Asian J. Med. Biol. Res. 2025, 11(2), 23-36; https://doi.org/10.3329/ajmbr.v11i2.79668

Asian Journal of Medical and Biological Research
ISSN 2411-4472 (Print) 2412-5571 (Online)
https://www.ebupress.com/journal/ajmbr/

Review

The role of DNA methylation and histone modifications in the pathogenesis of hematological malignancies and solid cancers: mechanisms, clinical implications, and therapeutic potential

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Received: 03 February 2025/Accepted: 27 March 2025/Published: 14 April 2025

Abstract: Epigenetic changes are increasingly acknowledged as crucial factors in the beginning of both blood cancers and solid tumors. These amendments, such as DNA methylation and histone changes, influence gene expression and cellular activities without altering the fundamental DNA sequence. This review aims to provide a comprehensive analysis of the role of DNA methylation and histone modifications in cancer pathogenesis, with a focus on their potential applications as diagnostic, prognostic, and therapeutic biomarkers. The review synthesizes findings from recent studies on epigenetic alterations in cancer, emphasizing their mechanistic roles in tumorigenesis, therapeutic resistance, and tumor heterogeneity. Relevant studies were chosen for their focus on DNA methylation, histone modifications, and their clinical significance. This review highlights the frequent occurrence of tumor suppressor gene hypermethylation and oncogene hypomethylation across various cancers. Additionally, changes in histone modifications, such as acetylation, methylation, and phosphorylation, can alter chromatin configuration and play a significant role in the emergence of oncogenic characteristics. The crosstalk between these epigenetic mechanisms contributes to the reprogramming of the cancer epigenome, driving tumor heterogeneity and resistance to therapy. Understanding the mechanisms of epigenetic alterations in cancer provides new opportunities for developing targeted therapies and improving patient outcomes. Epigenetic biomarkers hold promise for early diagnosis, prognosis, and personalized treatment strategies. This review underscores the importance of epigenetic research in oncology, offering insights into novel therapeutic targets and strategies. It also highlights the need for further studies to translate these findings into clinical applications, ultimately reshaping cancer treatment paradigms.

Keywords: epigenetics; gene silencing; therapeutic biomarkers; cancer stem cells; cancer therapy

1. Introduction

Epigenetics examines inherited changes in gene activity that do not involve changes to the DNA sequence itself. Instead, these changes are influenced by modifications to chromatin structure and the proteins interacting with DNA (Gu *et al.*, 2024; Wang *et al.*, 2024a). Epigenetic changes are essential for regulating gene expression, playing a key role in maintaining cellular functions, development, and tissue balance in response to both internal and external factors (Su *et al.*, 2024). Key modifications, such as DNA methylation and histone alterations, interact to reshape chromatin and control transcription (De Plano *et al.*, 2024; Zhang *et al.*, 2024). DNA methylation involves the addition of a methyl group to cytosine bases in CpG dinucleotides, often leading to gene silencing (El Omari *et al.*, 2025). Meanwhile, histone modifications, including acetylation, methylation,

phosphorylation, and ubiquitination, alter chromatin structure, affecting its accessibility and thus regulating gene activity (Lossi *et al.*, 2024). These processes work in concert to ensure accurate gene regulation under normal physiological conditions.

Epigenetic modifications are constantly changing and can be affected by both internal and external factors, such as environmental influences, the aging process, and different disease conditions (Griñán-Ferré *et al*., 2024). When these regulatory mechanisms are disrupted, it can lead to the onset of numerous diseases, particularly cancer. In the context of cancer progression, irregular DNA methylation and histone modification patterns may silence tumor suppressor genes or activate oncogenes, thereby promoting unchecked cell growth and malignant transformation (Dakal *et al*., 2024; Rahimi-Farsi *et al*., 2025). Additionally, these alterations often emerge at early stages of tumor development, underscoring their potential as biomarkers for early cancer detection. Increasing evidence supports the idea that epigenetic changes are reversible, offering valuable opportunities for therapeutic intervention. Unlike genetic mutations, which are irreversible, epigenetic changes can be modified by therapeutic agents, presenting a valuable opportunity for cancer treatment. Drugs targeting epigenetic modifications, such as DNA methyltransferase inhibitors (DNMTis) and histone deacetylase inhibitors (HDACis), have already been authorized for treating some blood cancers, and their potential for treating solid tumors is currently under investigation (López-Hernández *et al*., 2025). Pioneering research on DNA methyltransferases (DNMTs) and histone deacetylases (HDACs) has greatly enhanced our understanding of epigenetic regulation, particularly in relation to gene expression, cellular differentiation, and disease progression. DNMTs, such as DNMT1, DNMT3A, and DNMT3B, are enzymes that add methyl groups to cytosine residues in DNA, typically resulting in transcriptional repression. In the 1980s, Bestor and colleagues identified DNMT1 as a maintenance methyltransferase essential for maintaining DNA methylation patterns during replication. Subsequent research revealed that DNMT3A and DNMT3B function as de novo methyltransferases, crucial for establishing new DNA methylation patterns during development. These discoveries were pivotal in elucidating the role of DNA methylation in key biological processes such as genomic imprinting, X-chromosome inactivation, and the silencing of transposable elements (Bestor, 1992; Okano *et al*., 1999; Jones and Baylin, 2002).

