remodeling complexes cause histone-modification defects, a failure in DNA methylation. Mutation of the SWI/SNF complex—ARID1A (AT-rich interaction domain 1A) and SMARCA4 (SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin subfamily A member 4) are most frequently involved—results in a defect in nucleosomal repositioning. Simultaneous NuRD complex abnormalities involving CHD4 (chromodomain-helicase-DNA-binding protein 4) lead to reduction of chromatin accessibility. These remodeling deficiencies lead to deregulation of global histone modifications. Somatic mutations of the histone H3K27 methylase, EZH2 (enhancer of zeste homolog 2), also results in a loss of the repressive H3K27 trimethylation. Concomitantly, additional chromatin-regulatory machineries target the key epigenetic co-activator EP300 (histone acetyltransferase p300). Deletion or defect of EP300 or its paralogue CREBBP (CREB-binding protein) disrupts histone acetylation equilibrium and induces epigenetic silencing. These upstream chromatin alterations converge on DNA methylation, with genes becoming hypermethylated and silenced. Shown here are examples of CDKN2A, cellk-cycle control regulator, and RASSF1A, tumor-suppressor gene that is often inactivated by promoter hypermethylation. The diagram represents the cascade of events from chromatin-remodelling defect to epigenetic silencing in oncogenic transformation.

BET inhibitors disrupt super-enhancer–driven transcriptional programs, including oncogenes such as MYC and FGFR3, which are essential for tumour growth and survival [56]. Deconstruction of enhancer-mediated transcriptional addiction, BET inhibition, and tumor growth BET inhibition by super-enhancers disrupts tumor growth and transcriptional plasticity [57]. These agents are under preclinical or early clinical investigation in association with HDAC inhibitors or even therapeutic vaccines aiming to

Table 2. Epigenetic therapeutic strategies in urothelial bladder cancer.

Target	Drug class	Mechanism of action	Clinical status	Combination approaches
EZH2	EZH2 inhibitor	Reverses H3K27me3-mediated gene repression; restores differentiation and immune gene expression	Phase I/II trials	With immune checkpoint inhibitors or chemotherapy
HDACs	HDAC inhibitor	Modulates histone acetylation, restores tumor suppressor gene expression	Phase I/II trials	With immune checkpoint inhibitors or chemotherapy
BET proteins	BET inhibitor	Blocks super-enhancer–driven oncogene transcription (e.g., MYC, FGFR3)	Preclinical/early clinical	With HDAC inhibitors or immunotherapy
DNMTs	DNMT inhibitor	Reverses promoter hypermethylation, enhancing tumor immunogenicity	Preclinical/early clinical	With checkpoint inhibitors or chemotherapy
SWI/SNF	Chromatin remodeler-targeted agents (investigational)	Restores chromatin accessibility and enhancer function	Preclinical	Combination with EZH2 or HDAC inhibitors
KMT2C/D	Epigenetic modulators (investigational)	Corrects enhancer dysregulation, reduces oncogenic transcription	Preclinical	With BET or HDAC inhibitors

EZH2: enhancer of zeste homolog 2; HDACs: histone deacetylases; BET: bromodomain and extra-terminal domain proteins; DNMTs: DNA methyltransferases; SWI/SNF: SWItch/sucrose non-fermentable (chromatin remodeling complex); KMT2C/D: lysine methyltransferase 2C/2D.

potentiate antitumor responses.

DNMT inhibitors can reverse promoter hypermethylation thereby reactivating expression of tumor suppressor and immune-regulatory genes. This reactivation in turns increases immunogenicity of the tumors and sensitizes them to checkpoint blockade, raising the possibility of combining DNMT inhibitors with immunotherapeutic approaches [38, 58]. Early-phase trials are investigating their use in combination with chemotherapy or immune checkpoint inhibitors. Prospective drugs that can target chromatin remodelers (e.g., SWI/SNF) and enhancer regulators (e.g., KMT2D/C) toward restoring the chromatin accessibility and enhancing dysregulation [59]. These are still in the pre-clinical phase but combined with EZH2 or HDAC inhibitors (HDACI) could offer synthetic lethality and therefore represent a mechanism for future combination strategies [60].

