European Journal of Philosophical Research. 2026. 13(1)
E-ISSN: 2413-7286
Volume-13/Issue-1/2026

Epigenetic Modifications and Their Role in Cancer Progression

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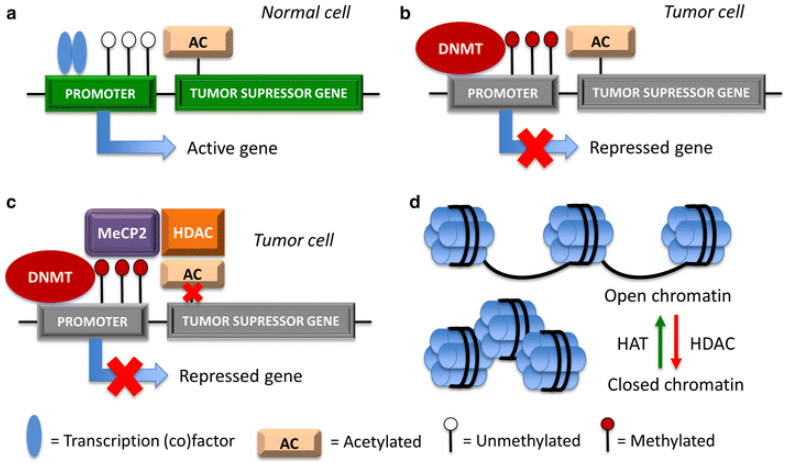
Submission: 26.11.2025| Acceptance: 06.03.2026| Publication: 04.06.2026

Abstract
Important epigenetic alterations that regulate gene expression without changing DNA sequence include DNA methylation, histone modifications, and non-coding RNA regulation. By impacting oncogene activation and tumor suppressor gene silencing, these alterations are being more and more acknowledged as critical drivers of tumor genesis, development, and metastasis in cancer biology. Genomic instability and unchecked cell proliferation are caused by aberrant DNA methylation patterns, which include promoter-specific hypermethylation and global hypomethylation. Similarly, a malignant environment can be established through histone changes like as acetylation, methylation, and phosphorylation, which change the structure of chromatin and affect transcriptional activity. MicroRNAs and long non-coding RNAs, in particular, shape cancer progression by regulating pathways that control cell cycle, apoptosis, and invasion. Epigenetic medicines, including inhibitors of DNA methyltransferase and histone deacetylase, have demonstrated promise in clinical settings, and the reversible character of epigenetic alterations has opened new pathways for therapeutic intervention.
Keywords: Epigenetics, DNA methylation, histone modifications, non-coding RNAs, cancer progression, oncogene activation

Introduction
Cancer is one of the most complicated and multifactorial diseases, caused by genetic abnormalities and epigenetic changes that drive cellular transformation, uncontrolled proliferation, and metastasis. Over the past two decades, epigenetic modifications—heritable but reversible changes in gene expression without DNA sequence changes—have become increasingly important in cancer biology, alongside genetic mutations in activating oncogenes and inactivating tumor suppressor genes. Epigenetics includes DNA methylation, histone modifications, and non-coding RNA regulation of gene expression, which affect chromatin structure and accessibility and determine whether genes are transcriptionally active or silenced. These systems regulate genomic stability, cell differentiation, and tissue-specific gene expression in healthy cells. These pathways are dysregulated in malignant cells, resulting in gene expression profiles that favor tumor genesis, development, and therapeutic resistance. Global DNA hypomethylation causes genomic instability and transposable element activation, while promoter-specific hypermethylation silences tumor suppressor genes such p16INK4a, BRCA1, and MLH1, encouraging oncogenesis. Similar to hyperacetylation of oncogene promoters and hypoacetylation of tumor suppressor sites, aberrant histone modifications affect chromatin accessibility, activating pro-cancer pathways and suppressing anti-cancer responses. Non-coding RNAs, such as microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), act