HDACs, on the in contrast, other hand, remove acetyl groups from histone proteins, leading toresulting in chromatin condensation and transcriptional repression. The discovery of HDACs originated from studies on histone acetylation and its correlation with gene activation in the 1960s. Notable research by Allis and colleagues in the 1990s identified specific HDAC enzymes, such as HDAC1 and HDAC2, and linked them to transcriptional co-repressor complexes. Additionally, research by Grunstein and others demonstrated the role of HDACs in maintaining chromatin structure and regulating gene expression (Grozinger and Schreiber, 2002; Marks and Xu, 2009). These investigations revealed the interplay between DNA methylation and histone modifications, uncovering a sophisticated epigenetic network that governs cellular activities. Disruptions in DNMTs and HDACs have been associated with a range of diseases, including cancers and neurological conditions, highlighting their significance as potential targets for therapeutic interventions.

Research into epigenetic modifications in cancer has greatly advanced our understanding of the molecular mechanisms driving malignancies and has paved the way for personalized medicine. The identification of epigenetic biomarkers holds promise for improving cancer diagnosis, prognosis, and treatment response prediction, leading to enhanced patient outcomes. This study aims to explore how epigenetic processes contribute to cancer progression and resistance to therapy, with the objective of identifying new therapeutic targets and biomarkers for more effective, individualized cancer treatments. The review delves into the fundamental roles of DNA methylation and histone modifications in the development of both hematological cancers and solid tumors, highlighting their potential as targets for innovative cancer therapies (Sadida *et al*., 2024; Shaik *et al*., 2025).

2. DNA methylation in cancer

DNA methylation is an essential epigenetic modification that regulates gene activity and helps preserve genomic integrity. This modification involves the attachment of a methyl group (-CH_3) to the 5' carbon of cytosine bases, most commonly within CpG dinucleotides, and is facilitated by DNMTs (De Riso *et al*., 2025). In normal cells, DNA methylation serves to regulate gene expression, silencing unwanted or repetitive sequences and stabilizing the genome (Xu *et al*., 2025). However, in cancer, abnormal DNA methylation patterns are a hallmark of tumorigenesis, contributing to both the initiation and progression of malignancies (Figure 1).

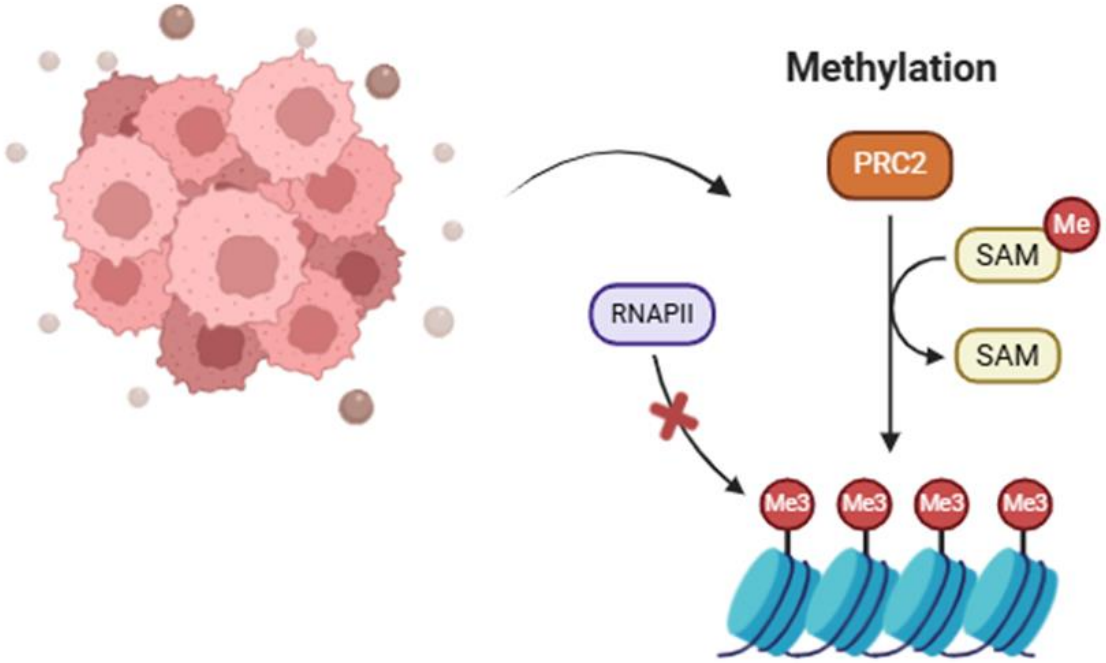

Figure 1. Illustrating DNA methylation in cancer. It highlights both hypermethylation of tumor suppressor genes (leading to gene silencing) and hypomethylation of oncogenes (leading to gene activation. The representation of DNA structure with methyl groups attached to cytosine bases in CpG dinucleotides. This figure is generated using Bio render.

