Epigenetic Mechanisms as Novel Therapeutic Avenues in Cancer Treatment

Sharmy Saimon Mano[1,*]

[1]*Department of Biotechnology, Hindusthan College of Arts and Science, Avinashi Road, Behind Nava India, Coimbatore, Tamil Nadu, India*

Abstract: Epigenetics encompasses heritable modifications in gene expression that do not alter the DNA sequence, playing a crucial role in regulating gene activity.Key mechanisms include DNA methylation, histone modifications, and non-coding RNAs (ncRNAs), all of which can be influenced by environmental factors.DNA methylation typically occurs at CpG islands, where the addition of methyl groups to cytosine bases can suppress gene transcription by obstructing transcription factor binding and recruiting proteins that condense chromatin, leading to gene silencing.Histone modifications can alter the structure of chromatin and thus interfere gene accessibility and transcriptional activity.NcRNAs, including microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), regulate gene expression at multiple levels, from chromatin remodeling to post-transcriptional processing. Epigenetic alterations either activate oncogenes or silence tumor suppressor genes, causes tumor initiation and progression.Unlike genetic mutations, these epigenetic changes are reversible, making them attractive targets for therapeutic intervention.Advancements in epigenetic research have led to the development of novel cancer biomarkers and therapies, offering promising avenues for early detection and personalized treatment strategies.

Keywords: DNA methylation, Histone modification, Oncogene, Tumor suppression, Epidrugs.

1. INTRODUCTION

Epigenetics encompasses heritable changes in gene expression that occur without alterations to the underlying DNA sequence. These modifications play a crucial role in regulating gene activity and can be influenced by various environmental factors [1].

A primary mechanism of epigenetic regulation is DNA methylation, where methyl groups are added to cytosine bases in DNA, particularly at CpG islands. This modification can repress gene transcription by hindering the binding of transcription factors and recruiting proteins that promote chromatin condensation, leading to gene silencing. For instance, methylation at CpG islands can impair transcription factor binding and recruit repressive methyl-binding proteins, stably silencing gene expression [2].

Another crucial epigenetic mechanism involves histone modifications. Histones proteins wrapped around DNA, forming a structure known as chromatin. Post-translational modifications (PTMs) of histones, such as methylation, acetylation, and phosphorylation, can alter chromatin structure, thereby influencing gene accessibility and transcriptional activity. For example, acetylation of histone tails reduces the positive charge of histones, disrupting their interaction with negatively charged DNA. This leads to a less compact chromatin structure, facilitating DNA access by transcriptional machinery [3].

*Address correspondence to this author at the Department of Biotechnology, Hindusthan College of Arts and Science, Avinashi Road, Behind Nava India, Coimbatore, Tamil Nadu, India; E-mail: sharmy.simon@gmail.com

Non-coding RNAs (ncRNAs), including microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), also play significant roles in epigenetic regulation. These RNA molecules do not code for proteins but can regulate gene expression at various levels, including chromatin remodeling, transcription, and post-transcriptional processing [4].

Cancer treatment encompasses a diverse array of modalities, each with distinct mechanisms, benefits, and limitations. Surgery is effective for localized tumors but may not address metastatic disease. Chemotherapy targets rapidly dividing cells systemically but can harm healthy tissues and lead to resistance. Radiation therapy precisely targets tumors but may affect surrounding healthy tissues and is less effective for certain cancer types. Hormonal therapy benefits hormone-sensitive cancers but can cause side effects and resistance over time. Immunotherapy leverages the immune system to combat cancer, showing promise in specific cases, though not all patients respond, and side effects can be significant. Targeted therapies aim at specific molecular pathways but are limited to cancers with identifiable targets and may lead to resistance [5]. Emerging treatments like Chimeric Antigen Receptor T-cell (CAR T-cell) therapy and sonodynamic therapy offer new hope but possess limitations such as high costs, complex administration, and limited efficacy in solid tumors. Overall, while advancements have improved outcomes, challenges like resistance, side effects, and accessibility persist, underscoring the need for continued research and personalized treatment approaches [6].