as post-transcriptional regulators of mRNA stability and translation, affecting cell cycle progression, apoptosis, angiogenesis, and metastasis. Dysregulated miRNAs can operate as oncogenes (oncomiRs) or tumor suppressors, highlighting their dual involvement in carcinogenesis. These epigenetic abnormalities cause cancer, tumor heterogeneity, therapeutic resistance, and disease relapse, making them a major challenge and opportunity in modern oncology. Reversibility distinguishes epigenetic modifications from genetic mutations, opening new therapeutic possibilities. DNMT inhibitors like azacitidine and decitabine and HDAC inhibitors like vorinostat and romidepsin have been clinically approved for hematological malignancies, and solid tumor research is ongoing. Epigenetic treatments combined with immunotherapy and chemotherapy are being studied to overcome resistance and enhance patient outcomes. Epigenetic modifications are becoming effective biomarkers for cancer diagnosis, prognosis, and treatment monitoring beyond medicines. Hypermethylation of gene promoters in circulating tumor DNA allows liquid biopsy for early cancer diagnosis without surgery. High-throughput sequencing and epigenomic profiling have revealed distinct DNA methylation, histone modifications, and non-coding RNA signatures that can stratify patients, predict therapeutic responses, and inform personalized treatment strategies. Despite these advances, translating epigenetic insights into clinical practice requires greater drug specificity to reduce off-target effects, improved delivery systems to ensure targeted action, and a better understanding of the complex interactions between genetic and epigenetic networks in tumor biology. Epigenome editing methods like CRISPR-based epigenetic modifiers require rigorous supervision in human health due to ethical concerns. The epigenome's complex involvement in cancer progression is becoming clear as research shows that epigenetic changes are active drivers of disease development and therapy response.



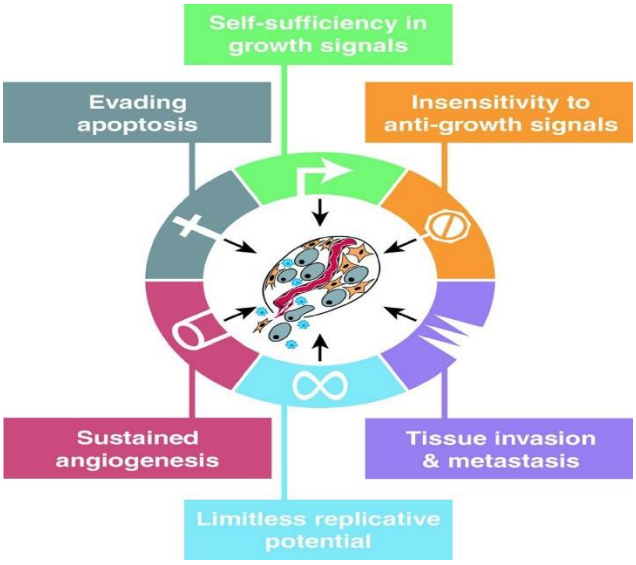
Epigenetic modifications refer to heritable changes in gene expression that occur without altering the underlying DNA sequence. These changes regulate whether genes are turned “on” or “off” and play a critical role in normal cellular function. In cancer, however, epigenetic mechanisms become dysregulated, leading to abnormal gene expression that contributes to tumor initiation, progression, and metastasis. One of the most well-studied epigenetic modifications is DNA methylation, where methyl groups are added to cytosine bases in DNA. In cancer cells, hypermethylation of promoter regions of tumor suppressor genes often leads to their silencing, preventing them from controlling cell growth and division. Conversely, global hypomethylation can activate oncogenes, promoting uncontrolled proliferation. Another key

mechanism involves histone modifications, such as acetylation and methylation, which alter chromatin structure and influence gene accessibility. For example, histone acetylation generally leads to a more open chromatin structure, allowing gene expression, while deacetylation results in gene repression. Epigenetic alterations are reversible, making them attractive targets for cancer therapy. Drugs such as DNA methyltransferase inhibitors and histone deacetylase inhibitors are already being used to reactivate silenced tumor suppressor genes and restore normal cellular function. Additionally, emerging technologies, including CRISPR-based epigenome editing, allow precise modification of epigenetic marks without cutting DNA, offering new possibilities for targeted cancer treatment.

