Epigenetics in Cancer: Mechanisms, Oncogenesis, and Therapeutic Potential

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Abstract: Epigenetics are able to influence gene expression without changing the nitrogenous base sequence of DNA. These modifications include DNA methylation, histone modifications, chromatin remodeling, and non-coding RNA regulation, which all contributes to cancer development. Abnormal epigenetic changes can lead to oncogene activation and tumor suppressor genes (TSGs) silencing, making epigenetics promising therapeutic targets. This review explores the mechanisms of these four epigenetic processes, their roles in carcinogenesis, and current strategies for epigenetic therapy. It highlights the importance of understanding these mechanisms to address challenges such as high toxicity and low specificity, and to advance precision medicine in cancer treatment.

1 INTRODUCTION

Cancer is a type of disease described as uncontrolled cell division which result in spread of abnormal cells and formation of tumor. Although genetic mutations are the primary and most well-known cause of cancer, epigenetics has emerged as a new focus in oncogenesis over the past decade. Epigenetic modifications alter the gene expression by influencing the ability of DNA to access to transcription and translation machinery. Because epigenetic changes are reversible, they can cause abnormal gene expression, leading to the oncogenes being over-expressed or the tumor suppressor genes (TSGs) being under-expressed, which is key of causing cancer. Given the role of epigenetics in actively causing cancer, the mechanisms underlying these changes and the potential for epigenetic treatments have become hot topics.

This review explores four key epigenetic mechanisms: DNA methylation, histone modifications, chromatin remodeling, and non-coding RNA regulation. It then examines the effects of these epigenetic alterations in causing cancer, including the oncogene activation and TSGs silencing. The therapeutic potential of epigenetic interventions is discussed, with a focus on targeting epigenetic "writers," "readers," and "erasers." While most of these interventions have demonstrated potential in preclinical studies, they require further optimization to address toxicity and specificity concerns. This review provides theoretical insights and practical recommendations for the study of epigenetics in the context of cancer development and treatment.

2 EPIGENETIC MECHANISM

2.1 DNA Methylation

DNA methylation involves the adding a methyl group (CH3) to the 5th carbon of the base, cytosine, and turning it to 5-methylcytosine. Depending on the location of methylation, it can either inhibit or enhance gene expression (Tibben & Rothbart 2024). The proteins methyltransferases (DNMTs) conduct the addition of methyl groups, whereas the removal of methyl groups is facilitated by TET proteins and the base excision repair (BER) pathway (Wyatt & Pittman 2006). Methylation significantly impacts the genome. Under random conditions, the probability of a particular dinucleotide occurring in a DNA sequence is 1/16, or 6.25%. However, CpG dinucleotides, composed of cytosine and guanine linked by a phosphodiester bond, occur at a frequency of only 1% in the genome. This underrepresentation is primarily due to the accidental deamination. When

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a normal cytosine undergoes deamination, it becomes an uracil, and uracil DNA glycosylase (UDG) can rapidly repair uracil back to cytosine. However, when a 5-methylcytosine deaminate, it turns to a thymine, but thymine DNA glycosylase (TDG) repairs thymine at a slower rate, which is insufficient to counteract the high rate of transcription. Consequently, CpG dinucleotides are underrepresented in the genome (Maiti & Drohat 2011, Silveira et al. 2024). DNA methylation at gene promoters generally inhibits transcription. When cytosine residues within promoters are methylated, the 5-methylcytosine makes the nucleosomes to be more stable and prevents transcription machinery such as transcriptional factors and polymerase from binding to the DNA. In contrast, gene body methylation (GbM) prevents the binding of repressive chromatin-modifying complexes thereby promotes transcription (Williams et al. 2023).

2.2 Histone Modification

The three types of histone modifications are acetylation, methylation, and phosphorylation. They influence expression of proteins through altering structure of chromatin and impacts the DNA's potential to bind to proteins that assist transcription to happen.