Cancer initiation and progression are governed by a complex interplay of both genetic and epigenetic events. While genetic mutations have traditionally been considered

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central to carcinogenesis, emerging evidence underscores the pivotal role of epigenetic alterations in driving cancer development. Importantly, abnormal epigenetic modifications often arise at the earliest stages of tumorigenesis and are now recognized as fundamental contributors to cancer progression [7]. In the context of cancer, epigenetic alterations can lead to the activation of oncogenes or the silencing of tumor suppressor genes, thereby contributing to tumor initiation and progression.Unlike genetic mutations, epigenetic changes are reversible, making them attractive targets for therapeutic intervention [8]. Recent advances in epigenetic research have significantly enhanced our understanding of the molecular mechanisms underpinning cancer and have revealed promising avenues for clinical applications. These include the development of novel cancer biomarkers for early detection, monitoring disease progression, prognostication, and assessing individual risk [9].

2. DNA METHYLATION

DNA methylation is a pivotal epigenetic modification that modulates gene activity without altering the underlying DNA sequence. This process involves the addition of a methyl group to the fifth carbon of the cytosine ring, primarily at CpG dinucleotides, resulting in 5-methylcytosine. DNA methylation plays a pivotal role in various biological processes, including development, genomic imprinting, X-chromosome inactivation, and suppression of transposable elements [10].

The methylation process is catalyzed by DNA methyltransferases (DNMTs), a family of enzymes responsible for establishing and maintaining methylation patterns. DNMT1 is primarily involved in maintenance methylation, ensuring that methylation patterns are preserved during DNA replication by targeting hemimethylated DNA strands. In contrast, DNMT3A and DNMT3B are de novo methyltransferases that establish new methylation patterns during embryonic development and cellular differentiation [11].

DNA methylation can lead to gene silencing through two primary mechanisms. First, methylation of CpG sites within gene promoter regions can directly impede the binding of transcription factors, thereby preventing the initiation of transcription. Second, methylated DNA can attract methyl-CpG-binding domain proteins (MBDs), such as MeCP2, which in turn recruit co-repressor complexes containing histone deacetylases (HDACs). These complexes modify the chromatin structure, leading to a more condensed and transcriptionally inactive state [12].

The removal of methyl groups from DNA, known as demethylation, can occur via passive or active mechanisms. Passive demethylation happens during DNA replication when the maintenance methylation machinery fails to methylate the new strand. Active demethylation involves enzymatic processes where Ten-Eleven Translocation (TET) enzymes oxidize 5-methylcytosine to 5-hydroxymethylcytosine and further derivatives, which are then replaced with unmethylated cytosine through base excision repair pathways [13].

Aberrant DNA methylation patterns are associated to diseases such as cancer. Hypermethylation of tumor suppressor gene promoters can lead to their silencing, contributing to uncontrolled cell proliferation. Therapeutic interventions targeting DNA methylation, such as DNMT inhibitors like azacitidine and decitabine, have been developed to reverse abnormal methylation patterns and are currently used in the treatment of certain cancers [14].

3. HISTONE MODIFICATION

Histone modifications, particularly acetylation and methylation, are pivotal epigenetic mechanisms that regulate chromatin structure and gene expression, playing crucial roles in cellular processes such as development, differentiation, and response to environmental cues. These modifications influence the accessibility of transcriptional machinery to DNA, thereby modulating gene activity without altering the underlying DNA sequence. In the context of cancer, dysregulation of histone modification patterns has emerged as a significant factor in tumorigenesis [15].

Histone acetylation, especially on lysine residues like H3K9ac and H4K16ac, is generally associated with transcriptional activation. For instance, decreased acetylation of histone H3 and H4 has been linked to the silencing of tumor suppressor genes, contributing to uncontrolled cell proliferation. Conversely, increased acetylation at specific loci can activate oncogenes, promoting tumorigenesis. The loss of H4K16ac, in particular, has been associated with defective DNA repair and premature senescence, further implicating its role in cancer development [16].

