OXFORD JOURNAL
OF STUDENT
SCHOLARSHIP

Cancer Beyond Mutations: Epigenetic Regulation in Tumor Development, Progression, and Therapeutic Resistance

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ABSTRACT

Cancer has historically been defined as a genetic disease driven by the accumulation of mutations that alter oncogenes, tumor suppressor genes, DNA repair pathways, and other regulators of cellular homeostasis. Although this genetic model remains central to modern oncology, it does not fully account for the phenotypic diversity, plasticity, and therapeutic adaptability observed in tumors. Epigenetic regulation provides an additional layer of biological control by modulating gene activity without altering the underlying DNA sequence. Through mechanisms such as DNA methylation, histone modification, chromatin remodeling, and non-coding RNA regulation, epigenetic processes determine whether genomic regions remain transcriptionally active, repressed, or poised for activation. In normal tissues, these mechanisms are essential for the development, differentiation, and maintenance of cell identity. In cancer, however, epigenetic dysregulation can silence tumor suppressor pathways, activate oncogenic transcriptional programs, promote cellular plasticity, and contribute to treatment resistance. Importantly, many epigenetic alterations are dynamic and potentially reversible, making the cancer epigenome an appealing yet complex therapeutic target. This review summarizes the major mechanisms of epigenetic regulation, examines their roles in tumor development and progression, and discusses how epigenetic plasticity contributes to therapeutic resistance. Finally, it considers current and emerging approaches to epigenetic therapy and highlights the need for improved biomarkers and integrated molecular profiling to guide future clinical applications.

Keywords: epigenetics; cancer; DNA methylation; histone modification; chromatin remodeling; non-coding RNA; therapeutic resistance; epigenetic therapy

METHODS

A comprehensive literature search was conducted across the PubMed, Web of Science, Science Direct, and Scopus databases to identify peer-reviewed articles published between January 2020 and August 2026. The search strategy used important keywords and MeSH terms, including combinations of “epigenetics,” “DNA methylation,” “histone modification,” “chromatin remodeling,” and “non-coding RNA” paired with “cancer,” “tumorigenesis,” "therapeutic resistance,” and “epigenetic therapy.”

Additional relevant publications were identified through manual cross-referencing or citations from primary review articles.

Articles were evaluated based on predefined eligibility criteria. Included publications comprised peer-reviewed original research studies, clinical trial reports, and comprehensive reviews written in English that directly investigated epigenetic mechanisms in oncogenesis, tumor plasticity, drug-tolerant persistence, or clinical epigenetic therapeutics. Publications were excluded if the abstracts were lacking in full methodological detail, non-peer-reviewed preprints, commentaries, or studies primarily focused on non-oncological conditions or purely genetic mutations without an epigenetic evaluation.

1. INTRODUCTION: CANCER BEYOND MUTATIONS

Cancer is commonly described as a genetic disease because malignant transformation is frequently associated with alterations in DNA sequence. These alterations may activate oncogenes, inactivate tumor suppressor genes, impair DNA repair mechanisms, or disrupt pathways that regulate proliferation, differentiation, senescence, and cell death (Bandlamudi et al., 2026). The genetic model of cancer has provided a powerful framework for understanding tumor initiation and progression and has contributed to major advances in molecular diagnostics, targeted therapy, and precision oncology (Riedl et al., 2023).

However, DNA sequence alterations alone do not fully explain the biological complexity of cancer. Tumors with similar driver mutations may differ substantially in growth rate, metastatic behavior, immune recognition, and therapeutic response (Riedl et al., 2023). Conversely, cells with nearly identical genomes can exhibit distinct phenotypes depending on which genes are expressed, repressed, or maintained in a regulatory state that allows future activation. This principle is evident in normal development, where diverse cell types arise from a shared genome through tightly regulated patterns of gene expression. In cancer, these regulatory systems can become disrupted, permitting cells to acquire malignant traits without requiring additional changes in DNA sequence (Hanahan, 2022).

Epigenetics refers to molecular mechanisms that regulate gene expression without altering the underlying DNA code. These mechanisms include DNA methylation, histone modifications, chromatin remodeling, and regulation by non-coding RNAs. Collectively, these processes influence chromatin accessibility, transcriptional activity, genome organization, and cellular identity. Rather than functioning as isolated pathways, epigenetic mechanisms interact to form a dynamic regulatory network that determines how genetic information is interpreted in specific cellular contexts (Bure et al., 2022; Hanahan, 2022).

In normal tissues, epigenetic regulation is essential for embryonic development, lineage specification, and maintenance of differentiated cell states (Wilkinson et al., 2023). In cancer, epigenetic dysregulation can cooperate with genetic alterations to promote tumor initiation, progression, and therapeutic resistance. For example, a tumor suppressor gene may remain genetically intact but become transcriptionally silenced through promoter DNA methylation or repressive chromatin structure. Similarly, oncogenic

transcriptional programs may be activated through altered enhancer activity, histone modification, or chromatin remodeling. These changes may increase cellular plasticity, enabling cancer cells to adapt to selective pressures imposed by nutrient limitation, replicative stress, immune surveillance, or therapy (Rembiałkowska et al., 2025).