Histone acetylation is adding of acetyl groups on histone, it is done by the protein histone acetyltransferases (HATs). Additionally, acetyl groups can be removed by histone deacetylases (HDACs). Acetylation occurs on the lysine residues of histone. Histone is positively charged, and DNA is negatively charge, meaning they are connected by electrostatic attraction. Acetyl groups can mask the positive charge of histone and weakening the electrostatic interactions between histones DNA. This modification loosens the chromatin structure, allowing transcription factors and other regulatory proteins to access the DNA more easily, thereby promoting gene expression (Liebner et al. 2024).

Histone methylation involves the incorporation of methyl groups to lysine or arginine residues, catalyzed by histone methyltransferases (HMTs) and removed by histone demethylases. On lysine residue, maximum of three methyl groups can be added, resulting in four states: unmethylated, mono-methylated, di-methylated, and tri-methylated. Whereas only two states of mono-methylated or di-methylated exist on arginine residue (Tollefsbol, 2023). Histone methylation can influence the basicity and hydrophobicity of histones, thereby affecting the affinity of certain effector proteins that either activate or repress gene expression, such as transcription factors (Tollefsbol 2023). The specific impact depends on how many methyl groups is added and on which residue it is added. For instance, trimethylation of histone H3 at lysine 4 promotes transcription to happen. On the other hand, trimethylation of histone H3 at lysine 27 can prevent expression and is often found in regions of condensed chromatin (Cavalheiro et al. 2021).

Histone phosphorylation, typically occurring on serine or threonine residues, can directly alter histone-DNA interactions, recruit other proteins that modify chromatin shape, and impact the addition of other epigenetic markers. For example, phosphorylation of histone H2AX at serine 139 is a key marker of DNA double-strand breaks and is involved in the DNA damage response. This modification helps recruit repair proteins to where damages occur, ensuring genomic stability (López-Hernández et al. 2025).

2.3 Chromatin Remodeling

Chromatin-remodeling complexes, which use the energy from ATP to change the shape, composition, or location of nucleosomes, are responsible for chromatin remodeling (Hota & Bruneau 2016). These complexes can slide nucleosomes along the DNA, eject them from specific sites, or incorporate histone variants, thereby modulating DNA accessibility. When chromatin is remodeled into a more open state, transcription factors and RNA polymerase can access the DNA more easily, leading to gene activation. Conversely, a more compact chromatin structure restricts access, resulting in gene repression (Alendar & Berns 2021).

2.4 Non-Coding RNA

There are two categories of non-coding RNAs: short ncRNAs, which include microRNAs (miRNAs) and small interfering RNAs (siRNAs), and long non-coding RNAs (lncRNAs). These ncRNAs can modulate gene expression through diverse mechanisms. Short non-coding RNAs function at the post-transcriptional stage by attaching to the 3-prime untranslated regions (3' UTRs) of specific mRNAs. which can lead to mRNA degradation or inhibit translation (Zhang et al. 2024). Long ncRNAs (lncRNAs) can recruit chromatin-modifying complexes, resulting in histone modifications. Additionally, lncRNAs can interact with proteins

such as methyltransferases and acetyltransferases to add or remove methyl or acetyl groups (Li J et al. 2024).

3 ROLE OF EPIGENETICS IN CANCER DEVELOPMENT

3.1 DNA Methylation

DNA methylation primarily acts through two key mechanisms to cause cancer: regional hypermethylation and global hypomethylation. Regional hypermethylation frequently occurs in the promoter regions of TSGs, resulting in the inactivation of these genes. This silencing disrupts the normal regulatory functions that would otherwise inhibit cell proliferation and promote apoptosis, thereby contributing to uncontrolled cell division (Su et al. 2018). On the other hand, global hypomethylation affects repetitive elements in the genome, such as retrotransposons. This widespread hypomethylation can lead to chromosomal rearrangements and genome instability. The absence of methyl group in these regions may activate transposable elements, causing insertional mutagenesis and further disrupting the normal functioning of genes (Jordà et al. 2017). Additionally, altered DNA methylation patterns can also affect the tumor microenvironment, influencing the behavior of immune cells and contributing to immune evasion by cancer cells (Zhong et al. 2023).