Histone methylation can either activate or repress gene expression based on the specific residues and methylation states [17]. Trimethylation of H3K4 (H3K4me3) is typically associated with active transcription, while trimethylation of H3K9 (H3K9me3) and H3K27 (H3K27me3) is linked to transcriptional repression. In cancer, aberrant histone methylation patterns are common [16]. For example, overexpression of EZH2, a histone methyltransferase responsible for H3K27 trimethylation, can lead to the silencing of tumor suppressor genes and promote oncogenesis. Additionally, mutations in genes encoding histone demethylases, such as IDH1 and IDH2, result in the accumulation of oncometabolites that inhibit histone demethylation, further contributing to tumorigenesis [18].

To maintain a proper gene expression the balance between histone acetylation and methylation is crucial. Disruption of this balanc pression of genes that inhibit tumor growth. Simultaneously, the gain of repressive histone methylation marks can further silence these genes, creating a permissive environment for tumorigenesis [19].

Given the central role of histone modifications in cancer, targeting the enzymes responsible for these modifications presents a promising therapeutic strategy. Histone deacetylase inhibitors (HDACi), such as vorinostat and romidepsin, have shown efficacy in treating certain cancers by reactivating silenced tumor suppressor genes [20]. Similarly, inhibitors targeting histone methyltransferases and demethylases are being explored to reverse aberrant methylation patterns and restore normal gene expression. These epigenetic therapies offer a novel approach to cancer treatment, aiming to

correct the underlying epigenetic alterations that drive tumorigenesis [21].

Non-coding RNAs (ncRNAs), particularly microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), play pivotal roles in post-transcriptional gene regulation, significantly influencing cancer cell behavior [22]. miRNAs are short RNA molecules, typically 18-25 nucleotides in length, that bind to complementary sequences on target messenger RNAs (mRNAs), leading to mRNA degradation or inhibition of translation. This mechanism allows miRNAs to function as oncogenes or tumor suppressors, depending on the genes they regulate [23]. For instance, miR-145 has been shown to suppress tumor growth by targeting genes involved in cell motility and invasiveness, such as fascin and junctional adhesion molecule A (JAM-A) [24]. Similarly, miR-34a acts as a tumor suppressor by down-regulating genes like SIRT1, thereby promoting apoptosis and inhibiting proliferation in cancer cells. Conversely, miR-21 is often overexpressed in various cancers and promotes tumor growth by targeting tumor suppressor genes like PTEN, leading to enhanced cell survival and proliferation lncRNAs, which are 200 nucleotides longer or more controls gene expression by chromatin remodeling, transcriptional control, and post-transcriptional modulation [25]. One well-characterized lncRNA, HOTAIR, promotes tumor progression by recruiting chromatin-modifying complexes to specific genomic loci, leading to histone modifications and gene silencing. Another lncRNA, MIR22HG, has been implicated in glioblastoma and ovarian cancer by activating signaling pathways that enhance cell proliferation and invasiveness. lncRNAs can also act as molecular sponges for miRNAs, sequestering them and preventing them from binding to their target mRNAs. For example, the lncRNA UCA1 promotes bladder cancer progression by sponging miR-145, thereby relieving repression on oncogenic targets [26].

The dysregulation of ncRNAs involved in uncontrolled tumor cell proliferation, evasion of apoptosis, metastasis, and resistance to therapy. Understanding the specific roles of miRNAs and lncRNAs in cancer has opened new avenues for therapeutic interventions. Strategies aimed at restoring the function of tumor-suppressive miRNAs or inhibiting oncogenic lncRNAs are being explored to counteract aberrant gene expression patterns in cancer cells. As research advances, targeting ncRNAs holds promise for developing more precise and effective cancer treatments [27].

4. EPIGENETIC THERAPIES FOR CANCER TREATMENT

Therapeutically, drugs known as epidrugs have been developed to reverse these aberrant epigenetic modifications. These agents have shown efficacy in treating hematological malignancies and are being explored for solid tumors. Moreover, combining epigenetic therapies with conventional treatments like chemotherapy and immunotherapy has shown promise [28]. Epigenetic drugs can sensitize tumors to chemotherapy by reversing resistance mechanisms and enhance immunotherapy efficacy by modulating the tumor microenvironment to improve immune recognition. Emerging approaches, such as epigenetic editing, aim to precisely modify epigenetic marks at specific genomic loci, offering the potential for targeted and durable cancer therapies [29].