In cancer, two main types of DNA methylation changes are typically observed. One key alteration is the hypermethylation of tumor suppressor genes, particularly the methylation of CpG islands in their promoter regions. This methylation silences the tumor suppressor genes, promoting uncontrolled cell division and contributing to the development of malignancy (Qian *et al*., 2025). This hypermethylation leads to the silencing of essential tumor suppressor genes, impairing their role in regulating processes such as cell growth, apoptosis, and DNA repair. Genes like p16INK4a, BRCA1, MLH1, and CDKN2A are frequently silenced through promoter hypermethylation in a wide range of cancers, including both hematological malignancies and solid tumors (El Omari *et al*., 2025). The inactivation of tumor suppressor genes leads to unchecked cell proliferation and tumor development. Additionally, hypomethylation of oncogenes and repetitive DNA sequences is another key characteristic of cancer, promoting the activation of oncogenes and enhancing genomic instability (Molefi *et al*., 2025). Decreased DNA methylation at the promoters of oncogenes can trigger their activation, leading to unchecked cell division and survival. Likewise, hypomethylation of repetitive sequences, like transposable elements, can cause genomic instability, which further accelerates cancer progression (Wang *et al*., 2023). Hypomethylation can also impact genes related to inflammation and immune evasion, thereby promoting tumorigenic processes and facilitating cancer progression.

2.1. Aberrant DNA methylation and cancer progression

In cancer, the disruption of DNA methylation patterns is frequently associated with other genomic abnormalities, including mutations, chromosomal instability, and loss of heterozygosity (Pappalardo and Barra, 2022; Chen *et al*., 2024a). These changes collectively drive the transformation of normal cells into cancerous ones, promoting uncontrolled growth and tumor progression. Aberrant methylation may also influence the tumor microenvironment, impacting immune evasion and tumor angiogenesis, which are critical for tumor survival and metastasis. Moreover, the reversal of abnormal DNA methylation offers therapeutic potential. DNA methylation-targeting drugs, such as azacitidine and decitabine, are currently used in treating certain hematological cancers, including myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML) (Hojjatipour *et al*., 2024). These agents inhibit DNMTs, leading to the reactivation of silenced tumor suppressor genes. However, the clinical efficacy of these therapies is still under investigation, and their use may be enhanced when combined with other targeted or immunotherapeutic approaches.

2.2. DNA methylation as a biomarker

In addition to its potential as a therapeutic target, DNA methylation holds promise as a diagnostic and prognostic biomarker (Parikh and Shah, 2024). Abnormal DNA methylation patterns found in circulating tumor DNA (ctDNA) or tissue biopsies can offer crucial insights for early cancer detection, prognosis, and predicting responses to treatment (Zhu *et al*., 2024). Distinct DNA methylation signatures have been discovered for various cancers, including breast, colon, lung, and hematological cancers, providing a non-invasive approach to monitor disease progression and assess treatment effectiveness (Zakari *et al*., 2024). DNA methylation plays a crucial role in the development of both hematological malignancies and solid tumors. Its dynamic and reversible changes in cancer make it a promising target for therapeutic strategies (Lee *et al*., 2024). Ongoing research into the mechanisms of DNA methylation in cancer, along with the advancement of methylation-targeted therapies, has the potential to greatly enhance cancer diagnosis, treatment, and overall patient outcomes (Table 1).

Table 1. Summarizing notable DNA methylation and histone modification biomarkers currently utilized in cancer diagnosis and treatment.

Biomarker	Type	Associated cancer(s)	Clinical application	Notes	References
MGMT promoter methylation	DNA methylation	Glioblastoma	Predictive	Indicates response to alkylating agents like temozolomide.	Liang *et al*., 2024
GSTP1 hypermethylation	DNA methylation	Prostate cancer	Diagnostic	Detected in over 90% of prostate cancer cases.	Muletier *et al*., 2025
SEPT9 methylation	DNA methylation	Colorectal cancer	Diagnostic	Basis for blood-based screening tests.	Khabbazpour *et al*., 2024
p16INK4a (CDKN2A) methylation	DNA methylation	Multiple cancers (e.g., cervical, lung)	Diagnostic/Prognostic	Associated with tumor suppressor gene silencing.	Farshadi, 2024
BRCA1 promoter methylation	DNA methylation	Breast and ovarian cancer	Prognostic	Linked to reduced gene expression and increased cancer risk.	Azaïs *et al*., 2024
H3K27me3 (trimethylation of histone H3 at lysine 27)	Histone modification	Various cancers	Prognostic	Associated with gene silencing and poor prognosis.	Miziak *et al*., 2024
H3K9ac (acetylation of histone H3 at lysine 9)	Histone modification	Various cancers	Prognostic	Correlates with active gene transcription and better outcomes.	Chen *et al*., 2024b

3. Histone modifications and cancer

Histone post-translational modifications (HPTMs) are essential components of epigenetic regulation, attracting increasing attention for their critical roles in disease development and progression. Additionally, their potential as therapeutic targets makes them a promising area of research (Pan *et al*., 2024). Recent developments in high-throughput molecular methods, alongside the increasing abundance of bioinformatics data, have paved the way for identifying new HPTMs. These modifications play pivotal roles in controlling gene expression, metabolism, and the overall structure of chromatin (Yu *et al*., 2024). Additionally, a growing body of research has highlighted that newly discovered histone modifications play critical roles in the onset and progression of numerous diseases, including various cancers, cardiovascular diseases, infections, psychiatric conditions, and disorders of the reproductive system (Figure 2). This review explores nine emerging histone modifications: lactylation, citrullination, crotonylation, succinylation, SUMOylation, propionylation, butyrylation, 2-hydroxyisobutyrylation, and 2-hydroxybutyrylation (Yao *et al*., 2024).

