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Review Article

INVESTIGATING THE ROLE OF EPIGENETIC MODIFICATIONS IN MEDIATING DRUG RESISTANCE IN CANCER CELL

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Abstract:

Cancer drug resistance remains a major barrier to effective treatment and long-term remission, often leading to therapeutic failure and disease relapse. While genetic mutations have traditionally been recognized as key drivers of resistance, recent evidence highlights the crucial role of epigenetic modifications heritable but reversible changes in gene expression that do not involve alterations in the DNA sequence in modulating cancer cell behavior and drug response. This study aims to investigate how key epigenetic mechanisms, including DNA methylation, histone modifications, and non-coding RNAs, contribute to the development and maintenance of drug resistance in cancer cells. By employing epigenetic profiling techniques, functional assays, and treatment with

Epigenetic modulators such as DNA thioltransferase and histone deacetylase inhibitors, we seek to elucidate the relationship between epigenetic alterations and drug resistance pathways. The findings are expected to provide insights into novel therapeutic strategies to reverse resistance and identify predictive biomarkers, ultimately contributing to the advancement of personalized cancer therapy.

Keywords : *Epigenetics, Drug resistance, Cancer cells, DNA methylation, Histone modification, Non-coding RNAs, Epigenetic therapy, Biomarkers*

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INTRODUCTION:

Cancer drug resistance remains one of the greatest challenges in oncology, often leading to treatment failure and poor patient outcomes. Drug resistance can be intrinsic (pre-existing) or acquired during therapy. While classical mechanisms such as genetic mutations, increased drug efflux, and altered drug metabolism have been extensively studied, emerging evidence highlights a pivotal role of epigenetic modifications heritable yet reversible changes in gene expression without alterations in DNA sequence in driving resistance.

In recent years, increasing attention has been directed toward the role of epigenetic modifications in mediating drug resistance in cancer cells. Unlike genetic mutations, epigenetic alterations such as DNA methylation, histone modifications, non-coding RNAs, and chromatin remodeling do not alter the DNA sequence but regulate gene expression in a heritable yet reversible manner. These modifications orchestrate key cellular processes, including cell cycle regulation, apoptosis, DNA repair, and drug metabolism all of which can be perturbed to promote therapeutic resistance.

This review aims to systematically explore the current understanding of how different epigenetic mechanisms contribute to drug resistance in cancer cells. We will discuss the molecular pathways influenced by DNA methylation, histone modifications, non-coding RNAs, and chromatin remodeling complexes, and highlight potential therapeutic strategies that leverage epigenetic modulators to desensitize resistant tumors. By elucidating the intricate role of epigenetics in cancer drug resistance, we hope to inform future directions for precision oncology and combination therapies. [1][2]

Epigenetic Mechanisms In Cancer And Roles In Carcinogenesis Therapeutic Approach

Epigenetic modifications refer to heritable and reversible changes in gene expression that do not involve alterations in the DNA sequence. These mechanisms play a pivotal role in regulating normal cellular functions such as gene expression, differentiation, and genomic stability. However, in cancer, dysregulation of epigenetic processes contributes significantly to carcinogenesis, tumor progression, and the development of therapy resistance.