The reversibility of many epigenetic states has made the cancer epigenome an important focus of therapeutic development. Drugs targeting epigenetic regulators, including DNA methyltransferases, histone deacetylases, histone methyltransferases, and epigenetic reader proteins, have demonstrated clinical activity in selected malignancies. Nevertheless, epigenetic therapy remains challenging because epigenetic regulators often control broad transcriptional programs rather than single genes. Effective clinical translation therefore requires a deeper understanding of context-specific epigenetic dependencies and reliable biomarkers of response (Gu et al., 2024).

This review examines cancer as a disease shaped not only by mutations, but also by altered gene regulation. It summarizes the principal mechanisms of epigenetic control, describes how epigenetic dysregulation contributes to tumor development and progression, and discusses the role of epigenetic plasticity in therapeutic resistance. It also evaluates current and emerging epigenetic therapies and highlights future directions for the field.

2. PRINCIPLES OF EPIGENETIC REGULATION

Epigenetic regulation refers to molecular processes that modulate gene expression without changing the nucleotide sequence of DNA. While the genome provides the inherited genetic template, epigenetic mechanisms influence how that template is packaged, accessed, and transcribed. These mechanisms are essential because not all genes are required in all cell types or under all biological conditions. Cellular identity depends not only on the presence of genes but also on the regulated use of those genes (Gu et al., 2024).

A central feature of epigenetic regulation is chromatin organization. In eukaryotic cells, DNA is packaged with histone and non-histone proteins into chromatin. The basic unit of chromatin is the nucleosome, which consists of DNA wrapped around histone proteins. This organization allows for the genome to fit within the nucleus, but it also creates a regulatory challenge: genes and regulatory elements must be made accessible when needed and restricted when inappropriate for a given cell state (Iyer et al., 2026).

Chromatin exists across a spectrum of accessibility (Mansisidor & Risca, 2022). Regions of open chromatin are generally more permissive to transcription factor binding and gene activation, whereas compact chromatin is often associated with transcriptional repression. However, this relationship is context dependent. Gene expression is regulated by coordinated interactions among promoters, enhancers, insulators, transcription factors, chromatin-modifying enzymes, and three-dimensional genome

architecture. Thus, epigenetic regulation should not be understood as a simple binary switch, but as a multilayered system that modulates transcriptional probability and cellular state (Chen et al., 2024).

Epigenetic regulation is both stable and dynamic. Stability is necessary for preserving cell identity across cell divisions. For example, differentiated cells must maintain lineage-specific gene expression programs despite ongoing replication and environmental fluctuations. At the same time, dynamic regulation allows cells to respond to stress, developmental cues, DNA damage, and extracellular signals. This dual property of stability and flexibility is especially relevant in cancer, where malignant cells may exploit epigenetic plasticity to survive changing conditions (Hanahan, 2022; Wilson & Scaffidi, 2025).

Epigenetic alterations differ from genetic mutations in both mechanism and consequence. A mutation changes the DNA sequence while an epigenetic alteration changes the regulatory state of a gene or genomic region. A gene may therefore be functionally inactivated despite having an intact coding sequence. This distinction is particularly important for tumor suppressor genes, which can be silenced by promoter methylation or repressive chromatin marks without requiring deletion or sequence mutation (Almalki, 2025). Conversely, oncogenic pathways may be activated through altered chromatin accessibility or enhancer activation rather than through mutation of the oncogene itself (Yang et al., 2025).

In cancer, epigenetic dysregulation can arise through multiple routes. Some tumors acquire mutations in genes encoding epigenetic regulators, including chromatin remodelers, histone modifiers, and DNA methylation enzymes. Other tumors display altered expression or activity of these regulators without direct mutation (Sadida et al., 2024). Additionally, oncogenic signaling pathways can reshape epigenetic states by changing transcription factor activity, chromatin accessibility, or metabolic inputs required for epigenetic modifications. The result is an altered regulatory landscape that supports malignant phenotypes (Chen et al., 2026).

3. MAJOR MECHANISMS OF EPIGENETIC REGULATION

3.1 DNA Methylation

DNA methylation is among the most extensively studied epigenetic mechanisms in cancer. In mammalian cells, DNA methylation most commonly occurs at cytosine residues within CpG dinucleotides. This modification is catalyzed by DNA methyltransferases and is generally associated with transcriptional repression when enriched at gene promoter regions (Wei & Wu, 2022). DNA methylation can inhibit gene expression directly by interfering with transcription factor binding or indirectly by recruiting methyl-binding proteins and repressive chromatin complexes (Tibben & Rothbart, 2023).

In normal cells, DNA methylation contributes to genomic stability, X-chromosome inactivation, imprinting, suppression of repetitive elements, and maintenance of cell identity. These functions are

essential for normal development and tissue homeostasis (Tibben & Rothbart, 2023). In cancer, DNA methylation patterns are frequently disrupted. Two major alterations are commonly observed: regional promoter hypermethylation and broader genomic hypomethylation (Zhu et al., 2023).

