

Epigenetic Dysregulation and Cancer Progression: How Epigenetic Modifications Shape Tumor Fate

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Abstract

Epigenetic modifications, including DNA methylation, histone modification, and non-coding RNAs, play crucial roles in regulating gene expression without altering the underlying DNA sequence. In cancer, these processes are frequently disrupted, leading to profound changes in cellular identity and function. Aberrant epigenetic regulation contributes not only to tumor initiation but also to disease progression, metastasis, immune evasion, and resistance to conventional therapies. Over the past few years, research has increasingly highlighted the dynamic interplay between genetic mutations and epigenetic alterations in shaping the tumor microenvironment and influencing patient prognosis. This article reviews the latest findings on epigenetic dysregulation in cancer, with an emphasis on how these modifications drive tumor heterogeneity and influence therapeutic response. We further examine emerging epigenetic drugs, including DNA methyltransferase inhibitors, histone deacetylase inhibitors, and RNA-based therapeutics, that are currently under investigation in clinical trials. Special attention is given to combination strategies that integrate epigenetic therapy with immunotherapy and targeted molecular agents, which have shown promise in overcoming drug resistance and improving treatment efficacy. Additionally, we explore the potential of epigenetic biomarkers as diagnostic, prognostic, and predictive tools in precision oncology. The incorporation of epigenetic signatures into clinical decision-making frameworks offers opportunities to tailor therapies to individual patient profiles and enhance survival outcomes. This review synthesizes recent advancements from 2022 to 2025, providing an updated perspective on how the expanding field of cancer epigenetics may transform future clinical practice.

Keywords Epigenetics · DNA methylation · Histone modifications · Cancer progression · Tumor fate

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Introduction

Cancer is fundamentally an epigenetic and genetic disorder. While gene mutations have long been recognized as the primary contributors to oncogenesis, increasing evidence indicates that epigenetic modifications also play a critical role in tumorigenesis (Smith et al., 2023). Epigenetic regulation involves heritable changes in gene expression through mechanisms such as DNA methylation, histone tail modification, chromatin remodeling, and non-coding RNA activity. (Guo et al., 2023). These modifications influence the expression or suppression of genes that are essential for cell growth, differentiation, apoptosis, and DNA repair (Zhang et al., 2024).

In contrast to genetic mutations, epigenetic changes are reversible, making them highly attractive targets for therapeutic intervention. Aberrant DNA methylation patterns, such as hypermethylation of tumor suppressor gene promoters and genomic instability resulting from global hypomethylation, are commonly observed across various malignancies (Patel et al., 2025). Additionally, irregular histone modifications and the expression of non-coding RNAs contribute to cancer heterogeneity, stemness, immune evasion, and resistance to therapy (Chen et al., 2025). This commentary highlights recent advancements in understanding how epigenetic dysregulation influences tumor behavior and the translational potential of targeting the epigenome in cancer treatment.

Epigenetic Modification and Mechanisms Alteration

Epigenetic modifications, including DNA methylation, histone modification, and non-coding RNAs, serve as critical regulators of gene expression without altering the primary sequence of the underlying DNA. Alterations in epigenetic mechanisms can contribute to cancer by facilitating abnormal patterns of gene expression that significantly enhance tumorigenesis and carcinogenesis (Wang et al., 2024).

DNA Methylation and Tumorigenesis

Recent evidence suggests that DNA methylation not only suppresses tumor suppressor genes but also alters the tumor microenvironment (Guo et al., 2023). Liquid biopsy strategies that identify methylated circulating tumor DNA (ctDNA) are being investigated as potential early diagnostic and prognostic biomarkers (Johnson et al., 2024). Patel et al. (2025) demonstrated that methylation signatures can predict

immunotherapy responses across various tumor types, marking a significant advancement in precision oncology.

Histone Modifications and Chromatin Remodeling

Recent advancements in chromatin profiling techniques, such as CUT&RUN and CUT&Tag, have uncovered new histone modification patterns linked to drug resistance and metastasis as illustrated in (Figure 1), epigenetics typically manifests through DNA methylation, histone modification, and higher-order chromatin regulation. These processes are influenced by the genome, transcriptome, and proteome, rendering them essential components of the intricate landscape of cancer progression. Epigenetics plays a crucial role in gene regulation, affecting cell fate, immune evasion, and drug resistance, thereby presenting valuable targets for therapeutic intervention and the development of novel pharmaceuticals. Findings from Kim et al. (2025) indicate that remodeling of H3K27ac is a key factor in endocrine resistance in hormone receptor-positive breast cancer, highlighting a therapeutic opportunity for the use of bromodomain inhibitors in combination therapy.