1. **DNA Methylation**
   - Mechanism **:** DNA methylation involves the covalent addition of a methyl group to the 5-carbon of cytosine residues, primarily within CpG dinucleotides. In normal cells, this process regulates gene expression, genomic stability, and X-chromosome inactivation. In cancer, aberrant hypermethylation of CpG islands in promoter regions of tumor suppressor genes (e.g., MLH1, p16, BRCA1) leads to their silencing, while global hypomethylation contributes to genomic instability and oncogene activation.
   - Therapeutic approach : DNA methyltransferase inhibitors (DNMTis) such as azacitidine and decitabine have been approved for the treatment of hematological malignancies like myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML). These agents demethylate silenced tumor suppressor genes and restore normal gene expression.
   - Example : Hypermethylation of the MLH1 gene promoter silences this DNA mismatch repair gene in colorectal cancer, contributing to microsatellite instability and tumorigenesis.[3]
2. **Histone Modifications**
   - Mechanism **:** Histone tails undergo post-translational modifications such as acetylation, methylation, phosphorylation, and ubiquitination, which regulate chromatin accessibility and transcription. Cancer cells often show deregulated histone acetylation (via overactive histone deacetylases, HDACs) and aberrant histone methylation patterns (e.g., increased H3K27me3 via EZH2). These alterations silence tumor suppressors and activate oncogenic pathways.
   - Therapeutic approach : HDAC inhibitors such as vorinostat, romidepsin, and panobinostat have been developed to restore acetylation levels, leading to reactivation of tumor suppressor genes and induction of apoptosis. EZH2 inhibitors (e.g., tazemetostat) target aberrant histone methylation and are being explored in clinical trials for lymphomas and other solid tumors.
   - Example: Loss of acetylation at histone H4 (H4Ac) in prostate cancer is associated with the silencing of genes involved in growth inhibition and apoptosis.[4]
3. **Non-coding RNAs (miRNAs and lncRNAs)**
   - Mechanism **:** MicroRNAs (miRNAs) and long non-coding RNAs (lncRNAs) regulate gene expression post-transcriptionally.

Dysregulation of these RNAs in cancer influences cell proliferation, apoptosis, invasion, and drug resistance. For instance, overexpression of miR-21 suppresses the tumor suppressor PTEN, promoting oncogenic pathways.

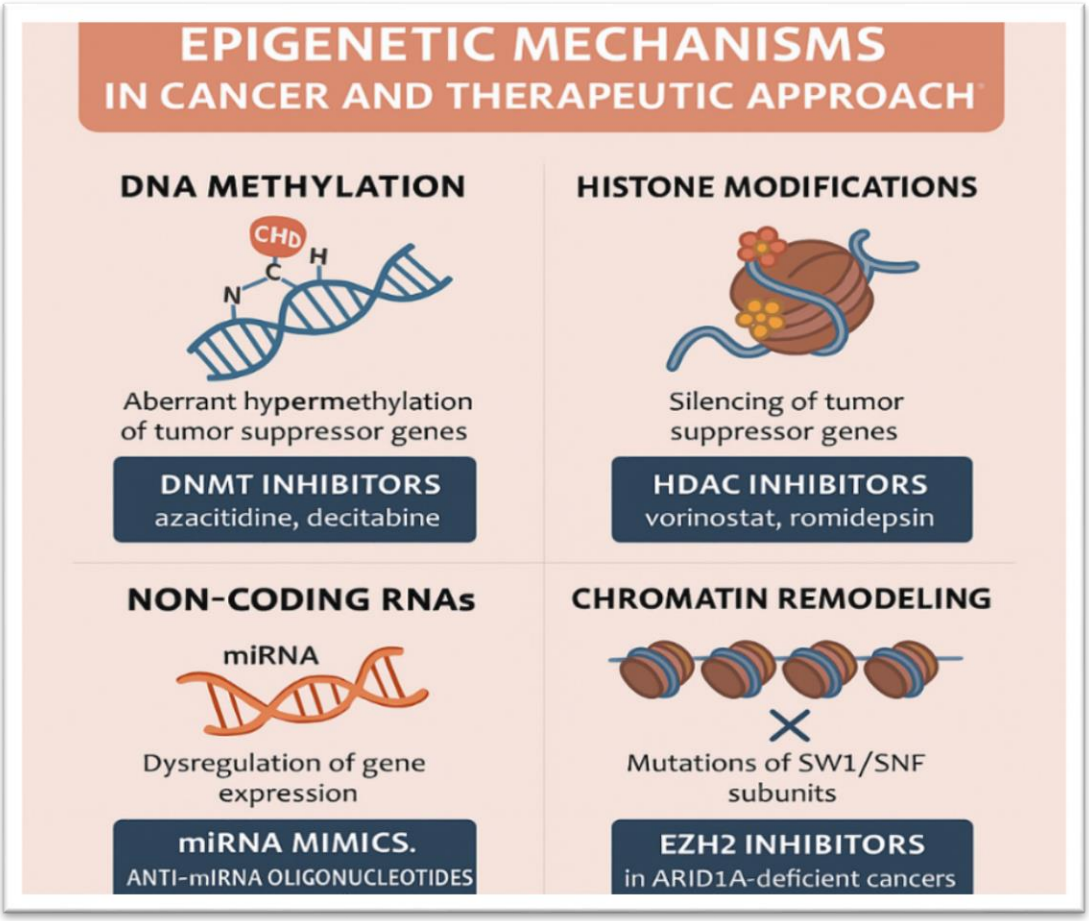
- Therapeutic approach : Therapeutic strategies targeting non-coding RNAs include miRNA mimics, anti-miRNA oligonucleotides, and lncRNA inhibitors to restore normal regulatory networks. While still largely preclinical, these approaches hold potential to reverse oncogenic signaling and drug resistance.
- Example: Loss of ARID1A, a SWI/SNF subunit, is frequently observed in ovarian clear cell carcinoma and endometrial cancer, driving abnormal transcription and tumorigenesis.[5][6]