Promoter hypermethylation can silence tumor suppressor genes involved in DNA repair, cell cycle control, apoptosis, differentiation, and cell adhesion. This form of silencing may produce functional consequences similar to genetic inactivation. For example, if a tumor suppressor gene is present but transcriptionally repressed through methylation, the cell may lose an important protective pathway despite retaining the gene sequence. This mechanism demonstrates how epigenetic dysregulation can cooperate with, or substitute for, genetic lesions in tumor development (Gu et al., 2024; Nam et al., 2026).

Global hypomethylation may also contribute to malignancy by promoting chromosomal instability, activation of transposable elements, and inappropriate expression of normally silenced genomic regions. Thus, cancer-associated methylation changes are not characterized by a uniform increase or decrease in methylation. Instead, tumors often display redistribution of methylation, with focal gains at regulatory regions and losses across broader genomic domains (Vaidya et al., 2025).

A comparison across tumor lineages highlights that DNA methylation alterations do not follow a uniform pathogenic paradigm. In colorectal cancer and glioblastoma, promoter hypermethylation operates as a primary epigenetic driver. In sporadic colorectal tumors with microsatellite instability, epigenetic silencing of the *MLH1* gene through promoter hypermethylation disrupts mismatch repair, directly driving microsatellite instability and hypermutation (Helderman et al., 2024; Ward et al., 2026). Similarly, promoter hypermethylation of the *MGMT* gene in glioblastoma disables DNA repair and serves as a clinical biomarker, sensitizing tumor cells to alkylating temozolomide chemotherapy (Brandner et al., 2021).

Conversely, in acute myeloid leukemia, widespread methylation changes are prominently driven by direct somatic mutations in the epigenetic machinery itself. These include *DNMT3A* loss of function or *TET2* inactivating mutations that disrupt hematopoietic stem cell differentiation (Schrezenmeier & Huntly, 2025).

Despite these established frameworks, significant scientific uncertainty remains regarding the biological consequences and sequence of DNA methylation. While promoter methylation is associated with transcriptional repression, epigenome-wide mapping demonstrates that gene-body methylation correlates with active, highly transcribed genes, where it functions to prevent abnormal intragenic transcription. Additionally, global hypomethylation yields different outcomes depending on genomic context, promoting chromosomal instability and transposable element activation in certain carcinomas while selectively reactivating pro-metastatic genes in others (Wang et al., 2022).

3.2 Histone Modification

Histone modifications are covalent chemical changes added to histone proteins, particularly on histone tail regions (Liu et al., 2023). Common modifications include acetylation, methylation, phosphorylation, ubiquitination, and sumoylation. These modifications influence chromatin structure and regulate interactions between DNA, histones, transcription factors, and chromatin-associated proteins (Xu et al., 2025).

Histone acetylation is generally associated with open chromatin and active transcription. Acetylation neutralizes positive charges on histones, weakening histone-DNA interactions and increasing chromatin accessibility (Nitsch et al., 2021). Histone deacetylation, mediated by histone deacetylases, is often associated with chromatin compaction and transcriptional repression (Zhang et al., 2026). Histone methylation is more context dependent. Depending on the modified residue and the number of methyl groups added, methylation can either activate or repress transcription (Tresas et al., 2025).

The enzymes that regulate histone modifications are often described as writers, erasers, and readers. Writers add epigenetic marks, erasers remove them, and readers recognize specific modifications to recruit additional regulatory proteins (Yang et al., 2022). This framework highlights the coordinated nature of epigenetic regulation. Histone marks do not act alone; they function within larger chromatin networks that influence transcription, DNA repair, replication, and genome organization (Malone et al., 2026).

In cancer, altered histone modification patterns can promote aberrant gene expression. Dysregulation of histone acetyltransferases, histone deacetylases, methyltransferases, demethylases, and reader proteins has been observed across multiple malignancies. These changes may silence differentiation programs, activate proliferative pathways, or alter the expression of genes involved in apoptosis and DNA damage response. Mutations or altered activity of histone-modifying enzymes may therefore contribute directly to oncogenesis and disease progression (Yang et al., 2022).

The pathogenic consequences of histone modifications vary considerably between tumor lineages. In certain pediatric cancers such as gliomas and sarcomas, histone pathway lesions operate as singular, well-defined genetic drivers that suppress global H3K27 trimethylation levels. In comparison, in follicular lymphoma and diffuse large B-cell lymphoma, somatic gain-of-function mutations within the *EZH2* SET domain (such as *Y641*) cooperatively hyper-trimethylate H3K27, resulting in the accumulation of repressive H3K27me3 marks, locking the B cells in a proliferative germinal center state. In contrast to these tumors driven by genetic lesions in histones or chromatin-modifying enzymes, epithelial carcinomas such as lung and breast cancer seldom harbor recurring oncohistone mutations. Instead, they exhibit dynamic and non-mutational modulations of histone acetylation and methylation that dictate lineage plasticity, epithelial-mesenchymal transition (EMT), and stress adaptation.