Mechanistic Insights into Cancer Progression

Genetic mutations and widespread and dynamic epigenetic modifications reprogramme gene expression profiles to favor tumor initiation, growth, and dissemination, causing cancer to progress from a normal cell to a malignant and often therapy-resistant phenotype. Aberrant DNA methylation is one of the earliest and most consistent epigenetic changes in cancer. Global hypomethylation causes chromosomal instability, reactivation of transposable elements, and inappropriate expression of oncogenes, while site-specific promoter hypermethylation silences tumor suppressor genes like RB1, MLH1, and BRCA1, dismantling crucial cellular checkpoints for growth. This twofold disruption destabilizes the DNA and promotes cancer. Meanwhile, histone changes regulate chromatin architecture and accessibility, and their dysregulation directly affects cancer cell activity. Hypoacetylation of histones in tumor suppressor areas compacts chromatin, while hyperacetylation in oncogenic loci increases accessibility and transcriptional output, boosting proliferative and survival pathways. Histone methylation adds complexity, as specific methylation marks, such as H3K4me3, are associated with active transcription, while H3K27me3 is associated with repression. Cancer cells often exploit these regulatory codes by upregulating histone methyltransferases or demethylases to promote oncogenesis. Overexpression of EZH2, a histone methyltransferase that catalyzes H3K27me3, has been related to aggressive prostate and breast malignancies by suppressing tumor suppressors and promoting stem-like features. MicroRNAs (miRNAs) and long non-coding RNAs (lncRNAs) post-transcriptionally modulate gene expression networks that are essential for cancer hallmarks, providing mechanistic insight. Oncogenic miRNAs, known as oncomiRs, like miR-21 and miR-155, downregulate tumor suppressor transcripts and promote survival, angiogenesis, and metastasis, while the loss of tumor-suppressive miRNAs, like the let-7 family, causes unexcused proliferation and apoptosis. HOTAIR and other LncRNAs bind histone modification complexes to genomic loci to change the transcriptional landscape in favor of metastatic potential. Epigenetic changes establish interconnected regulatory networks that dynamically interact with genetic abnormalities, boosting malignancy. Epigenetic dysregulation allows tumor cells to circumvent growth arrest signals and gain stem-cell-like flexibility, enabling self-renewal and differentiation resistance. Epigenetic pathways regulate epithelial-to-mesenchymal transition (EMT), which decreases polarity and adhesion and increases invasiveness and migration as malignancies grow. Through DNA methylation and histone changes, transcription factors including SNAIL, TWIST, and ZEB1 tightly govern EMT, allowing tumor cells to spread and

colonize distant regions. Epigenetic modulation of matrix metalloproteinases and angiogenic factors aids invasion and support of the tumor microenvironment. Epigenetic processes also affect therapy resistance, a major oncology problem. Reversible epigenetic modifications can quiet pro-apoptotic genes, activate multidrug resistance transporters, or produce quiescent states in cancer cells, allowing them to survive chemotherapy, radiation, or targeted therapy. As a molecular driver of resistance and predictive biomarker, hypermethylation of the MGMT promoter in glioblastoma affects alkylating drug response, such as temozolomide. Cancer stem cells, which are hypothesized to drive recurrence and metastasis, depend on epigenetic programs for survival, emphasizing the need of targeting these processes for long-term treatment success. Recent studies also suggest that tumor epigenetics and the immune system interact to promote cancer progression, as epigenetic silencing of antigen presentation pathways allows tumor cells to avoid immune surveillance and epigenetic drugs can reactivate these pathways to re-sensitize tumors to immunotherapy. These molecular findings show that epigenetic alterations are active and dynamic drivers that affect practically every stage of cancer progression, from initiation and local invasion to metastasis and therapeutic resistance. Understanding these pathways provides a conceptual framework for cancer biology and a practical roadmap for epigenome-reversible treatment methods. Researchers and doctors target DNA methylation, histone changes, and non-coding RNA enzymes and regulators to reprogram malignant cells to be less aggressive or more sensitive to existing medicines. As epigenetic contributions to cancer progression are increasingly understood, integrating epigenetic insights with genetic and immunological perspectives gives the best path to comprehensive and permanent cancer management.