4. Chromatin Remodeling Complexes

- Mechanism **:** ATP-dependent chromatin remodelers like SWI/SNF complexes reposition nucleosomes to regulate gene expression. Mutations or loss of SWI/SNF subunits (e.g., ARID1A, SMARCA4) are frequent in various cancers and disrupt normal transcriptional control, contributing to tumorigenesis.
- Therapeutic approach: Synthetic lethality strategies are under investigation to target vulnerabilities in SWI/SNF-deficient tumors. For example, EZH2 inhibitors show selective lethality in ARID1A-mutant cancers.
- Example: Loss of ARID1A, a SWI/SNF subunit, is frequently observed in ovarian clear cell carcinoma and endometrial cancer, driving abnormal transcription and tumorigenesis.[7][8]

5. Combined Epigenetic Therapies

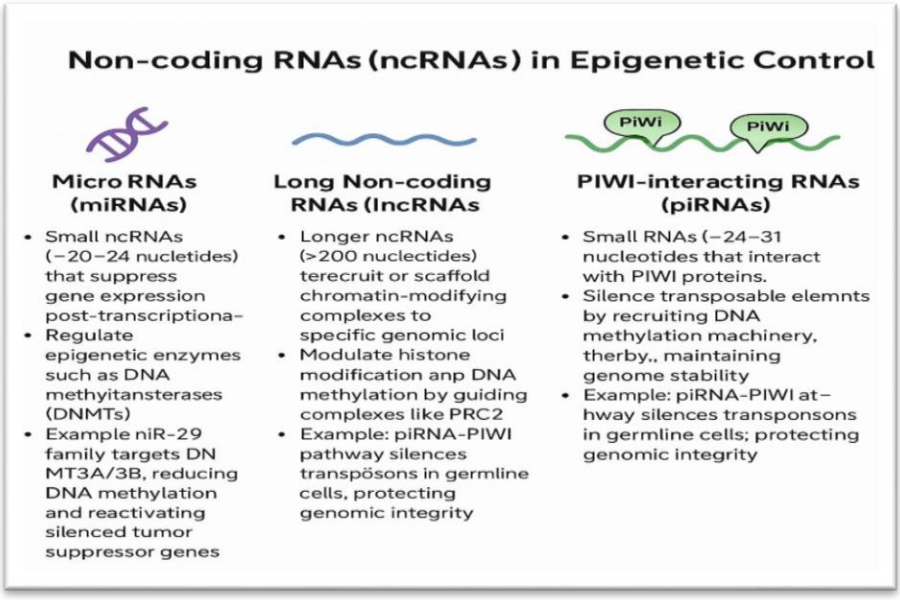
- Given the interplay between different epigenetic mechanisms, combination therapies integrating DNMT inhibitors, HDAC inhibitors, and other epigenetic modulators are being explored to achieve synergistic reactivation of silenced genes and enhance antitumor effects. These combinations can also be paired with conventional chemotherapy, immunotherapy, or targeted agents to overcome resistance.[9]