Evidence shows that the histone code is an oversimplification of complex cellular processes. Individual histone marks display context-dependent functionality. For example, while H3K4me3 marks open promoters, bivalent chromatin domains in embryonic and cancer stem cells simultaneously harbor activating H3K4me3 and repressive H3K27me3 marks, positioning developmental genes for rapid activation or persistent silencing during treatment. Moreover, there is conflicting mechanistic evidence surrounding histone deacetylase activity. Chemical HDAC inhibition alters only a small fraction of the transcriptome rather than triggering global transcription, and HDAC enzymes deacetylate extensive non-histone substrates, including p53, HSP90, and *MYC*. Consequently, the phenotypic consequences of HDAC activity frequently stem from non-chromatin cellular signaling pathways rather than strictly defined histone tail modifications.

3.3 Chromatin Remodeling

Chromatin remodeling refers to ATP-dependent changes in nucleosome positioning, composition, or occupancy. Chromatin remodeling complexes regulate access to DNA by repositioning, ejecting, or restructuring nucleosomes. These processes are essential for transcription, DNA repair, replication, and maintenance of genome integrity (Wang et al., 2026).

The importance of chromatin remodeling in cancer is underscored by the frequent alteration of genes encoding remodeling complex components. When chromatin remodelers are disrupted, cells may lose normal control over gene accessibility. Regulatory regions that should remain silent may become active, while genes required for differentiation or tumor suppression may become inaccessible. Such changes can alter cell identity and contribute to malignant transformation (Luo et al., 2026).

Chromatin remodeling also contributes to cancer cell plasticity. By changing the accessibility of regulatory elements, remodeling complexes can permit transitions between cellular states. These transitions may allow cancer cells to adopt stem-like, invasive, slow-cycling, or drug-tolerant phenotypes. Unlike genetic mutations, these state changes may be reversible, allowing cancer cells to respond flexibly to changing selective pressures (He et al., 2024).

Cross-cancer genomic analyses demonstrate distinct patterns of chromatin remodeling disruption across cancer types. In solid tumors, the structural loss-of-function mutations in SWI/SNF subunits are highly prevalent. Over 50% of ovarian clear cell carcinomas and roughly 30% endometriod tumors carry inactivating mutations of *ARID1A*, disrupting BAF complex regulation. In pediatric malignant rhabdoid tumors and epithelioid sarcomas, biallelic loss of *SMARCB1* (INI1/SNF5) acts as an isolated driver mutation that disrupts SWI/SNF integrity and unleashes unopposed, oncogenic PRC2/EZH2 transcriptional silencing. Conversely, acute leukemias rarely possess primary inactivating mutations in core SWI/SNF genes but are instead functionally redirected to aberrant loci via oncogenic fusion proteins, such as *KMT2A* (*MLL*) rearrangements.

Mechanistic models of chromatin remodeling in cancer remain subject to debate and competing hypotheses. A major unresolved question is whether SWI/SNF inactivation drives transformation primarily by closing specific promoter elements of tumor suppressors, or by dismantling distal super-enhancers that maintain tissue-specific differentiation. Furthermore, synthetic lethality models involving SWI/SNF subunits show context-dependent variation. While *ARID1A*-deficient ovarian cancers exhibit clear synthetic lethal dependence on the paralog *ARID1B* and catalytic EZH2 activity, this synthetic vulnerability is not uniformly reproduced in other *ARID1A*-mutant solid tumors. Finally, emerging evidence reveals that SWI/SNF complexes do not function solely as tumor suppressors, as specific non-canonical BAF complexes and the *SMARCA4* ATPase are required oncogenic dependencies in synovial sarcomas and acute myeloid leukemia, highlighting that their functional role strictly depends on subunit composition and cell lineage.

3.4 Non-coding RNAs

Non-coding RNAs are RNA molecules that do not encode proteins but regulate gene expression through diverse mechanisms. Major classes include microRNAs, long non-coding RNAs, and other regulatory RNA species. These molecules can influence messenger RNA stability, translation, chromatin organization, transcription factor activity, and recruitment of chromatin-modifying complexes (Desind et al., 2026).

MicroRNAs are short non-coding RNAs that typically bind target messenger RNAs and repress protein production. In cancer, microRNAs may function as tumor suppressors or oncogenic regulators depending on their targets. A microRNA that suppresses an oncogene may inhibit tumor growth, whereas a microRNA that represses a tumor suppressor pathway may promote malignancy (Arghiani & Shah, 2021).

Long non-coding RNAs regulate gene expression through more varied mechanisms. Some act as scaffolds for chromatin-modifying complexes, while others guide epigenetic regulators to specific genomic regions. Long non-coding RNAs may also regulate transcription, RNA splicing, messenger RNA stability, or protein interactions (Poltronieri, 2024). In cancer, dysregulated long non-coding RNAs have been implicated in proliferation, metastasis, immune evasion, and therapy resistance (Ma et al., 2025).