Non-Coding RNAs and Cancer Progression

Recent advancements in high-throughput sequencing have elucidated a complex landscape of non-coding RNA networks associated with cancer. Wang et al. (2025) demonstrated that specific long non-coding RNAs (lncRNAs) regulate the expression of immune checkpoint molecules, highlighting new potential targets for the optimization of immunotherapy. Additionally, contemporary findings indicate that miRNA editing processes serve as critical determinants of metastasis (Chen et al., 2025).

Epigenetic Influence on Tumor Progression and Metastasis

Epigenetic modification serves as a critical source of tumor heterogeneity and plays a significant role in the metastasis cascade. Epithelial-mesenchymal transition (EMT), a process in which epithelial cells acquire mesenchymal characteristics, is regulated by epigenetic modifications that repress epithelial markers while activating mesenchymal genes. This transformation enhances the motility and invasive capabilities of cancer cells, thereby facilitating metastasis (Sadida et al., 2024). Furthermore, epigenetic reprogramming contributes to the generation of cancer stem-like cells, which exhibit self-renewal properties and are implicated in tumor recurrence and resistance to standard therapies (Pote et al., 2024).

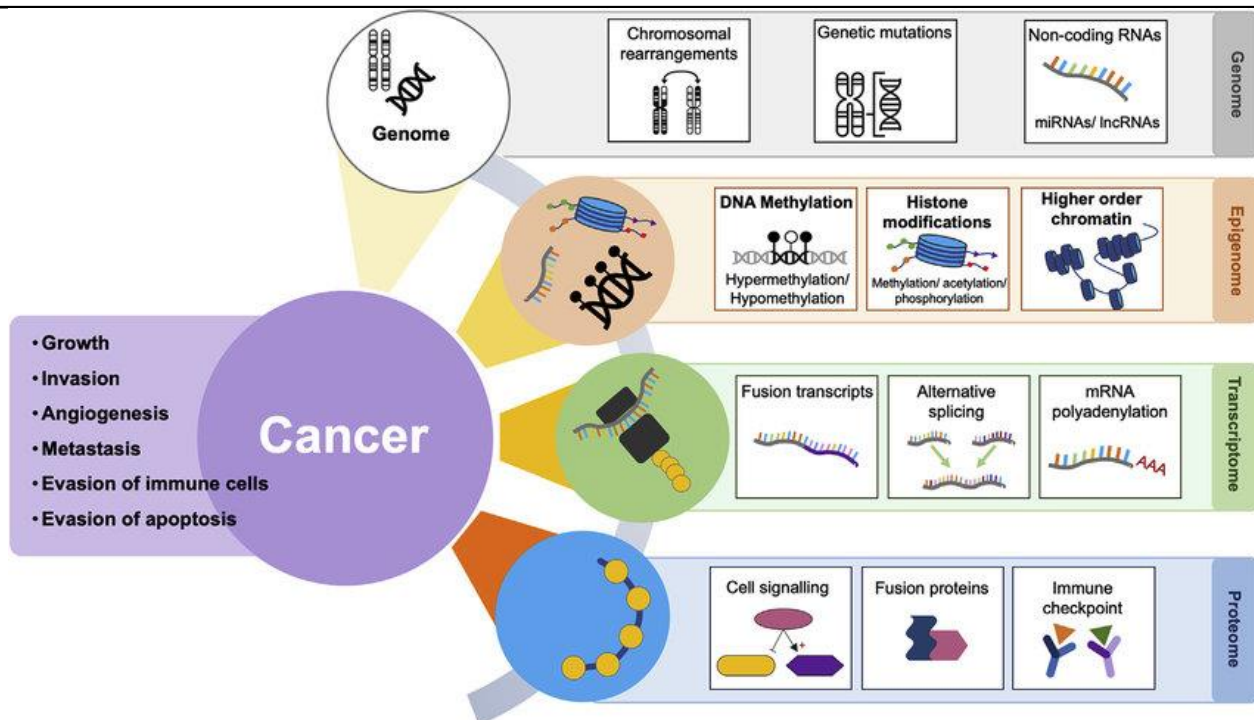


Figure 1. Overview of Epigenetic Alterations in Cancer

Epigenetic Modifications and Drug Resistance

Epigenetic modifications can also contribute to the development of drug resistance in cancer cells. Changes in histone modification and DNA methylation may lead to the silencing of genes associated with drug sensitivity, thereby reducing the efficacy of therapeutic interventions. For instance, hypermethylation of the *MLH1* gene, a key DNA mismatch repair gene, has been linked to resistance to alkylating agents in colorectal cancer (Castro-Muñoz et al., 2023). Understanding these epigenetic mechanisms is essential for the development of therapeutic strategies aimed at overcoming drug resistance.