A prominent class of epigenetic drugs includes DNA methyltransferase inhibitors (DNMTis**)**. Aberrant DNA methylation, particularly in the promoter regions of tumor suppressor genes, is a hallmark of many cancers and contributes to transcriptional silencing. Agents such as azacitidine and decitabine, which are nucleoside analogs, integrate into DNA and inhibit the enzymatic activity of DNA methyltransferases (DNMTs). This inhibition results in DNA demethylation, thereby reactivating silenced tumor suppressor genes. Clinically, DNMT inhibitors have demonstrated efficacy, especially in hematological malignancies such as myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML). These drugs can restore normal gene expression and improve the response of cancer cells to additional therapeutic interventions [30].

Another key group of epigenetic agents **is** histone deacetylase inhibitors (HDACis). Histone acetylation is associated with an open chromatin conformation that facilitates transcription. In many cancers, histone deacetylases (HDACs) are overexpressed, leading to histone hypoacetylation and suppression of tumor suppressor genes. HDAC inhibitors like vorinostat (SAHA) and entinostat prevent the removal of acetyl groups from histones, resulting in hyperacetylation. This causes chromatin relaxation, reactivation of gene expression, and ultimately leads to cell cycle arrest, differentiation, or apoptosis in malignant cells. These agents have received approval for the treatment of cutaneous T-cell lymphoma and are under investigation for broader oncological applications, both as standalone therapies and in combination with chemotherapy or immunotherapy [31].

Bromodomain and extra-terminal domain inhibitors (BETis) represent a novel class of epidrugs that target proteins involved in reading histone acetylation marks. BET proteins, such as BRD4, bind to acetylated lysine residues on histones and regulate the transcription of oncogenes like MYC. BET inhibitors interfere with this binding, thereby disrupting oncogenic transcriptional programs and inhibiting cancer cell proliferation. These agents are currently being evaluated in clinical trials for a range of malignancies, including both solid tumors and hematologic cancers [32].

A further therapeutic strategy targets enhancer of zeste homolog 2 (EZH2), a histone methyltransferase responsible for the trimethylation of histone H3 at lysine 27 (H3K27me3), a marker of gene repression. Dysregulated EZH2 activity is implicated in various cancers, including lymphomas and head and neck squamous cell carcinoma. Inhibitors such as tazemetostat have shown clinical benefit in patients with EZH2 mutations or overexpression. By inhibiting EZH2, these drugs can restore the expression of previously silenced genes, reduce tumor cell proliferation, and induce programmed cell death [33].

Together, these classes of epidrugs offer exciting opportunities to reshape cancer therapy by targeting the epigenetic abnormalities that underpin malignancy. Ongoing clinical trials and preclinical studies aim to refine their use, explore synergistic drug combinations, and overcome resistance,