Non-coding RNAs demonstrate that epigenetic regulation extends beyond DNA and histone modifications. They participate in regulatory networks that connect chromatin structure, transcriptional control, and post-transcriptional gene regulation. Their disease-associated expression patterns have also made them candidates for biomarker development and therapeutic targeting (Bure et al., 2022).

A key difference must be recognized between epigenetic regulation and post-transcriptional gene control when evaluating non-coding RNAs. Strictly defined, epigenetic mechanisms involve structural modifications to chromatin or DNA templates that regulate transcription without altering sequence. When nuclear, long-coding RNAs directly recruit or scaffold chromatin-modifying complexes to specific genomic loci, they perform genuine epigenetic functions. In contrast, the majority of microRNA actions

involve cytoplasmic binding to messenger RNAs, leading to mRNA cleavage or translational repression, which is post-transcriptional regulation rather than chromatin-based epigenetic inheritance. Maintaining this distinction prevents the overgeneralization of all non-coding RNA pathways as epigenetic mechanisms.

In cancer, the established roles of non-coding RNAs differ widely across clinical contexts, while several proposed mechanisms remain controversial. An established example of non-coding RNA regulation is the *miR-200* family, which functions as a verified suppressor of epithelial-mesenchymal transition by representing *ZEB1* and *ZEB2*. In advanced carcinomas, hypermethylation of the *miR-200* promoter depresses these ZEB factors, driving cellular plasticity and invasion. For long non-coding RNAs, however, there is significant debate that surrounds the competing endogenous RNA hypothesis, which suggests that cytoplasmic IncRNAs regulate oncogenesis by acting as sponges for shared microRNAs, though many studies challenge the validity of the model. Similarly, while nuclear IncRNAs such as HOTAIR have been widely reported to recruit PRC2 to specific promoters in the breast and colorectal tumors, studies reveal that PRC2 binds RNA with non-specific, low-sequence specificity outside of the cell, raising many questions regarding whether IncRNA-mediated targeting is an epigenetic mechanism or a consequence of local transcriptional activity.

The major epigenetic mechanisms, their tumor specific patterns, representative clinical examples, and current debates are summarized in Table 1.

Table 1: Overview of Major Epigenetic Mechanisms in Cancer

Epigenetic Mechanism	Core Molecular Processes	Representative Cancer Types & Alterations	Pathological Consequences	Mechanistic Debates & Uncertainties
DNA Methylation	CpG cytosine methylation by DNMTs Demethylation mediated by TET enzymes	Colorectal cancer (*MLH1* hypermethylation) Glioblastoma (*MGMT* hypermethylation) AML (*DNMT3A* loss of function, *TET2* mutations)	Loss of DNA repair pathways (*MLH1*, *MGMT*) Impaired stem cell differentiation (AML) Genomic instability via repeat element hypomethylation	Gene-body methylation correlates with active transcription, not repression Debate over whether CpG methylation initiates silencing or only locks in pre-existing repression
Histone Modification	Post-translational marks placed by writers, erasers, and readers Pediatric gliomas (H3K27M oncohistone) Epithelial carcinomas (aberrant HDAC activity)	Diffuse large B-cell lymphoma (*EZH2* Y641 mutations) Pediatric gliomas (H3K27M oncohistone) Epithelial carcinomas (aberrant HDAC activity)	Repression of B-cell terminal differentiation Suppression of global H3K27me3 in midline gliomas Non-mutational drives toward EMT and plasticity	Histone code is non-deterministic; bivalent marks (H3K4me3/H3K27me3) create positioned states HDAC inhibitors affect only 2–5% of transcripts; phenotypes often reflect non-histone substrates (p53, HSP90)
Chromatin Remodeling	ATP-dependent nucleosome sliding, ejection, or restructuring (e.g., SWI/SNF complexes)	Ovarian clear cell and endometrioid carcinomas (*ARID1A* loss) Malignant rhabdoid tumors (*SMARCB1* loss) Acute leukemias	Disrupted BAF complex targeting Unopposed, oncogenic PRC2/EZH2 silencing Functional retargeting to	Unresolved whether SWI/SNF loss acts via specific promoter closure vs. broad super-enhancer disruption Context-dependent synthetic

		(*KMT2A* fusions)	oncogenic loci	lethalities (e.g., ARID1B dependence in *ARID1A*-null tumors is not universal)
Non-Coding RNAs	Post-transcriptional mRNA repression (miRNAs) Chromatin complex scaffolding and localization (lncRNAs)	Advanced epithelial carcinomas (loss/hypermethylation of *miR-200*) Breast and colorectal cancers (*HOTAIR* upregulation)	*miR-200* silencing relieves repression on *ZEB1/2*, driving EMT and metastasis Scaffolding of chromatin modifiers	MicroRNAs act via cytoplasmic post-transcriptional mechanisms rather than direct epigenetic marks The competing endogenous RNA (ceRNA) "sponge" hypothesis is debated due to stoichiometric imbalances Non-specific RNA binding by PRC2 challenges targeted lncRNA recruitment models

4. EPIGENETIC DYSREGULATION IN TUMOR DEVELOPMENT AND PROGRESSION

Tumorigenesis requires the acquisition of cellular traits that permit sustained proliferation, survival, altered differentiation, invasion, and adaptation to stress. Epigenetic dysregulation can contribute to each of these processes by reshaping gene expression programs (Zhang et al., 2024). Rather than acting as a secondary consequence of transformation, epigenetic alteration can function as a driver of malignant phenotype (Lai et al., 2023).

