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Targeting the epigenome: Emerging epigenetic moulators as therapeutic agents in cancer and chronic diseases

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Abstract
Epigenetics involves heritable changes in gene expression without altering DNA sequences, significantly influencing development, differentiation, and disease susceptibility. Key mechanisms include DNA methylation, histone modifications, and non-coding RNAs, all crucial for regulating chromatin structure and transcription. Dysregulation relates to various diseases, including cancer and metabolic disorders.Recent advances in epigenetic therapeutics, such as DNA methyltransferase and histone deacetylase inhibitors, indicate the potential for successful cancer treatments. However, challenges like delivery systems and ethical issues persist. Further exploration of epigenetic mechanisms can enhance human health and precision medicine.

Keywords: Epigenetics, DNA methylation, Histone modification, non-coding RNAs, Chromatin remodelling, Metabolic diseases, Combination therapy

1. Introduction
Epigenetics, coined by Conrad H. Waddington in 1942, refers to heritable changes in gene expression without altering DNA sequences. The epigenome is a collection of mechanisms that influence chromatin structure to regulate gene activity. These mechanisms include DNA methylation, histone modification, and RNA interference. [1]
Epigenetic modifications play crucial roles in cellular differentiation, development, and disease, particularly cancer, with specific alterations being involved in tumorigenesis. New therapeutic techniques, such as DNMT and HDAC inhibitors, aim to improve cancer treatment by restoring gene function while having less adverse effects than older medicines. Ongoing research is essential to fully understand epigenetic mechanisms and their implications for health and disease management.[2]

2. Types of Epigenetic Modifiers
Proteins like cohesin and CTCF, which form topologically associating domains (TADs) to organize the genome, promote chromatin looping, a mechanism by which regulatory elements connect with genes. [7]

2.1. DNA Methylation Modifiers: DNA methyltransferases (Dnmts) add methyl groups to CpG sites to silence genes. There are three types: Dnmt1 (maintains methylation), Dnmt3a/3b (de novo methylation), and Dnmt2 (RNA methyl transferase). Demethylases like the TET family remove methyl groups, promoting gene expression. [3]

2.2. Histone Modifiers: Enzymes that modify histones (e.g., HATs add acetyl groups, HDACs remove them) alter chromatin structure. Acetylation generally increases transcription, while methylation can either activate or repress it. [4]

2.3. Non-coding RNA Mediators: Include microRNAs (miRNAs) that regulate gene expression by binding to target mRNAs, long non-coding RNAs (lncRNAs) vital for transcriptional regulation, and circular RNAs (circRNAs), which are more stable and can sequester other molecules like miRNAs.[5]

2.4. Chromatin Remodeling Complexes: The SWI/SNF complexes are an example of these ATP-dependent complexes that alter chromatin structure without chemically altering DNA or histones, hence promoting gene accessibility. [6]

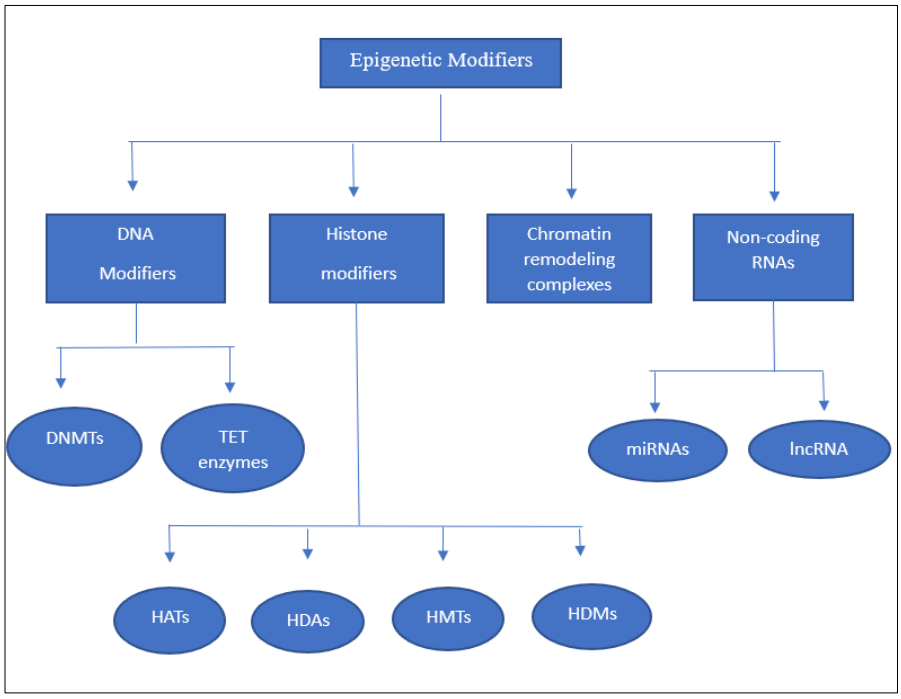

Fig 1: Types of epigenetic modifiers

3. Mechanisms of Epigenetic Regulation

Epigenetic modifications include DNA methylation, histone modification, non-coding RNA regulation, and chromatin remodeling.