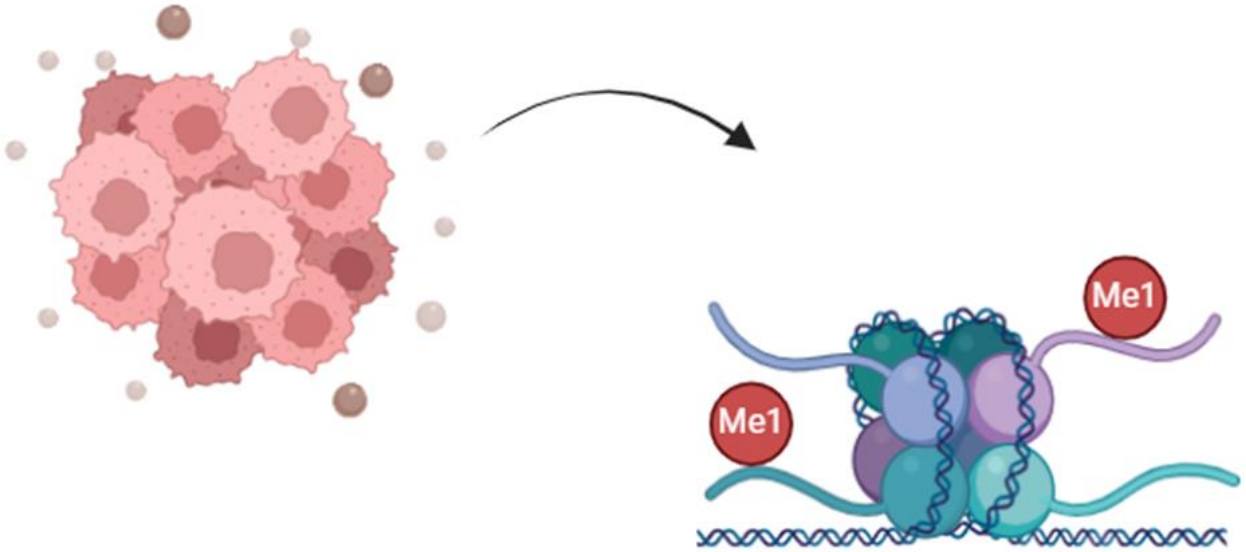

Figure 2. Schematic overview of histone modification in cancer cells. This figure is generated using Bio render.

Histone lactylation is a non-enzymatic acylation involving lactate-derived acetyl donors, influencing gene activation, particularly in inflammatory responses and tumor microenvironments. It has been implicated in macrophage polarization and cancer metabolism. Catalyzed by peptidylarginine deiminases (PADs), citrullination converts arginine residues to citrulline, leading to chromatin decondensation. This modification plays critical roles in neutrophil extracellular trap formation, autoimmune diseases, and cancer progression. Histone crotonylation, an acylation modification similar to acetylation, enhances transcriptional activation (Bruno *et al*., 2025). It is linked to spermatogenesis, stem cell differentiation, and oncogene regulation, with potential as a cancer biomarker. This modification involves the addition of succinyl groups to lysine residues, leading to significant structural changes in histones. It is associated with metabolic pathways, mitochondrial function, and tumorigenesis, often regulated by sirtuins. Small ubiquitin-like modifier (SUMO) proteins attach to histones, influencing chromatin condensation and transcriptional repression. SUMOylation plays a key role in DNA damage repair, neurodegenerative diseases, and cancer. Histone propionylation affects nucleosome stability and transcriptional regulation, particularly in fatty acid metabolism and immune response modulation. Dysregulation has been linked to metabolic disorders and cancer. Butyrylation, similar to acetylation, facilitates gene activation by altering chromatin accessibility. It has been found in metabolic tissues and has potential implications in obesity, diabetes, and cancer. This modification affects lysine residues and has been identified as a regulator of active transcription in spermatogenesis, metabolic pathways, and cancer progression. 2-Hydroxybutyrylation, Related to metabolic stress, this modification impacts gene expression linked to glycolysis and oxidative stress, with emerging roles in tumorigenesis and metabolic disorders (Yao *et al*., 2024).

This review offers an in-depth overview of the modification mechanisms of nine novel HPTMs, highlighting their influence on transcription, replication, DNA repair and recombination, metabolism, and chromatin architecture. Additionally, it examines their contribution to the onset and development of various diseases and explores their potential as therapeutic targets and biomarkers in clinical applications (Table 1). This review also presents a thorough analysis of inhibitors targeting novel HPTMs across different pathways, highlighting new therapeutic strategies for addressing a variety of diseases. It explores the future prospects and challenges associated with the development of these inhibitors. In addition, we provide an overview of emerging epigenetic research techniques and their role in advancing the study of novel HPTMs (Yao *et al*., 2024).