One of the most established roles of epigenetics in cancer is the silencing of tumor suppressor genes. Tumor suppressor pathways normally restrain proliferation, maintain genome stability, promote DNA repair, and initiate apoptosis or senescence in response to cellular damage. Epigenetic silencing of these genes can weaken normal safeguards and allow damaged cells to persist. Promoter methylation and

repressive histone marks are two major mechanisms by which such silencing occurs (Almalki, 2025; Gu et al., 2024).

Epigenetic dysregulation can also activate oncogenic transcriptional programs (Marei, 2025). Cancer cells frequently reactivate developmental or tissue repair pathways that are normally restricted in adult tissues. These programs may support proliferation, migration, survival, epithelial-mesenchymal transition, or stem-like properties. Abnormal enhancer activity is especially relevant in this context because enhancers regulate cell type-specific transcriptional programs (Srinivasan et al., 2025). Changes in enhancer accessibility or activity can therefore shift cellular identity and promote malignant behavior (Yang et al., 2025).

Tumor progression is also influenced by intratumoral heterogeneity. Tumors are composed of diverse cell populations that may differ in proliferative capacity, differentiation state, metabolic activity, and therapeutic sensitivity. While genetic subclones contribute to this heterogeneity, epigenetic variation can generate phenotypic diversity without requiring sequence divergence. This allows genetically similar cancer cells to occupy distinct transcriptional states within the same tumor (Zhang et al., 2026).

Epigenetic plasticity is particularly important during metastasis. Metastatic dissemination requires cancer cells to invade surrounding tissue, survive detachment, enter and exit circulation, and colonize distant organs. These steps impose strong selective pressures and require extensive changes in gene expression. Epigenetic regulation can facilitate these transitions by enabling reversible changes in adhesion, motility, survival, and differentiation state. In this way, epigenetic plasticity may support the ability of cancer cells to adapt to unfamiliar tissue environments (Turna & Demokan, 2026; Chen & Yan, 2021).

Genetic and epigenetic mechanisms are deeply interconnected. Mutations in signaling pathways can alter transcription factor activity and thereby remodel chromatin landscapes. Conversely, mutations in epigenetic regulators can reshape gene expression programs and alter the functional consequences of other oncogenic events (Song et al., 2025). Epigenetic states may also influence whether a genetic alteration produces a strong or weak phenotype. Thus, the behavior of a tumor reflects the combined effects of DNA sequence, chromatin state, transcriptional regulation, and selective pressure (Farhana et al., 2024; Gu et al., 2024).

5. EPIGENETIC PLASTICITY AND THERAPEUTIC RESISTANCE

Therapeutic resistance remains a major barrier to durable cancer control. Resistance can be intrinsic, in which tumor cells are resistant before treatment begins, or acquired, in which resistance emerges during therapy. Genetic mechanisms of resistance include secondary mutations, pathway reactivation, drug target alteration, and selection of resistant subclones. However, increasing evidence indicates that resistance can also arise through non-genetic adaptation (Bivona et al., 2026; Kholodenko et al., 2021).

Epigenetic plasticity provides a mechanism by which cancer cells can survive therapeutic stress without immediately acquiring new resistance mutations (Reichart et al., 2026). Under drug pressure, a subset of cells may enter a transient drug-tolerant state characterized by altered transcription, chromatin reorganization, reduced proliferation, enhanced stress response, or stem-like properties (Kalkavan et al., 2022; Li et al., 2025). These cells are often referred to as drug-tolerant persister cells. Although they may represent only a small fraction of the tumor population, their survival can provide a source for relapse (Li et al., 2025).

Drug-tolerant states are clinically significant because they may precede stable resistance. A cell that survives therapy through reversible epigenetic adaptation may later acquire genetic or additional epigenetic changes that establish long-term resistance. In this model, non-genetic tolerance is not an alternative to genetic evolution but a potential bridge to it. Epigenetic plasticity may allow cells to persist long enough for resistant clones to emerge (Mani et al., 2023; Oren et al., 2021).

The reversibility of drug-tolerant states distinguishes them from many genetic resistance mechanisms. A genetically resistant clone may remain resistant because the DNA sequence has changed. In contrast, an epigenetically tolerant cell may return to a more drug-sensitive state if treatment pressure is removed. This reversibility complicates detection because genomic sequencing alone may fail to identify the basis of survival (Rehman et al., 2021). Transcriptomic, chromatin accessibility, and epigenomic profiling are therefore increasingly important for understanding residual disease (Song et al., 2023).