3.1. DNA Methylation

DNA methylation, a key epigenetic change, involves the addition of a methyl group to cytosine residues in CpG dinucleotides, mediated by DNA methyltransferases (DNMTs). This modification predominantly occurs in gene promoter regions, leading to gene silencing. In cancer, abnormal methylation patterns, such as hypermethylation of tumor suppressor genes and hypomethylation of oncogenes, contribute to aberrant cell growth. DNA methylation patterns are established during development, are stably inherited, and are associated with various diseases, including cancer. [8]

3.2. Histone Modification

Histone modification involves covalent modifications to histone proteins, particularly the core histones H2A, H2B, H3, and H4, targeting amino acid residues like serine, arginine, and lysine by processes such as methylation, acetylation, phosphorylation, and ubiquitination. Catalyzed by enzymes like histone acetyltransferases (HATs) and histone deacetylases (HDAs), these modifications are reversible and dynamic, playing a vital role in regulating gene expression and chromatin structure in response to cellular needs.

Common modifications include acetylation, which influences chromatin compaction and gene transcription, and methylation, which can activate or silence genes depending on the modification site.Phosphorylation controls chromatin structure and is required for the cell cycle and DNA repair, whereas ubiquitination involves the addition of ubiquitin, which influences gene expression and interacts with other changes. The complex histone modification network, which includes lesser-known modifications such as glycosylation and ADP-ribosylation, contributes to epigenetic regulation by changing chromatin packing and transcription factor accessibility, hence impacting gene expression. [9]

3.3. Chromatin Remodeling

Chromatin remodeling refers to the dynamic alteration of chromatin structure to enable access to DNA for transcription regulation, primarily through ATP-dependent chromatin remodeling complexes and covalent histone modifications by enzymes like histone acetyltransferases. This process is crucial not only for gene expression but also for various biological functions such as chromosome segregation, DNA repair, and development.

ATP-dependent complexes, divided into SWI2/SNF2 and ISWI groups, use ATP hydrolysis to rearrange nucleosomes and increase transcriptional activity. Conversely, non-coding RNAs (ncRNAs) like miRNAs and lncRNA also regulate gene expression, with miRNAs inhibiting translation and lncRNAs acting as transcriptional regulators. Together, they play significant roles in processes such as apoptosis, immune responses, and cancer pathology, although further unified research on lncRNAs is still necessary.

3.4. Non-coding RNA Regulation

miRNAs and lncRNAs can inhibit gene expression post-transcriptionally or via chromatin modification recruitment. Altered expression of such RNAs is implicated in cancer, immunity, and development.

miRNAs are short non-coding RNAs (19-23nucleotides) that attach to target mRNAs' 3' untranslated regions and

frequently prevent translation, hence controlling gene expression.The human genome contains around 2500 identified miRNAs, which play crucial roles in apoptosis, inflammation, and tumor-associated diseases. For instance, miRNA-21 influences gene transcription related to apoptosis in rat hippocampal neurons and impacts growth factor receptor production.

lncRNAs, longer RNA molecules exceeding 200 nucleotides, primarily function as transcriptional regulators without encoding proteins. They can interact with miRNAs, affecting gene expression through mechanisms like miRNA sponging. Research on lncRNA is complex and lacks a unified consensus, despite significant findings, including eight lncRNAs binding miRNA-107 in laryngeal carcinoma. Recognized lncRNA databases include lncATLAS and lncRBase. [10]

4. Therapeutic Applications

4.1. Approved Epigenetic Drugs

Epigenetic modulators play a crucial role in cancer treatment by stimulating or inhibiting epigenetic processes. Notable classes include histone deacetylase inhibitors (HDACis) that restore acetylation homeostasis, improving tumor suppressor gene expression, with FDA-approved drugs like vorinostat and romidepsin for certain lymphomas. DNA methyltransferase inhibitors (DNMTis), such as azacitidine and decitabine, reverse DNA methylation, reactivating repressed genes in myelodysplastic syndromes. [11]

4.2. Emerging Therapies

Emerging modulators target a variety of different enzymes and pathways, including lysine acetyltransferases (KATs) and histone demethylases (KDMs), which have shown promise against multiple malignancies. [12] Bromodomain and extra-terminal domain (BET) inhibitors disrupt oncogenic transcription, providing new therapeutic avenues. [13]

- KAT inhibitors (e.g., Tip60 inhibitors)
- KMT and KDM inhibitors (targeting writers and erasers of histone methyl marks)
- BET inhibitors (targeting bromodomain proteins)
- TET inhibitors (affecting DNA demethylation). [14, 15]

4.3. Combination Therapy

Combination therapy uses various medications with diverse mechanisms of action to improve efficacy over monotherapy. This method aids in the fight against highly resistant virus strains by increasing the selection barrier for resistance while reducing toxicity through lower medication dosages. It is very useful for treating serious infections and immunocompromised patients.