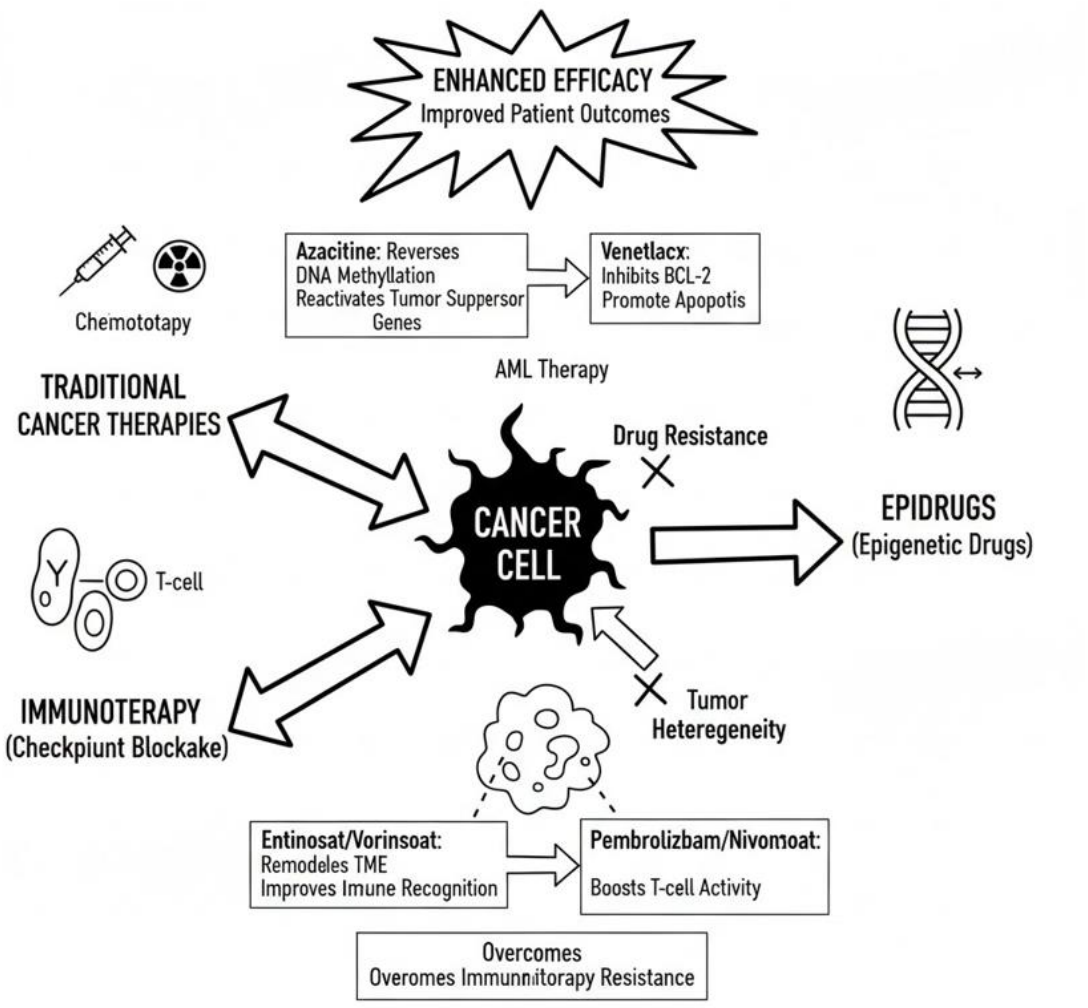

Fig. (1). Synergistic combination of cancer therapy. A conceptual model illustrating how epidrugs are combined with traditional therapies like chemotherapy and immunotherapy to overcome major challenges like drug resistance and tumor heterogeneity, leading to enhanced therapeutic efficacy and improved patient outcomes.

paving the way for more effective and personalized treatment strategies.

5. COMBINATION THERAPIES FOR CANCER TREATMENT

Combining epidrugs with traditional cancer therapies such as chemotherapy, radiotherapy, and immunotherapy has demonstrated significantly enhanced efficacy in both preclinical and clinical studies. This synergistic approach addresses one of the major challenges in oncology such as drug resistance and tumor heterogeneity.

Several promising combinations of epidrugs with other therapies are making significant strides in cancer treatment by simultaneously targeting multiple oncogenic pathways. A prominent example is the combination of azacitidine and venetoclax, which has demonstrated notable clinical success in acute myeloid leukemia (AML). Azacitidine, a DNA methyltransferase inhibitor, works by reversing abnormal DNA methylation and reactivating silenced tumor suppressor genes, while venetoclax promotes apoptosis by inhibiting BCL-2, a protein that prevents programmed cell death. Together, this pairing enhances cancer cell death, resulting in improved response rates and survival in AML patients [34].

In immunotherapy, combining epidrugs with immune checkpoint inhibitors seeks to overcome resistance mechanisms. For instance, entinostat, a histone deacetylase inhibitor (HDACi), paired with pembrolizumab, an anti-PD-1 antibody, has shown encouraging results in microsatellite-stable colorectal cancer, a tumor type typically resistant to checkpoint blockade. Entinostat's epigenetic effects help remodel the tumor microenvironment, improving immune recognition and boosting pembrolizumab's efficacy [35].