It is widely recognized that epigenetic alterations are central to the initiation and progression of cancer (Wang *et al*., 2024b). Epigenetic regulation of chromatin is characterized by covalent modifications, including acetylation, methylation, phosphorylation, and ubiquitination, of histones and other core nucleosomal proteins (Chen *et al*., 2024c). Recent progress in histone modification and chromatin research has significantly deepened our understanding of the mechanisms governing essential physiological and pathological processes (Tonti *et al*., 2024). Histone modifications, together with other epigenetic mechanisms, work in concert to define and maintain gene expression patterns, playing a crucial role in controlling various cellular functions (Kiri and

Ryba, 2024). Different histone modifications operate in a coordinated and structured way to influence key cellular functions such as gene transcription, DNA replication, and DNA repair (Wong and Tremethick, 2024). In the last ten years, interest in histone modifications has grown considerably, driven by the identification and detailed study of a wide range of histone-modifying enzymes and associated protein complexes (Das *et al*., 2024). Malfunctions in histone-modifying complexes are believed to disturb the distribution and levels of histone marks, disrupting chromatin regulation and playing a role in oncogenic transformation and the progression of cancer (Kawaf *et al*., 2024). Supporting this notion, abnormal histone modification patterns have been associated with numerous types of human cancers.

Additionally, cancer cells exhibit significant alterations in histone mark patterns. The disruption of epigenetic regulation through histone-modifying complexes and histone marks may play a crucial role in the initiation and progression of cancer (Ramazi *et al*., 2024). These mechanisms can promote on cogenesis by disrupting gene transcription and DNA repair processes. Additionally, growing evidence suggests that distinct types and subtypes of cancer exhibit unique patterns of histone modifications, known as histone modification signatures, which could be leveraged for biomarker discovery. Moreover, given that histone modifications are reversible, they present promising targets for cancer therapy and prevention.

3.1. Cross-talk between DNA methylation and histone modifications

The interplay between DNA methylation and histone modifications is flexible and involves several pathways. Methylation of DNA at promoter regions can lead to the recruitment of methyl-CpG-binding domain (MBD) proteins, which then facilitate the binding of HDACs and histone methyltransferases like SUV39H1 (Figure 3). These enzymes modify histones (e.g., H3K9me3), establishing a repressive chromatin environment (Delphin *et al*., 2024). In contrast, histone H3K4me3, associated with active transcription, can inhibit DNMTs, preventing DNA methylation at active promoters (Sinha *et al*., 2024). H3K9me3, linked to heterochromatin formation, promotes the recruitment of DNMTs, enhancing DNA methylation at repressed regions (Pan *et al*., 2025).

The presence of DNA methylation can also influence chromatin structure, promoting histone modifications that either further reinforce repression or activate transcription. For example, DNA methylation recruit's histone-modifying enzymes, leading to the establishment of repressive marks like H3K9me3 (Marques *et al*., 2024). Conversely, active histone modifications such as H3K4me3 at gene promoters prevent DNMT binding, maintaining gene expression by avoiding DNA methylation (Sinha *et al*., 2024). This interaction plays a vital role in controlling gene expression. Genes that are actively transcribed typically exhibit low DNA methylation along with activating histone modifications, whereas genes that are silenced tend to display elevated DNA methylation accompanied by repressive histone marks (Han *et al*., 2024). This dynamic interaction also affects the accessibility of chromatin. Repressive marks, such as DNA methylation and H3K9me3, promote a tightly packed chromatin configuration, thereby restricting the access of transcriptional machinery to the DNA (Li *et al*., 2024). Conversely, activating modifications—such as the lack of DNA methylation and the presence of H3K4me3—lead to a relaxed, open chromatin state that facilitates transcription (Yu and Lesch, 2024). The interplay between DNA methylation and histone modifications is crucial for proper development, cell differentiation, and preserving epigenetic stability. When this coordination is disrupted, it can contribute to various diseases, including cancer, where irregular patterns of DNA methylation and histone marks can cause inappropriate gene silencing or activation of oncogenes (Xie *et al*., 2024).

4. Epigenetic drivers of cancer stem cells (CSCs)

Epigenetic control of CSCs is a key factor in cancer biology, impacting tumor onset, development, and the ability of cancer cells to resist treatment (El-Tanani *et al*., 2025). The CSCs represent a unique subset within tumors, characterized by stem-like properties including self-renewal and the ability to differentiate. They are thought to be major contributors to tumor initiation and the recurrence of cancer following therapy (Ruszkowska-Ciastek *et al*., 2024). The activity of CSCs is largely governed by epigenetic changes, which influence gene expression without altering the underlying DNA sequence (Bhartiya *et al*., 2024). These epigenetic changes—such as DNA methylation, histone modifications, and non-coding RNA activity—collaborate to maintain the stem-like traits of CSCs and may also play a role in converting normal stem cells into malignant ones.

4.1. DNA methylation and cancer stem cells

DNA methylation is crucial in regulating CSCs. This process involves the addition of a methyl group to cytosine residues, primarily at CpG sites. In cancer, abnormal DNA methylation patterns disrupt normal gene regulation, promoting the self-renewal and malignant characteristics of CSCs, which contribute to tumor initiation,

progression, and therapy resistance (Gupta *et al*., 2024). Typically, in normal stem cells, gene promoters remain unmethylated to permit the expression of pluripotency genes such as OCT4 and SOX2 (Ma *et al*., 2024). However, in CSCs, hypermethylation of tumor suppressor genes like PTEN, TP53, and BRCA1 can silence these genes, facilitating cancer progression (Nagasaka, 2024). Conversely, hypomethylation of oncogenes or transposable elements, including MYC and K-RAS, often leads to their activation, contributing to tumorigenesis and promoting CSC proliferation. A significant DNA methylation phenotype, called the CpG island methylator phenotype (CIMP), is found in some cancers, where widespread hypermethylation across large genomic regions contributes to the establishment of CSCs (Zhao *et al*., 2024). The association between DNA methylation and the regulation of CSC self-renewal highlights the potential for methylation biomarkers in diagnosing and prognosticating cancer. However, challenges remain in validating these biomarkers clinically, as their role can vary depending on the type of cancer and its microenvironment.