3.2 Histone Modification

Abnormal acetylation patterns can disrupt the normal level of oncogenes and TSGs. High level of histone deacetylases (HDACs) can cause hypoacetylation of histones, as a result TSGs inactivated, such as p53. In contrast, hyperacetylation of oncogenes can boost their expression and accelerate cancer progression (Bu et al. 2024). Histone methylation plays a more intricate role in cancer, with different methylation sites exerting distinct effects. For instance, mutations in H3K27 methyltransferases, such as EZH2, have been implicated in many cancers, including breast cancer and hepatocellular carcinoma (Gu et al.2022, Ning et al.2016).

3.3 Chromatin Remodeling

Aberrant chromatin remodeling can result in the activation of oncogenes and the silencing of TSGs. For example, a number of cancers, including leukemia, prostate cancer, and neurodevelopmental disorders, are known to have mutations in parts of the SWI/SNF chromatin remodeling complex. These alterations have the potential to impair the complex's regular operation and alter gene expression, which encourages carcinogenesis. (Kadoch et al. 2013).
Moreover, SWI/SNF participates in the regulation promoters, which are critical for maintaining the expression of oncogenic transcription factors. Dysregulation of these complexes can result in the aberrant activation of oncogenic pathways. Additionally, chromatin remodeling can influence the microenvironment of tumors by affecting the immune systen and the response to DNA damage. This can lead to immune evasion and increased genomic instability, further contributing to cancer progression (Kadoch et al. 2013).

3.4 Non-Coding RNA

Non-coding RNAsnc (RNAs) can act as both tumor suppressors and oncogenes depending on their targets and cellular context. For example, the abnormal level of expression of microRNAs is frequently observed in patients with cancer. These miRNAs can either promote tumor growth by silencing TSGs or inhibit oncogenic pathways by targeting oncogenes. Long non-coding RNAs (lncRNAs) can sequester miRNAs, thereby diminishing the regulatory impact of miRNAs on their target mRNAs (John et al. 2025, Kim et al. 2024).

4 EPIGENETIC THERAPIES FOR CANCER TREATMENT

4.1 Targeting Epigenetic Writers

Epigenetic writers are proteins that add epigenetic markers to target sites, thereby influencing gene expression.

4.1.1 DNA Methyltransferase Inhibition

DNA methyltransferases (DNMTs) are important proteins that can bring of methyl groups to DNA. Methylation of the promoters of TSGs often leads to inactivation. This mechanism is frequently

dysregulated in cancer, making DNMTs attractive therapeutic targets. DNMT inhibitors, such as azacitidine and decitabine, have been extensively studied and are now approved for the treatment of hematologic malignancies. These nucleoside analogs are incorporated into DNA, inhibiting DNMTs and leading to DNA demethylation, which in turn reactivates silenced TSGs. However, their efficacy in solid tumors has been limited due to toxicity and pharmacokinetic challenges (Ren et al. 2023).

4.1.2 Histone Methyltransferase Inhibition

Histone methyltransferases (HMTs) are proteins that bring methyl groups to histone, thereby influencing gene expression. Among these, HMTs such as EZH2 and DOT1L have been identified as critical targets in cancer therapy. EZH2 inhibitors, like tazemetostat, have demonstrated significant efficacy in cancers with EZH2 mutations or loss of SMARCB1. They achieve this by reducing H3K27me3 levels and reactivating target genes. Similarly, DOT1L inhibitors, such as pinometostat, have shown antitumor activity in MLL-rearranged leukemia by targeting H3K79 methylation.These inhibitors have shown promise in clinical trials. However, challenges remain in optimizing their use, particularly in solid tumors (Li D et al. 2024).

4.2 Targeting Epigenetic Readers for Cancer Therapy

Epigenetic readers are proteins that identify and attach to particular epigenetic modifications on DNA and histones, subsequently affecting gene expression and cellular outcomes. The bromodomain and extra-terminal domain (BET) family consists of BRD2, BRD3, BRD4, and BRDt, is a key group of epigenetic readers. These proteins specifically recognize acetylated lysine residues, making them attractive targets for cancer therapy. BET inhibitors, such as JQ1, have been developed to selectively target these proteins, resulting in the downregulation of oncogenic targets like MYC. However, concerns over toxicity and the development of resistance have prompted the search for second-generation inhibitors. Natural compounds, particularly those derived from plants and marine sources, have emerged as potential alternatives. For example, naringenin triacetate from bitter orange, resveratrol from grapes, and magnolol from the magnolia tree have shown promise in targeting BET proteins. These natural compounds offer the advantages of lower toxicity and potential synergistic effects when combined with other therapies (Damiani et al. 2020).