Fig(1):- Epigenetic Mechanisms In Cancer And Roles In Carcinogenesis Therapeutic Approach

Non-coding RNAs (ncRNAs) in Epigenetic Control
Non-coding RNAs (ncRNAs) are RNA molecules that are not translated into proteins but regulate gene expression at multiple levels, including transcriptional, post-transcriptional, and epigenetic. They play critical roles in controlling the epigenetic landscape of cells and are now recognized as key players in both normal development and disease processes, including cancer.[10]
There are two major types of ncRNAs involved in epigenetic control

1. **MicroRNAs (miRNAs)**
   - Role: miRNAs are small (around 20–24 nucleotides) ncRNAs that regulate gene expression post-transcriptionally by binding to complementary sequences in messenger RNAs (mRNAs), leading to mRNA degradation or inhibition of translation.
   - Epigenetic Control: miRNAs can directly regulate epigenetic regulators like DNA methyltransferases (DNMTs), histone deacetylases (HDACs), and polycomb group proteins. Epigenetic modifications (e.g., promoter methylation) can silence or activate miRNA genes, creating feedback loops.
   - Example : miR-29 family targets DNMT3A and DNMT3B; loss of miR-29 leads to increased DNA methylation and silencing of tumor suppressor genes in cancer.[11]
2. **Long Non-coding RNAs (lncRNAs)**
   - Role: lncRNAs are longer transcripts (>200 nucleotides) that regulate gene expression by interacting with DNA, RNA, and proteins.
   - Epigenetic Control: lncRNAs can recruit chromatin-modifying complexes to specific genomic loci, altering chromatin structure and gene activity. They can act as scaffolds, guides, or decoys for epigenetic regulators.
   - Example: HOTAIR (HOX Transcript Antisense RNA) interacts with the PRC2 complex (Polycomb Repressive Complex 2), guiding it to specific genomic regions to promote H3K27 trimethylation and gene silencing — a mechanism important in breast and other cancers.[12][13]
3. **PIWI-interacting RNAs (piRNAs)**
   - Small RNAs (~24–31 nucleotides) that interact with PIWI proteins.
   - Silence transposable elements by recruiting DNA methylation machinery, thereby maintaining genome stability.
   - Example: The piRNA-PIWI pathway silences transposons in germline cells, protecting genomic integrity.[14]
4. **Small nucleolar RNAs (snoRNAs)**
   - Small RNAs (60–300 nucleotides) that primarily guide chemical modifications (methylation or pseudouridylation) of other RNAs (rRNA, tRNA, snRNA).
   - Emerging evidence suggests they influence chromatin structure indirectly and may be involved in cancer development.
   - Example: Dysregulated SNORDs (snoRNAs) have been linked to oncogenesis in several cancers.[15]



Fig(2):- Non-coding RNAs (ncRNAs) in Epigenetic Control

Epigenetic Regulation of Drug Transporters

Epigenetic alterations profoundly affect the expression of drug efflux transporters, especially members of the ATP-binding cassette (ABC) transporter family, such as ABCB1 (P-glycoprotein) and ABCG2 (Breast Cancer Resistance Protein). These transporters actively export chemotherapeutic agents, reducing their intracellular concentrations and diminishing drug efficacy. The expression of ABCB1 is tightly controlled by epigenetic mechanisms, with DNA hypo methylation of its promoter region leading to its upregulation. This upregulation enhances the cell's ability to expel cytotoxic drugs and confers resistance to agents like doxorubicin and paclitaxel, widely used in breast, ovarian, and colorectal cancers. For example, studies in ovarian cancer cell lines have shown that hypo methylation of the ABCB1 promoter correlates with high P-gp expression and resistance to paclitaxel. [16][17]

histone modifications such as increased acetylation of histones H3 and H4 in the ABCB1 locus can further augment its transcription, exacerbating drug resistance. These findings underscore how epigenetic reprogramming directly regulates transporter activity and highlights the therapeutic potential of epigenetic inhibitors to reverse transporter-mediated resistance.