Figure 3. Interaction between DNA methylation and histone modifications in the regulation of gene expression.

4.2. Histone modifications and CSC regulation

Histone modifications like acetylation, methylation, and phosphorylation are crucial for controlling chromatin organization and modulating gene expression. In CSCs, these modifications are often dysregulated, affecting the expression of genes involved in CSC self-renewal, differentiation, and resistance to therapy. This dysregulation contributes to the persistence and aggressiveness of CSCs within tumors (Prabhu *et al*., 2024). In CSCs, histone acetylation is associated with active transcription, with marks such as H3K27ac and H3K9ac being prominent.

Reduced acetylation, typically due to the upregulation of HDACs, is linked to CSC maintenance and therapy resistance. HDAC inhibitors (HDACi) are being explored as potential treatments to target CSCs and overcome therapeutic resistance (Chen *et al*., 2024d). The dysregulation of specific histone methylation marks also plays a key role in CSC behavior. For instance, H3K4me3, typically found in the promoters of stemness genes such as SOX2 and OCT4, maintains their expression and promotes CSC properties (Fatma and Siddique, 2024). On the other hand, H3K27me3, catalyzed by the polycomb repressive complex 2 (PRC2), is linked to gene repression and helps maintain the undifferentiated state of cancer stem cells by preventing their differentiation (Shaalan *et al*., 2025). Additionally, the collaboration of H3K9me3, a heterochromatin mark, with DNA methylation in CSCs serves to silence genes that regulate differentiation, reinforcing stemness and contributing to cancer progression (Rajendran *et al*., 2025).

4.3. Non-coding RNAs in CSC regulation

Non-coding RNAs, such as microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), have emerged as important modulators of CSC activity. They regulate gene expression at transcriptional and post-transcriptional stages, significantly impacting CSC traits like self-renewal, differentiation, and therapeutic resistance (Yang *et al*., 2024). MicroRNAs (miRNAs) are short RNA molecules that control gene expression by targeting the 3' untranslated regions (UTRs) of specific mRNAs. In cancer stem cells, miRNAs can act as oncogenes (oncomiRs) promoting tumor growth, or as tumor suppressors inhibiting it. For instance, miR-34a, which targets key pathways such as NOTCH and p53, is often downregulated in CSCs. This downregulation contributes to the maintenance of stemness and enhances resistance to chemotherapy, highlighting its role in CSC biology (Muthukumar *et al*., 2024). Likewise, the miR-200 family is critically involved in controlling the epithelial-to-mesenchymal transition (EMT), a key mechanism that facilitates the migration and metastatic potential of cancer stem cells. By modulating key EMT-related genes, miR-200 family members influence the acquisition of invasive and metastatic properties in CSCs, further contributing to tumor progression and resistance to therapy (Khan *et al*., 2024). LncRNAs, which can act as scaffolds or decoys for epigenetic regulators and transcription factors, also influence CSC behavior. Some lncRNAs, such as HOTAIR and MALAT1, are overexpressed in CSCs and help maintain their self-renewal properties by interacting with chromatin-modifying enzymes, thereby promoting tumor progression (Huang *et al*., 2024).

Although epigenetic modifications are central to the regulation of CSCs, translating this understanding into clinical practice presents a number of significant challenges. The development and validation of reliable methylation biomarkers for CSC detection and prognosis are hindered by the complexity of tumor heterogeneity and the dynamic nature of epigenetic modifications. Clinical trials targeting epigenetic regulators, such as HDACi, have shown promise in preclinical models but are limited by issues of toxicity, specificity, and off-target effects in patients (Chen *et al*., 2024a). Moreover, the complex interactions among DNA methylation, histone modifications, and non-coding RNAs in cancer stem cells call for a comprehensive strategy to effectively target these regulatory networks. Continued investigation is essential to fully understand how these epigenetic changes influence CSC behavior and to design precise, low-toxicity therapeutic interventions. In summary, while epigenetic regulation of CSCs is crucial in cancer progression, the clinical validation of these mechanisms and the challenges associated with epigenetic therapies must be critically addressed. Expanding on these aspects will provide a more comprehensive understanding of CSC biology and improve the development of effective therapeutic strategies.

4.4. Signaling pathways modulating epigenetics in CSCs

Multiple critical signaling pathways contribute to the epigenetic control of cancer stem cells, notably the Wnt/β-catenin pathway. Wnt signaling is fundamental for maintaining stemness and self-renewal in both normal stem cells and CSCs. In CSCs, abnormal activation of this pathway frequently results in changes to DNA methylation and histone modifications, reinforcing their undifferentiated and tumor-promoting state (Lei *et al*., 2024). The notch pathway also regulates CSC self-renewal and differentiation. Aberrant notch signaling in CSCs can affect the expression of genes that are epigenetically regulated, such as HES1 and HEY1, which are linked to stem cell maintenance (Pandey *et al*., 2024). Hippo pathway: the hippo pathway, which regulates cell proliferation and organ size, also controls CSC self-renewal. Epigenetic modifications can influence the transcription factors involved in this pathway, such as YAP/TAZ, which are critical for CSC maintenance (Sadri *et al*., 2024). TGF-β Signaling: TGF-β can induce EMT and promote stemness in CSCs, in part by altering epigenetic marks such as DNA methylation and histone modifications (Lei *et al*., 2024) (Figure 4).