Epigenetic Therapy and Precision Oncology

The reversible nature of epigenetic modifications offers significant opportunities for therapeutic intervention. Several clinical trials (2022–2025) are currently evaluating next-generation epigenetic drugs, as presented in (Table 1). It highlights promising epigenetic drugs in development or undergoing clinical trials from 2022 to 2025, categorizing them by type, listing representative drugs, defining their molecular targets, and outlining the major cancer indications. These advancements underscore the increasing potential for precision epigenetic therapy aimed at preventing tumor resistance and personalizing cancer treatments, including selective HDAC6 inhibitors, novel

BET degraders, DNA Methyltransferase Inhibitors (DNMTi), and EZH2 dual inhibitors (Patel et al., 2025). The integration of epigenomic and transcriptomic data is enhancing patient stratification, with multi-omics signatures now informing precision treatments (Wang et al., 2025). These therapies seek to restore normal gene expression patterns, thereby inhibiting tumor growth and overcoming drug resistance.

Challenges and Future Directions

Despite the growing promise of epigenetic therapies in oncology, several critical challenges continue to hinder their clinical effectiveness. Target selectivity, achieving specificity against cancer cells with low activity against normal cells is essential to reduce off-target toxicity. Additionally, many epigenetic regulators possess non-canonical functions beyond their enzymatic activity, making it difficult to design drugs that inhibit specific pathways without unintended consequences. Another major obstacle is the absence of reliable epigenetic biomarkers capable of predicting therapeutic response, which limits patient stratification and impedes personalized treatment approaches. Resistance to epigenetic therapies also poses a substantial hurdle; mechanisms of drug resistance must be better understood to inform effective combination strategies and enhance treatment durability in cancer epigenetic therapies.

Table 1. Recent Advances in Epigenetic Therapies (2022–2025) epigenetic drugs in development or undergoing clinical trials.

Therapy Type	Example Drugs	Targets	Indications
Selective HDAC inhibitors	Ricolinostat, ACY-1215	HDAC6	Solid tumors, lymphomas
BET degraders	ARV-771, dBET6	BET proteins	Breast, prostate cancer
EZH2 dual inhibitors	CPI-0209, Tazemetostat combos	H3K27 methylation	Solid tumors, lymphomas
Non-coding RNA modulators	Antisense oligos, siRNAs	Oncogenic lncRNAs, miRNAs	Metastatic cancers, immune modulation

Note: HDAC (Histone Deacetylase), BET (Bromodomain and Extra-Terminal domain), EZH2 (Enhancer of Zeste Homolog 2), and H3K27 (Histone 3 Lysine 27). Non-coding RNA modulators include lncRNA (Long Non-Coding RNA), miRNA (MicroRNA), and siRNA (Small Interfering RNA).

Looking ahead, future research should focus on unraveling the complex interactions between genetic mutations and epigenetic modifications in tumor biology. Developing next-generation epigenetic drugs with greater specificity and reduced systemic toxicity is essential for improving clinical outcomes. Moreover, the identification and validation of robust biomarkers will enable more precise patient selection, tailoring interventions to individuals most likely to benefit. A multidisciplinary approach integrating molecular biology, bioinformatics, and clinical oncology is imperative to translate these insights into tangible therapeutic advancements and reshape the future landscape of cancer treatment, ultimately moving toward more personalized, effective, and sustainable strategies in oncology.

Conclusion

Epigenetic deregulation is the primary driver of cancer growth and development by altering gene expression patterns and repatterning cellular behavior. A comprehensive understanding of these processes is essential for identifying novel therapeutic avenues and enhancing treatment outcomes. Ongoing research is revealing the complex interplay between genetic and epigenetic factors, paving the way for advancements in personalized medicine and improved cancer care. Moving forward, it will be crucial to integrate these findings into clinical practice to benefit patients across a diverse spectrum of cancer types.

Statements and Declarations

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Transparency Statement The author, Farzand Farhad Hamid, asserts that this manuscript provides an honest, accurate, and transparent account of the reported study. He confirms that no significant aspects of the study have been omitted and that any deviations from the original study plan, including registration if applicable, have been properly explained.

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