In summary, rational combinations based on insight into chromatin dynamics and enhancer reprogramming and immune modulation are becoming a centerpiece of precision epigenetic therapy in UBC. **Table 2** provides an overview on the main targets and classes of drugs, their mechanism of action, therapeutic stage (clinical phase) and potential combination therapies that can be considered as quick-reference for present and prospective drug development.

Emerging tools for epigenetic research

The advancement of UBC epigenetics has been ushered in by technological breakthroughs. Single-cell epigenomics allows the cellular resolution profiling of chromatin accessibility, DNA methylation and histone modification to unveil subclonal heterogeneity and dynamic transcriptional programs [61, 62]. This mode of spatial epigenomics maps such features in the tumor microenvironment and reveals how they are interconnected between tumor cells, immune infiltrates, and stromal compartments. Integration of multi-omics with AI can correlate chromatin states and transcriptional outputs, metabolic rewiring and immune signaling [63]. These analyses enable novel biomarker discovery, candidate targets for therapy and predictive signatures of response to treatment. Circulating methylated DNA in urine or plasma also provides a non-invasive means of early detection, monitoring response to therapy and following tumor progression longitudinally [17, 64]. Taken together, these resources lay the groundwork for precision oncology approaches in UBC and allow data-driven stratification of patients and therapy design.

Clinical translation and biomarker development

This increasing recognition of epigenetic dysfunction in UBC has also set the stage for clinical application of chromatin- and histone-based biomarkers [23]. Specific mutations in chromatin remodeling genes including ARID1A, KMT2C, and KMT2D have been associated with differential prognostic and treatmentresponsive phenotypes and also mutations in histone-modifying enzymes such as EP300,CREBBP, EZH2 [24, 26]. For example, ARID1A-deficient tumors usually have defective DNA damage repair and immune infiltrates, which could prospectively stratify patients for epigenetic-immunotherapy combinations sensitivity whereas EZH2-high level tumors correlate with poor outcome, possibly highlighting drugs especially active in this patient subset [65]. Besides gene mutations, epigenetic signatures such as chromatin accessibility, histone modification patterns and DNA methylation profile form additional biomarkers for patient stratification [23]. Specifically, urine- or plasma-based DNA methylation tests have

been developed as noninvasive approaches for early diagnosis and monitoring minimal residual disease and therapy response [17, 66]. These "liquid" biopsy strategies permit the monitoring of tumor dynamics in real time and allow immediate evaluation of treatment response as a result are particularly appealing in metastatic or recurring UBC patients where obtaining enough of distributionsal based tissue biopsies could be difficult [67].

The combination of these epigenetic biomarkers with genomic, transcriptomic and proteomic information improves the predictive accuracy and it sustains precision oncology. Multimodal analyses should help to find patient subclasses that could benefit from distinct therapeutic strategies, such as targeted epigenetic therapies or rational combinations of drugs [68, 69]. For example, a combination of epigenetic modulators and immune checkpoint inhibitors could boost antitumor immune responses in tumors with suppressive chromatin landscapes, whereas methylation-based monitoring might facilitate dose normalization or timely treatment change [70]. Finally, application of these UBC-related insights to clinical practice could lead to the development of increasingly individualized and mechanism-based treatments that take advantage of UBC's distinct Achilles' heels [71].

Future directions and challenges

The development of UBC epigenetic research in the coming years should seek to fine-tune molecular subtypes by incorporating information on chromatin remodelers, histone modifications, DNA methylation and enhancer landscapes [72]. This will enable more accurate patient stratification, better prognostication and help to select therapy. Understanding of the epigenetic landscape in concert with tumor-intrinsic and microenvironmental signatures is essential to identify actionable susceptibilities and predict treatment responses.

Design of highly selective inhibitors against chromatin remodelers and histone-modifying enzymes remains an urgent need. Such highly selective inhibitors with few offtarget effects should increase the therapeutic index [5, 30]. In parallel, rational combination strategies coupling epigenetic modulators with immunotherapy, targeted therapy or chemotherapy should be optimized in order to defeat tumor plasticity and resistance [73]. Temporal tracking of epigenetic transitions during treatment is also important, because dynamic epigenomic alterations can inform on adaptive resistance mechanisms and novel vulnerabilities [73, 74].