Example: Hypo methylation of the ABCB1 promoter increases P-glycoprotein (P-gp) expression, leading to resistance to doxorubicin and paclitaxel in ovarian cancer cell lines.[18][20]

Epigenetic Modulation of Apoptosis Pathways

Apoptosis evasion is a critical mechanism by which cancer cells resist the cytotoxic effects of chemotherapy. Epigenetic silencing of key pro-apoptotic genes, such as BAX, PUMA, and DAPK1, allows tumor cells to circumvent drug-induced cell death. Promoter hypermethylation of DAPK1, a serine/threonine kinase integral to apoptosis induction, has been documented in multiple cancers, including lung, colorectal, and bladder carcinomas. For instance, hyper methylation of DAPK1 in lung cancer correlates with resistance to cisplatin, a commonly used DNA-damaging agent.[21][22]

Additionally, histone deacetylation reduces the accessibility of apoptotic gene promoters, silencing genes such as PUMA, thereby diminishing intrinsic apoptotic responses. The combined epigenetic repression of these pathways not only confers survival advantages but also complicates treatment outcomes. Importantly, HDAC inhibitors like vorinostat have been shown to restore pro-apoptotic gene expression, sensitizing resistant cells to chemotherapeutic agents, which highlights their utility in combinational therapy settings.

Example: Hypermethylation of the DAPK1 (death-associated protein kinase 1) promoter has been associated with resistance to cisplatin and other apoptosis-inducing drugs in lung and colorectal cancers.[23]

Cancer Stem Cells (CSCs) and Epigenetics

The tumor microenvironment (TME) exerts profound influence on cancer progression, metastasis, and treatment resistance through a complex interplay of stromal, immune, and vascular components. Epigenetic modifications enable cancer cells to adapt to microenvironmental stresses, particularly hypoxia, by reprogramming gene expression to promote survival. Hypoxia-inducible factor 1-alpha (HIF-1α) is stabilized under low oxygen conditions and collaborates with epigenetic modifiers such as histone deacetylases (HDACs) and lysine demethylases to remodel chromatin.

Example: EZH2-mediated H3K27 trimethylation promotes CSC maintenance and drug resistance in glioblastoma and breast cancer, especially by silencing tumor suppressor genes like CDKN2A and differentiation genes.[24][25]

Interplay Between Epigenetics and Tumor Microenvironment (TME)

The tumor microenvironment (TME) exerts profound influence on cancer progression, metastasis, and treatment resistance through a complex interplay of stromal, immune, and vascular components. Epigenetic modifications enable cancer cells to adapt to microenvironmental stresses, particularly hypoxia, by reprogramming gene expression to promote survival. Hypoxia-inducible factor 1-alpha (HIF-1α) is stabilized under low oxygen conditions and collaborates with epigenetic modifiers such as histone deacetylases (HDACs) and lysine demethylases to remodel chromatin. For example, in colorectal cancer, HIF-1α recruits HDAC1 to repress the expression of E-cadherin and promote metastasis and resistance to 5-fluorouracil (5-FU).

Similarly, histone methylation patterns altered by hypoxia-driven enzymes, such as JMJD1A, facilitate expression of genes supporting angiogenesis and glycolysis, favoring a drug-resistant phenotype. Importantly, epigenetic modulation of immune checkpoint ligands (e.g., PD-L1) in hypoxic tumors further contributes to immune evasion, complicating therapeutic intervention.