Cancer progression is a complex, multistep process driven by the accumulation of genetic and epigenetic alterations that disrupt normal cellular regulation. These changes transform healthy cells into malignant ones by affecting key biological pathways that control cell growth, survival, and differentiation.

At the molecular level, cancer begins with genetic mutations in critical genes such as oncogenes and tumor suppressor genes. Activation of oncogenes promotes uncontrolled cell proliferation, while inactivation of tumor suppressor genes like *p53* removes essential regulatory

checkpoints. Alongside genetic mutations, epigenetic modifications further alter gene expression, often silencing genes that would normally prevent tumor growth. A major hallmark of cancer progression is dysregulation of the cell cycle. Normal cells follow tightly controlled checkpoints, but cancer cells bypass these controls, leading to continuous and unregulated division. In addition, cancer cells develop resistance to apoptosis (programmed cell death), allowing damaged or abnormal cells to survive and accumulate.

Another critical mechanism is angiogenesis, the formation of new blood vessels that supply tumors with oxygen and nutrients, enabling them to grow beyond a limited size. As tumors evolve, they acquire the ability to invade surrounding tissues and spread to distant organs, a process known as metastasis. This involves changes in cell adhesion, increased motility, and degradation of extracellular matrix components. The tumor microenvironment also plays a significant role in cancer progression. Interactions between cancer cells, immune cells, and surrounding stromal cells can promote tumor growth and help cancer evade immune detection. Cancer cells often develop mechanisms to suppress immune responses, allowing them to survive and proliferate unchecked.

Clinical Applications of Epigenetic Research

For cancer diagnosis, prognosis, and treatment, epigenetic modifications' reversibility allows them to intervene in disease progression at multiple stages, making them biomarkers and therapeutic targets. The development of epigenetic biomarkers, which may be identified in tumor tissues or circulating cell-free DNA, provides less invasive techniques for early identification, prognosis, and therapy monitoring. In numerous malignancies, promoter hypermethylation of tumor suppressor genes such p16INK4a, MGMT, and BRCA1 has been shown to be a reliable biomarker, allowing doctors to stratify patients and adjust treatment. Histone modification patterns and dysregulated non-coding RNAs, such as miR-21, are also being used as prognostic indicators to assess tumor aggressiveness, metastatic potential, and therapy resistance. High-throughput sequencing and epigenome-wide association studies (EWAS) have expanded the catalog of clinically relevant epigenetic signatures, making it possible to integrate these datasets into personalized medicine approaches to stratify patients by genetic mutations and epigenetic landscapes. Therapeutic epigenetic alteration manipulation has become an important clinical advance beyond diagnostics. DNMT inhibitors like azacitidine and decitabine, approved for myelodysplastic syndromes and acute myeloid leukemia, were the first epigenetic therapies to enter clinical practice, showing that targeting the cancer epigenome could produce durable responses, especially in hematological malignancies. These nucleoside analogs incorporate into DNA and block DNMTs, correcting hypermethylation-mediated tumor suppressor gene silence and restoring gene expression. Histone deacetylase (HDAC) inhibitors like vorinostat, romidepsin, and belinostat alter chromatin structure to reactivate silenced genes and induce apoptosis, cell cycle arrest, and differentiation in cutaneous and peripheral T-cell lymphomas. These clinical accomplishments demonstrate epigenetic medicines' potential, but they also highlight issues including solid tumor effectiveness, off-target effects, and resistance, which require continued drug design and delivery system modification. Combination therapies using epigenetic medicines with chemotherapy, radiation, targeted therapies, or immunotherapies to improve efficacy and