Synthetic lethality strategies offer an attractive option for adding chromatin or epigenetic vulnerabilities with other targeted agents to result in specific tumor cell death [32]. Nevertheless, significant obstacles persist, such as intratumoral heterogeneity, the dynamic nature of epigenetic marks and off-target effects of epigenetic therapeutics. To overcome these challenges, we need advanced preclinical models, single-cell and spatial epigenomic profiling, and multi-omics integration. To unlock the full potential of epigenetic dependencies and enable mechanistic observations to be translated into better clinical results for patients with UBC, these barriers must be addressed.

Conclusion

The progress of technology has transformed investigation of UBC epigenetics. Single-cell epigenome measurements can profile chromatin accessibility, DNA methylation and histone modifications at the level of individual cells to uncover subclonal heterogeneity and dynamic transcription programs [75]. Spatial epigenomics has the potential to map these and other features in the tumor microenvironment, revealing relationships between tumor cells, immune infiltrates, and stromal elements [76]. Artificial intelligence-based multi-omics data integration enables the correlation between chromatin states, transcriptional outputs, metabolic rewiring and immune signaling. Such analyses help in discovering until now unknown biomarkers, potential therapeutic targets and predictive treatment response signatures. Furthermore, the presence of the circulating methylated DNA from urine or plasma sample is non-invasive and can be used for early detection, monitoring therapeutic efficacy and following cancer evolution. Taken together, these techniques establish the groundwork for potential precision oncology approaches in UBC by demonstrating that patient stratification and therapy can be data-informed [77].

The increasing recognition of epigenetic deregulation in UBC has established the foundation for translation of chromatin- and histone-based markers into the clinics. Mutations in chromatin-remodeling genes, such as ARID1A and KMT2C/KMT2D, or histone-modifying enzymes (e.g., EP300/CREBBP/EZH2) are associated with unique prognostic and therapeutic phenotypes. For instance, ARID1A-deficient tumors have frequently defective DNA damage response and immune infiltration, therefore may be sensitive to the combination of epigenetic-immunotherapy whereas EZH2-overexpressed tumors are correlated with a high-risk phenotype and are also possible candidates for preferential sensitivity to EZH2 inhibition. In addition to gene mutations, epigenetic characteristics such as chromatin accessibility, histone modification profile and DNA methylation status serve as independent biomarkers for the stratification of patients. Notably, urine- or plasma-based DNA meUrothelial bladder cancer (UBC) is a molecular and clinically heterogeneous disease in which epigenetic alterations have been proven critical for tumor behavior, progression and response to therapy. Abnormalities in chromatin remodeling, imbalances in histone modifications, and changes in DNA methylation all contribute to reprogramming of transcriptional programs, enhancer landscapes and tumor–immune interactions leading to intratumoral heterogeneity, immune escape and resistance to therapy. Somatic mutations, especially those in major epigenetic regulators such as ARID1A, KMT2C, KMT2D, EP300, CREBBP and EZH2 play both mechanistic roles but also present promising biomarkers for patient stratification and prognosis evaluation and potential targeted therapy.

The epigenetic changes are reversible, which provides special opportunities for therapy. Pharmacologic inhibition of EZH2, HDACs, BET proteins, DNMTs and selected chromatin remodelers, as monoagents or in combination with immunotherapy, chemotherapy or targeted therapy hold promise to reactivate TS gene expression, control enhancer function and to sensitize tumors to killing by immunity. Recent advances in single-cell and spatial epigenomics when combined with multi-omics and AI-driven approaches are making it possible to map the heterogeneity of tumors in ever increasing precision allowing for identification of actionable vulnerabilities. Future research focuses are chromatin subtypes characterization, pharmacological targeting of the epigenome, discovery of synthetic lethality programs and real-time longitudinal assessments of evolving epigenomic states during therapy. It will be necessary to address these challenges, as well as intratumoral heterogeneity, and off-target effects of agents targeting the epigenome at high doses to fully exploit epigenetic vulnerabilities.

To conclude, the combination of mechanisms understanding, biomarker discovery and development, targeted therapeutics will place epigenetics at the center of precision oncology for UBC. These developments have the potential to facilitate early diagnosis, direct rational treatment choice and ultimately improve clinical outcomes in this aggressive and diverse condition.

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Non applicable.

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All data generated or analysed during this study are included in this publication.

Author contributions

Amr Abd-Elraheem Abdo, Ahmed Mohamed Kamel contributed to design of the work, data collection, and drafting the article.

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