Similarly, vorinostat, another HDAC inhibitor, has been studied in combination with pembrolizumab in non-small cell lung cancer (NSCLC). Vorinostat's capacity to relax chromatin and promote immune-related gene expression may sensitize tumors to immune checkpoint inhibitors, enhancing therapeutic outcomes [36].

Other investigational agents include zabadinostat, tested with nivolumab in metastatic microsatellite-stable colorectal cancer to replicate similar immune-enhancing effects; PRT543, a protein arginine methyltransferase 5 (PRMT5)

inhibitor in trials for advanced adenoid cystic carcinoma, which disrupts key methylation processes essential for tumor growth; and pevonedistat, a NEDD8-activating enzyme inhibitor under study for mantle cell lymphoma, targeting protein degradation pathways critical to cancer cell survival [37].

Together, these drug combinations and emerging epidrugs underscore the growing potential of epigenetic therapies to complement traditional and immune-based treatments, offering promising avenues for improved outcomes in a variety of cancers (Fig. **1**).

6. CHALLENGES AND FUTURE DIRECTIONS

Epigenetic drugs impact broad regulatory systems, including DNA methylation and histone modifications, which control the expression of thousands of genes across the genome. While this wide-ranging influence enables epidrugs to reactivate silenced tumor suppressor genes or inhibit oncogenes, it also raises the possibility of unintended effects. These off-target actions can alter the expression of genes unrelated to cancer, potentially causing toxicity in healthy tissues [38]. For instance, demethylation of genes involved in immune function or cell cycle regulation may provoke adverse immune responses or abnormal cell proliferation in normal cells. Furthermore, the non-specific modulation of gene expression can lead to side effects such as fatigue, gastrointestinal upset, or low blood cell counts, which are frequently observed in patients undergoing epidrug treatment. Therefore, developing more selective agents remains a critical challenge to enhance the safety and tolerability of epigenetic therapies [39].

Tumor heterogeneity presents another significant obstacle. Both differences between tumors from different patients (intertumoral heterogeneity) and variability within a single tumor (intratumoral heterogeneity) complicate treatment. Cancer cells within the same tumor often exhibit diverse epigenetic patterns, with variations in DNA methylation and histone modifications. This heterogeneity means that while some tumor cells may respond to a particular epidrug, others may evade its effects, allowing resistant populations to persist and promote disease progression. Additionally, epigenetic profiles can shift dynamically in response to environmental factors or treatment, adding further complexity. These challenges highlight the limitations of a uniform treatment approach and underscore the importance of personalized therapies based on detailed epigenetic profiling and tailored drug combinations [39].

Resistance to epigenetic therapies can arise through multiple mechanisms. Mutations or altered levels of epigenetic enzymes, such as DNA methyltransferases or histone deacetylases, may decrease drug effectiveness. Cancer cells can also activate alternative signaling pathways to circumvent the drugs' impact or increase the activity of efflux pumps to reduce intracellular drug concentrations. Moreover, the flexible nature of the epigenome allows cancer cells to rapidly adapt by re-establishing oncogenic gene expression or maintaining suppression of tumor suppressors despite treatment. Addressing resistance will require a deeper understanding of these processes and may involve combining epigenetic drugs with other targeted therapies or immunotherapies to block escape routes and sustain therapeutic responses [40].

CONCLUSION

Epigenetic mechanisms play a pivotal role in regulating gene expression and contribute significantly to cancer development through reversible modifications. The dynamic nature of epigenetic changes, influenced by both intrinsic and environmental factors, presents a unique opportunity for therapeutic targeting. As our understanding of epigenetic regulation deepens, it paves the way for innovative diagnostic tools, prognostic biomarkers, and personalized treatment strategies, positioning epigenetics at the forefront of precision oncology.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest to disclose.

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AUTHORS' CONTRIBUTIONS

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