4.3 Targeting Epigenetic Erasers for Cancer Therapy

Epigenetic erasers eliminate modifications on DNA or histones, thus influencing gene expression. Notable epigenetic erasers consist of TET enzymes, histone lysine demethylases (HDMs), and histone deacetylases (HDACs). The TET enzymes are essential for DNA demethylation as they restrict DNMT1's ability to recognize 5-hydroxymethylcytosine (5-hmC). As a result, dividing cells gradually lose their methylation. Lysine-specific demethylase (LSD) and JmjC domain-containing lysine demethylases are the two groups of histone lysine demethylases (HDMs). LSD1 (KDM1A) and LSD2 (KDM1B) remove methyl groups from histone lysines through their oxidase-like domains. These enzymes are often overexpressed in cancers such as prostate, breast, and colorectal cancer (Yang et al. 2016).

5 COMBINED TREATMENT OF EPIGENETIC THERAPY WITH OTHER CANCER THERAPIES

5.1 Epigenetic Therapy and Chemotherapy

Epigenetic therapies have demonstrated the potential to enhance the effects of chemotherapy. For example, histone deacetylase inhibitors (HDACi) have demonstrated ability to amplify the effects of chemotherapeutic agents, for example, topotecan, in small cell lung cancer. Similarly, combining DNA methyltransferase inhibitors like decitabine with cytarabine has exhibited synergistic effects in leukemia cell lines. These combinations can overcome chemotherapy resistance by reactivating silenced TSGs and enhancing drug-induced apoptosis (Li et al. 2017).

5.2 Epigenetic Therapy and Radiotherapy

Epigenetic modifications can sensitize cancer cells to radiotherapy. For instance, HDAC inhibitors seemed to enhance response to DNA damage induced by radiation, which causes increased cells to die. This

combination takes advantage of the ability of epigenetic drugs to modulate the tumor microenvironment and thereby improve the efficacy of radiation therapy (Camphausen & Tofilon 2007).

5.3 Epigenetic Therapy and Immunotherapy

Combining epigenetic therapies with immunotherapy has emerged as a positive treatment to enhance antitumor immunity. Epigenetic drugs can upregulate tumor antigens and major histocompatibility complex (MHC) molecules, thereby improving the ability to identify and killing of cancer cells by immune cells. For instance, dual targeting of EZH2 and HDAC with tazemetostat and belinostat has been shown to promote immunogenicity in certain cancers (Marx et al. 2005).

5.4 Epigenetic Therapy and Hormone Therapy

In the context of hormone therapy, HDAC inhibitors have shown potential to enhance therapeutic effects and overcome drug resistance. For instance, in breast cancer, HDAC inhibitors have consistently demonstrated their ability to disrupt estrogen-receptor signaling pathways in estrogen-receptor-positive (ER+) breast cancer (Margueron et al. 2004).

6 CONCLUSION

To conclude, the four types of epigenetic mechanisms including DNA methylation, histone modifications, chromatin remodeling, and non-coding RNAs actively cause cancer. These epigenetic alterations can trigger oncogenes being overexpressed or TSGs being under-expressed. Moreover, environmental factors like smoking, diet, and pollution can induce such epigenetic changes, thereby further contributing to cancer risk. Despite the immense potential of epigenetics as a target for cancer treatment, current epigenetic therapies face challenges of high toxicity and low specificity. This is partly due to the broad-spectrum nature of drugs such as DNMT inhibitors and HDAC inhibitors. Future research should focus on optimizing drug doses and developing targeted delivery methods—such as nanoparticles—to improve efficacy while minimizing effects on non-cancerous cells. Overall, addressing these limitations and exploring new strategies will be essential for advancing epigenetic cancer therapies.

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