Epigenetic mechanisms associated with resistance include altered DNA methylation, histone modification, chromatin remodeling, enhancer reprogramming, and non-coding RNA regulation. These changes may reduce drug-induced apoptosis, increase DNA repair capacity, activate compensatory signaling pathways, or shift cells into less proliferative states (Yang et al., 2026). In targeted therapy, epigenetic adaptation can reduce dependence on the inhibited pathway (de Miguel et al., 2023). In chemotherapy, it may enhance survival under genotoxic stress (Oliveira et al., 2025). In immunotherapy, epigenetic regulation may influence antigen presentation, interferon signaling, and immune evasion (Wang et al., 2020).

The therapeutic implication is that resistance should not be viewed solely as a problem of fixed mutations. It may also reflect adaptive regulatory states that are dynamic, heterogeneous, and context dependent (França et al., 2024). Targeting these states may require combination strategies that pair conventional or targeted treatments with therapies that disrupt epigenetic survival programs. However, this approach requires careful design because epigenetic regulators are also essential in normal cells (Soragni et al., 2025).

6. EPIGENETIC THERAPY IN CANCER

The reversibility of epigenetic regulation has made the cancer epigenome an attractive therapeutic target. Epigenetic therapies aim to modify abnormal gene regulation by targeting enzymes or proteins that write, erase, read, or remodel epigenetic marks. Several classes of epigenetic therapies have entered clinical use or clinical investigation. including DNA methyltransferase inhibitors, histone deacetylase inhibitors, histone methyltransferase inhibitors, isocitrate dehydrogenase inhibitors, and inhibitors of epigenetic reader proteins (Ma et al., 2025; Marei, 2025).

DNA methyltransferase inhibitors are among the earliest epigenetic therapies. These agents reduce DNA methylation by inhibiting enzymes responsible for methylation maintenance or establishment. In cancer cells, this may reactivate genes silenced by promoter methylation, including genes involved in differentiation, tumor suppression, immune signaling, or apoptosis. DNA methyltransferase inhibitors have demonstrated clinical benefit in selected hematologic malignancies, including myelodysplastic syndromes and acute myeloid leukemia. Their efficacy in solid tumors has been more limited, possibly due to tumor heterogeneity, drug delivery challenges, toxicity, and incomplete understanding of predictive biomarkers (Kim, 2025; Michael and Mehdipour, 2024).

Histone deacetylase inhibitors alter chromatin structure by increasing histone acetylation and affecting transcriptional regulation. These agents can induce cell cycle arrest, apoptosis, differentiation, or immune modulation depending on cellular context. Several histone deacetylase inhibitors have been approved for specific hematologic malignancies. However, their broad effects on gene expression can produce complex biological outcomes and clinically significant toxicities. Their use in solid tumors has generally been more challenging (Abdallah, 2026; Wen et al., 2025).

Histone methyltransferase inhibitors represent a more targeted epigenetic approach. EZH2, the catalytic component of Polycomb repressive complex 2, is one example of a clinically relevant epigenetic target (Rugo et al., 2020). EZH2 regulates histone H3 lysine 27 trimethylation, a repressive chromatin mark involved in gene silencing. Aberrant EZH2 activity can contribute to the repression of differentiation and tumor suppressor programs. Inhibitors of EZH2 have shown activity in selected molecular contexts, supporting the principle that epigenetic therapy may be most effective when matched to specific tumor dependencies (Morschhauser et al., 2020).

Epigenetic reader proteins have also emerged as therapeutic targets. BET proteins recognize acetylated histones and help regulate transcriptional elongation and enhancer-driven gene expression (Xie et al., 2026). BET inhibition may disrupt oncogenic transcriptional programs, including those associated with MYC and other growth-promoting factors. Although BET inhibitors have shown preclinical promise, clinical development has required careful attention to toxicity, resistance, and patient selection (Wang et al., 2023).

An important trend in epigenetic therapy is the movement from single-agent treatment toward rational combinations. Epigenetic agents may sensitize tumors to chemotherapy, targeted therapy, radiation, or immunotherapy by altering chromatin accessibility and gene expression. For example, epigenetic therapy may increase expression of immune-related genes, restore apoptotic pathways, or reduce drug-tolerant cell states (Fukumoto et al., 2025). Combination strategies may therefore be particularly relevant for overcoming therapeutic resistance (Liu et al., 2022).

Despite these opportunities, epigenetic therapy remains complex. Epigenetic regulators often control many genes across multiple tissues, making therapeutic effects difficult to predict. In addition, the same epigenetic regulator may have different functions depending on cancer type, lineage, mutation profile, and disease stage (Marei, 2025; Tu et al., 2025). Effective clinical translation will require biomarkers that identify tumors dependent on specific epigenetic mechanisms and determine when epigenetic intervention is most likely to improve outcome (Dai et al., 2024).