Example: In colorectal cancer, hypoxia-induced HIF-1α recruits HDAC1 to repress E-cadherin expression,

enhancing invasion, metastasis, and resistance to 5-fluorouracil (5-FU).[26][27]

Epigenetic Plasticity and Phenotypic Switching (EMT)

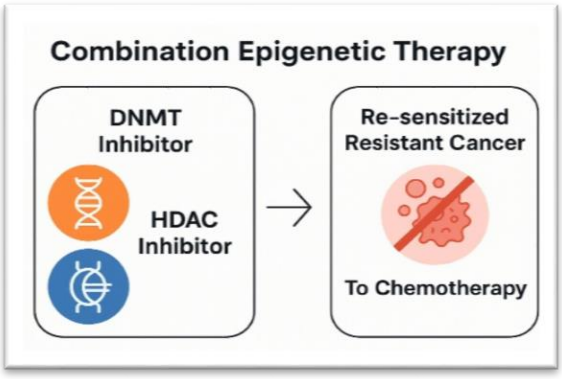
Epithelial-to-mesenchymal transition (EMT) is a key phenotypic switch that imparts migratory, invasive, and drug-resistant capabilities to epithelial tumor cells. Epigenetic regulation underpins this process by modulating the expression of EMT-associated transcription factors such as ZEB1, SNAIL, and TWIST1. Histone modifications, including increased H3K27 acetylation and H3K4 methylation at the ZEB1 promoter, promote its expression and drive EMT.

Example: Histone modifications regulating ZEB1 expression drive EMT-associated resistance to EGFR-TKIs in non-small cell lung cancer (NSCLC).[28][29]

Combination Epigenetic Therapy

Recognizing the reversibility of epigenetic modifications, epigenetic drugs (epi-drugs) have emerged as promising adjuncts to existing cancer therapies. DNA methyltransferase inhibitors (DNMTis) such as decitabine and azacitidine, as well as HDAC inhibitors like entinostat and vorinostat, can reverse silencing of tumor suppressor genes and sensitize tumors to chemotherapy or immunotherapy. For instance, a clinical study in non-small cell lung cancer (NSCLC) demonstrated that a combination of decitabine with entinostat restored chemosensitivity in patients with previously resistant tumors, leading to increased response rates. Moreover, combining epigenetic therapy with immune checkpoint inhibitors (e.g., anti-PD-1/PD-L1) is showing promise by reactivating immune surveillance genes silenced by hyper methylation.

Example: The combination of decitabine (DNMT inhibitor) and entinostat (HDAC inhibitor) re-sensitized resistant non-small cell lung cancer (NSCLC) to chemotherapy in clinical studies, restoring drug response and reducing tumor burden.[30]



Fig(3):- Combination Epigenetic Therapy

CONCLUSION:

Epigenetic modifications play a pivotal role in driving drug resistance in cancer cells by orchestrating complex regulatory networks that modulate gene expression without altering the underlying DNA sequence. Mechanisms such as DNA methylation, histone modifications, non-coding RNA regulation, and chromatin remodeling contribute to the silencing of tumor suppressor genes, activation of drug efflux transporters, evasion of apoptosis, maintenance of cancer stem cells, and promotion of phenotypic plasticity, all of which converge to reduce therapeutic efficacy. Moreover, the dynamic interplay between epigenetic alterations and the tumor microenvironment further complicates treatment strategies, reinforcing resistance and tumor progression.

Importantly, emerging evidence highlights that epigenetic modifications are reversible, offering a unique therapeutic window. Combination epigenetic therapies — integrating DNA methyltransferase inhibitors, histone deacetylase inhibitors, and conventional chemotherapeutics — have shown promise in re-sensitizing resistant cancers and improving patient outcomes in both preclinical and clinical settings. Moving forward, a deeper understanding of cancer-specific epigenetic landscapes, combined with the development of highly selective and less toxic epigenetic drugs, holds potential to revolutionize precision oncology and combat drug resistance more effectively.

Continued research into the integration of epigenetic biomarkers for early detection of resistance and personalized epigenetic intervention strategies will be crucial for optimizing cancer treatment and overcoming therapeutic hurdles.

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