Epigenetic changes are reversible, which makes targeting the epigenetic regulators of CSCs a promising therapeutic strategy. Some potential approaches include, the epigenetic modifiers such as drugs that target

DNMTs (e.g., decitabine), HDACs (e.g., vorinostat), and histone methyltransferases are being explored to reverse the epigenetic marks that maintain CSC properties (Mungly *et al*., 2024). Inhibition of signaling pathways which targeting pathways like Wnt, notch, or TGF-β that influence epigenetic changes in CSCs could also provide therapeutic benefits (Joshi and Basu, 2024). Combination therapies, which involve integrating epigenetic treatments with standard chemotherapy or immunotherapy, have the potential to improve the eradication of cancer stem cells (CSCs), minimize tumor relapse, and help overcome resistance to treatment (Gu *et al*., 2025) (Figure 4).

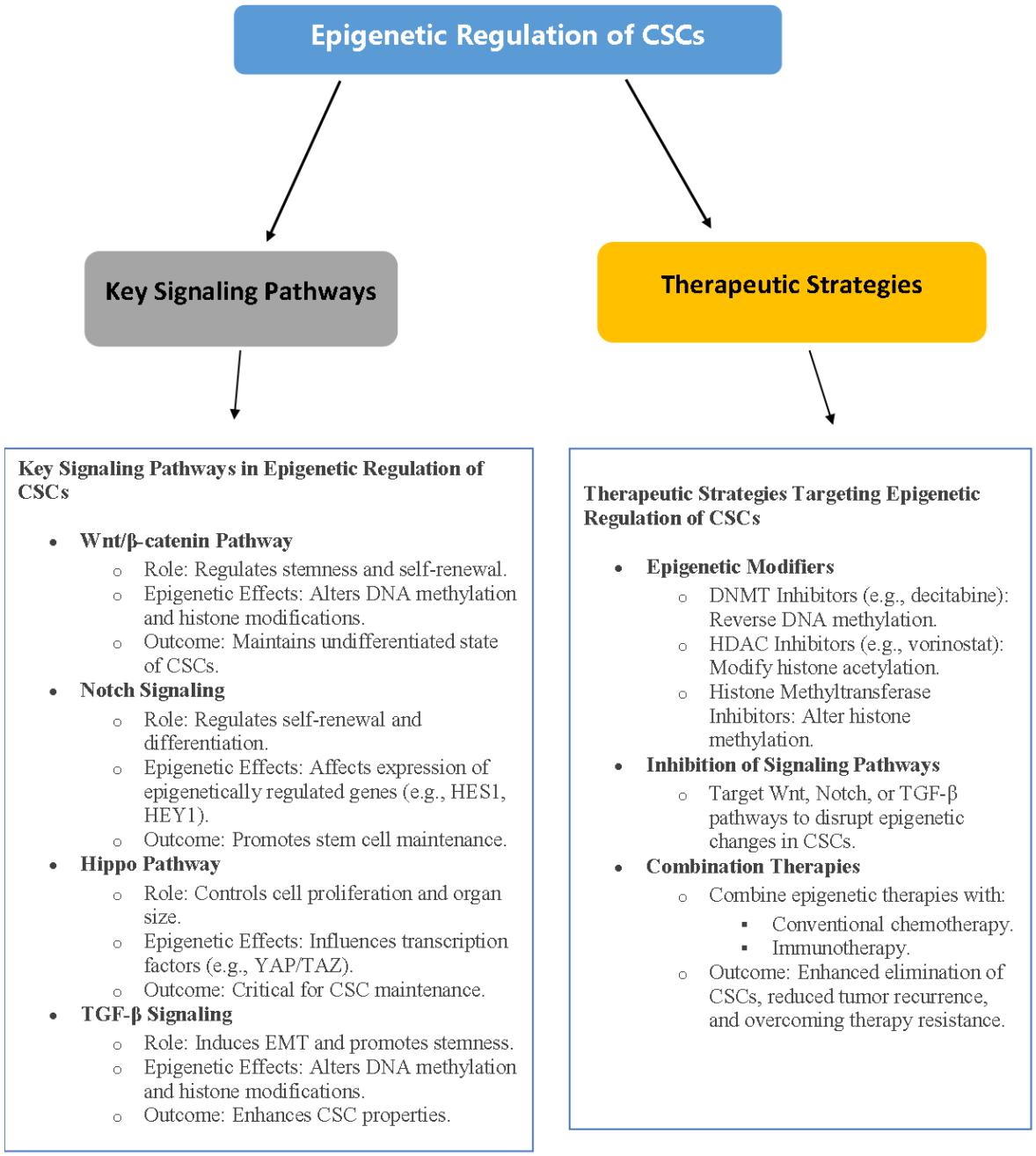

Figure 4. The key signaling pathways involved in the epigenetic regulation of cancer stem cells (CSCs) and potential therapeutic strategies. The Wnt/β-catenin, notch, hippo, and TGF-β pathways play critical roles in maintaining CSC stemness and self-renewal through epigenetic mechanisms such as DNA methylation and histone modifications. Targeting these pathways and employing epigenetic modifiers (e.g., DNMT and HDAC inhibitors) or combination therapies (e.g., chemotherapy and immunotherapy) offers promising approaches to eliminate CSCs, reduce tumor recurrence, and overcome therapy resistance.