7. FUTURE DIRECTIONS

The future of cancer epigenetics will depend on the integration of mechanistic biology, advanced technologies, and clinically useful biomarkers (Dai et al., 2024). A major challenge is distinguishing epigenetic alterations that drive malignant behavior from those that occur as secondary consequences of transformation. Not every epigenetic change observed in a tumor is therapeutically relevant (Mancarella & Plass, 2021). Identifying functionally important regulatory states will require experimental models that connect epigenomic features with tumor phenotype and treatment response (Nuñez et al., 2021).

Single-cell technologies are particularly important for this goal. Bulk tumor profiling averages signals across many cells and may obscure rare populations that drive relapse or resistance. Single-cell RNA sequencing, single-cell chromatin accessibility assays, and emerging single-cell multi-omic approaches allow investigators to characterize distinct cellular states within tumors. These methods may help identify drug-tolerant populations before they expand clinically (Le et al., 2025; Quek et al., 2024).

Multi-omic integration is another major direction. Cancer behavior reflects the combined influence of genomic alterations, epigenetic states, transcriptional programs, protein activity, metabolism, and microenvironmental signals. Integrating these layers may clarify how mutations interact with epigenetic regulation and why tumors with similar genomic profiles can respond differently to therapy. Such approaches may also improve classification of tumors beyond histology or mutation status alone (Hu et al., 2026; Liu et al., 2026).

Epigenetic biomarkers may improve cancer detection, prognosis, and treatment selection. DNA methylation patterns are already being explored for early detection and tumor classification because they

can reflect tissue identity and disease-associated regulatory changes (Ibrahim et al., 2023). Similarly, chromatin accessibility and non-coding RNA profiles may provide information about tumor state, lineage, and therapeutic vulnerability (Boyvatlı et al., 2026; Iglesia et al., 2024). For epigenetic biomarkers to become clinically useful, they must be reproducible, interpretable, and linked to actionable treatment decisions (Iyer et al., 2026).

Future therapeutic development will likely focus on precision epigenetic strategies. Rather than broadly altering chromatin, next-generation approaches may aim to target specific dependencies created by mutations in epigenetic regulators, lineage-specific transcriptional programs, or drug-tolerant states. Protein degradation technologies, improved selective inhibitors, and combination regimens may expand the therapeutic potential of epigenetic targeting (Vatapalli et al., 2024).

Ultimately, a central question must be addressed: when does modifying the epigenome improve patient outcome? Answering this will require careful trial design, molecularly defined patient populations, longitudinal sampling, and integration of epigenetic biomarkers into therapeutic decision-making.

8. DISCUSSION AND CONCLUSION

The genetic model of cancer remains foundational, but it is incomplete without consideration of epigenetic regulation (Bandlamudi et al., 2026; Riedl et al., 2023). Mutations can initiate and drive malignant transformation but the functional consequences of those mutations depend on regulatory context. Epigenetic mechanisms determine which genes are accessible, which transcriptional programs are active, and how cells respond to selective pressure (Bure et al., 2022; Hanahan, 2022).

Cancer-associated epigenetic dysregulation can silence tumor suppressor genes, activate oncogenic programs, alter differentiation, promote plasticity, and contribute to therapeutic resistance (Almalki, 2025; Gu et al., 2024; Yang et al., 2025). These processes help explain why tumors with similar mutations may behave differently and why some cancer cells survive treatment despite lacking identifiable resistance mutations (Bivona et al., 2026; Reichart et al., 2026). Epigenetic plasticity allows malignant cells to occupy reversible states that support persistence, adaptation, and eventual relapse ((Li et al., 2025; Mani et al., 2023).

Therapeutically, the reversibility of epigenetic regulation creates both opportunity and challenge. Epigenetic drugs have demonstrated clinical value in selected malignancies, particularly hematologic cancers (Kim, 2025; Marei, 2025). However, their broader application requires improved specificity, better biomarkers, and more rational combination strategies (Fukumoto et al., 2025; Liu et al., 2022). Since epigenetic regulators control complex gene networks, therapeutic success will depend on identifying context-specific vulnerabilities rather than broadly altering chromatin state (Dai et al., 2024;Vatapalli et al., 2024).

In conclusion, cancer should be understood not only as a disease of altered DNA sequence, but also as a disease of altered gene regulation. The cancer epigenome provides a framework for understanding tumor heterogeneity, plasticity, progression, and resistance. Continued investigation of epigenetic mechanisms may improve cancer classification, reveal new therapeutic targets, and support more effective strategies to prevent or overcome treatment resistance (Iyer et al., 2026).

ACKNOWLEDGEMENTS

I would like to thank my mentor, Dr. Nick Pulliam, Ph.D. in Molecular and Cellular Biochemistry from Indiana University, BS in Biology and Pharmacology from Purdue University, and a Scientific Lead, Translational Oncology, at Loxo Oncology at Lilly, for his endless support, help, guidance, and editing with my research and analysis into the mechanisms of epigenetics and how they drive tumor development, progression, and therapeutic resistance. I connected with Dr. Pulliam through the College Impact program.

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