overcome resistance are promising. DNMT inhibitors reactivate silenced immune-related genes to sensitize tumors to immune checkpoint inhibitors, while HDAC inhibitors are being tested with hormonal therapies in breast and prostate cancers to counteract resistance mechanisms. Integrating epigenetic therapy with immuno-oncology is possible because epigenetic alterations can transform cancer cells and immune cells, restoring anti-tumor immunity. Besides small-molecule inhibitors, novel technologies like CRISPR-based epigenome editing can target and precisely modulate the cancer epigenome to activate or silence genes without altering the DNA sequence, reducing the risks of permanent genetic changes. These preclinical epigenetic treatments could enable very targeted tumor cell reprogramming and persistent, customized interventions. Epigenetic markers can identify people at high risk of cancer due to environmental exposures, lifestyle factors, or inherited predispositions, informing surveillance and intervention strategies. Non-invasive liquid biopsies of circulating tumor DNA methylation profiles are being developed for colorectal, lung, and breast cancer screening to enhance patient outcomes. Epigenetic changes generally precede histological changes, making them promising for predictive medicine, where therapies can be started before illness symptoms appear. Despite these breakthroughs, epigenetic discoveries are difficult to apply clinically. Epigenetic therapeutics are limited by selectivity, toxicity, tumor epigenome heterogeneity, and poorly understood long-term effects. Next-generation inhibitors and sensible medication combinations are needed to combat compensatory mechanisms that cause epigenetic drug resistance.

Conclusion

Epigenetic modifications regulate every stage of tumor development, from initiation and progression to metastasis and therapy resistance, and their study has reshaped our understanding of malignancy as a disease of genetic mutations and dynamic, reversible gene expression changes. DNA methylation, histone modifications, and non-coding RNAs form an intricate regulatory network that controls chromatin structure and accessibility, silencing tumor suppressors, activating oncogenes, and allowing cancer cells to develop uncontrolled proliferation, apoptosis evasion, angiogenesis, invasion, and immune escape. Epigenetic dysregulation, unlike irreversible genetic mutations, is reversible, allowing for therapies to restore normal cellular function. Epigenetic biomarkers for early cancer detection, prognosis, and treatment monitoring are being developed, and epigenetic drugs like DNA methyltransferase and histone deacetylase inhibitors have shown efficacy in hematological cancers and are being tested in solid tumors, often in combination with chemotherapy, immunotherapy, or targeted agents to overcome resistance. High-throughput sequencing, liquid biopsy, and epigenome-wide association studies have helped clinicians grasp cancer heterogeneity and stratify patients, bringing personalized oncology closer to reality. These advances are accompanied by significant challenges, such as the limited specificity and potential toxicity of current epigenetic drugs, tumor epigenome heterogeneity, resistance mechanisms, and the incomplete understanding of the long-term effects of widespread epigenetic reprogramming. Epigenome editing technologies, notably CRISPR-based methods, provide intriguing opportunities for highly targeted therapies but pose ethical considerations concerning unintended effects, heredity, and the larger ramifications of epigenome

manipulation. Epigenetic applications in cancer will require rigorous validation, robust regulatory frameworks, and ethical oversight to guarantee that therapeutic discoveries benefit patients without harming them. Translation of epigenetic science into durable cancer prevention, diagnosis, and therapy will need international collaboration, interdisciplinary research, and integration of genetics, epigenomics, and immunology. Epigenetic research shows that cancer is a dynamic disease shaped by reversible molecular events that can be regulated for therapeutic benefit. By using epigenetic alterations' reversibility in precision medicine frameworks, oncology could diagnose and cure tumors earlier, prevent them, or reprogramme them. In conclusion, epigenetic modifications are active drivers of cancer progression, and their study provides profound mechanistic insights and powerful clinical opportunities. The challenge ahead is refining these approaches, addressing limitations, and embedding ethical responsibility into epigenetic science to realize its transformative potential for patients and society.

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