5. Clinical implications

Epigenetic changes, such as DNA methylation and histone modifications, are crucial in the diagnosis, prognosis, and therapeutic management of both solid tumors and hematological cancers (Hojjatipour *et al*., 2024). Abnormal DNA methylation patterns, particularly promoter hypermethylation of tumor suppressor genes, are commonly utilized as biomarkers for early cancer diagnosis and assessing patient risk levels. For example, hypermethylation of *BRCA1* in breast cancer or *MLH1* in colorectal cancer is indicative of specific cancer subtypes and guides treatment decisions (Li *et al*., 2025). Similarly, hypomethylation of oncogenes can serve as a prognostic marker in aggressive cancers, such as AML. Histone modifications, including acetylation and methylation patterns, also influence chromatin accessibility and gene expression, making them valuable in identifying tumor aggressiveness or predicting therapeutic response (Roy *et al*., 2024). Incorporating epigenetic profiles into clinical settings enhances personalized medicine by enabling treatments to be customized according to the unique epigenetic characteristics of an individual's tumor.

Epigenetic therapies that target DNA methylation and histone modifications have transformed cancer treatment by reactivating normal gene expression patterns (Su *et al*., 2024). FDA-approved hypomethylating agents, such as azacitidine and decitabine, have shown significant success in treating hematological malignancies like MDS and AML. Similarly, HDAC inhibitors, such as vorinostat and romidepsin, are effective in treating T-cell lymphomas and other cancers (Merz *et al*., 2024). Combining these epigenetic therapies with traditional chemotherapies, immunotherapies, or targeted agents has further enhanced treatment efficacy and reduced resistance (Garg *et al*., 2024). Additionally, epigenetic alterations are now being explored as predictors of response to novel immunotherapies, such as checkpoint inhibitors. The growing understanding of epigenetic regulation and its clinical implications underscores the importance of integrating epigenetic biomarkers and therapies into routine cancer care to improve outcomes and extend survival.

6. Therapeutic potential

DNA methylation and histone modifications are emerging as valuable therapeutic targets for both hematological cancers and solid tumors. Agents designed to target these epigenetic changes have demonstrated promise in correcting abnormal modifications and reestablishing proper gene expression (Sadida *et al*., 2024; Sriwastava, 2025). Hypomethylating agents, such as azacitidine and decitabine, have been successfully used to treat conditions like MDS and AML, with evidence of improved survival and reduced disease progression. Similarly, HDAC inhibitors, including vorinostat and belinostat, have demonstrated efficacy in treating various cancers, particularly T-cell lymphomas (Temitope *et al*., 2025). These agents disrupt the cancer-promoting epigenetic landscape, leading to apoptosis, cell cycle arrest, and increased sensitivity to other therapies.

Emerging therapies that target more specific epigenetic regulators, such as bromodomain and extra-terminal (BET) inhibitors and histone methyltransferase (HMT) inhibitors, hold great promise for cancers resistant to conventional treatments (El Omari *et al*., 2025). BET inhibitors, for example, disrupt transcriptional programs driven by oncogenes like *MYC* and are being actively explored in clinical trials for both solid tumors and hematological malignancies (Ji *et al*., 2025). Additionally, combinations of epigenetic drugs with immunotherapies, such as checkpoint inhibitors, are being investigated to enhance antitumor immune responses. Advances in epigenetic editing technologies, such as CRISPR-dCas9 systems, also offer potential for precise and durable modifications of the epigenome, providing new avenues for cancer treatment. These therapeutic approaches underscore the transformative potential of epigenetics in developing more effective, targeted, and personalized cancer treatments.

7. Conclusions

The integration of epigenetic mechanisms into cancer research has unveiled new insights into tumor biology, offering promising avenues for the development of more personalized and precise therapeutic strategies. By utilizing advanced tools like next-generation sequencing, single-cell epigenomics, and CRISPR-dCas9-mediated epigenetic editing, researchers are gaining a deeper understanding of cancer heterogeneity and its underlying epigenetic alterations. These advancements pave the way for more targeted therapies with minimal off-target effects, although challenges such as resistance, toxicity, and therapy optimization remain. The ongoing exploration of epigenetic dysregulation in both hematological and solid tumors has already shown clinical potential, and continued research is crucial for overcoming existing obstacles and improving outcomes in cancer care.

Acknowledgements
The authors are thankful to Ala-Too International University for financial support and rewards for publication.

Data availability
All relevant data are presented within the manuscript.

Conflict of interest
None to declare.

Authors' contribution
Shafee Ur Rehman: collected the data and wrote the manuscript; Muhammad Abdullah, Zarak Khurshid Khan, and Moriom Shurovi: reviewed, edited and improved the final version of the article. All authors have read and approved the final manuscript.

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