Notably, combinations such as Oseltamivir-amantadine and favipiravir-oseltamivir have shown improved effectiveness in H5N1-infected mice. The oseltamivir-ribavirin combination has also proven beneficial against H5N1 in mouse models. Furthermore, combining oseltamivir with sirolimus and corticosteroids reduced mortality in critically ill patients, while favipiravir-peramivir demonstrated increased survival rates against H1N1 infections. [16]

5. Epigenetic Roles in Human Disease

5.1. Cancer: Cancer significantly illustrates the influence of epigenetics on human diseases, where abnormal epigenetic changes contribute to oncogenesis and disease progression. DNA methylation, which can silence tumor suppressor genes such as BRCA1 in breast cancer and GSTP1 in prostate cancer, as well as histone alterations, which impact chromatin structure and gene expression, are important processes.

Non-coding RNAs also play a crucial role, with their dysregulation further promoting malignant transformation. Overall, understanding these epigenetic modifiers is essential for developing targeted cancer therapies. [17]

5.2. Neurological Disorders: Neurological disorders exhibit significant epigenetic changes, impacting gene expression and susceptibility to conditions like Alzheimer's, Parkinson's, and schizophrenia. Environmental factors and lifestyle choices such as nutrition and physical activity play critical roles in health. For Alzheimer's, alterations in DNA methylation affect cognitive functions and memory. In Parkinson's, the loss of dopamine neurons causes tremors and motor dysfunction. Schizophrenia involves disrupted regulatory genes leading to cognitive and emotional instability. Additionally, metabolic disorders like diabetes and obesity also demonstrate epigenetic influences, with specific DNA methylation changes linked to disease pathology and body mass index. [18]

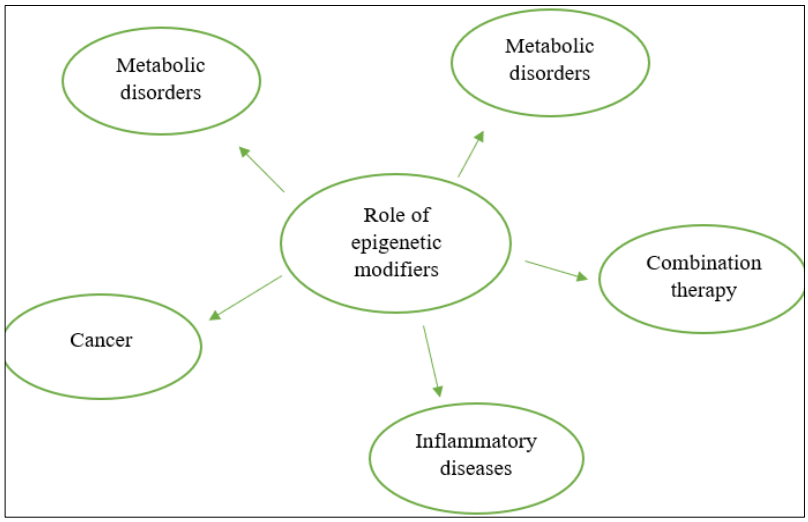

Fig 2: Role of epigenetic modifiers in human diseases

5.3. Metabolic and Other Disorders

Epigenetic mechanisms also contribute to metabolic diseases, with growing evidence linking changes in epigenetic markers to obesity, type 2 diabetes (T2D), and non-alcoholic fatty liver disease (NAFLD).

- **Type 2 Diabetes:** Altered DNA methylation in key metabolic tissues (e.g., liver, pancreatic islets) disrupts insulin signaling and glucose metabolism. Increased methylation of genes like PGC-1α, which regulates mitochondrial function, has been observed in T2D patients.
- **Obesity:** Epigenome-wide association studies (EWAS) have identified multiple CpG methylation sites correlated with body mass index (BMI) and waist circumference. These changes may influence genes related to adipogenesis, appetite regulation, and inflammation.
- **Other Conditions:** NAFLD and osteoporosis also exhibit disease-specific epigenetic signatures. Understanding these signatures offers potential for early detection and personalized treatment strategies. [19]

6. Challenges and Future Directions

- **Target Specificity:** Many epigenetic drugs lack sufficient selectivity, raising concerns about off-target effects and safety.
- **Delivery:** Effective targeting of drugs to specific tissues or cell types is a significant hurdle.
- **Biomarker Discovery:** Reliable biomarkers are needed to identify responsive patients and monitor treatment.
- **Epigenetic Heterogeneity:** Differences within and between tissues complicate universal therapy development.
- **Precision Epigenome Editing:** Novel technologies, such as CRISPR-based epigenome editors, offer the promise of site-specific modification with fewer off-target effects.
- **Personalized Epigenetic Therapies:** Integration with genomic profiling for tailored interventions.
- **Ethical and Societal Implications:** Emerging applications require robust regulatory and ethical frameworks due to their potential heritability. [20]

7. Conclusion

Epigenetic modifications are vital for gene regulation, affecting development and disease, particularly in cancer and other disorders. They include DNA methylation, histone modifications, non-coding RNAs, and chromatin remodeling, influencing gene expression and cellular identity. Abnormalities in these processes are linked to various diseases, marking them as critical therapeutic targets. Advances in epigenetic medications like as DNMT and HDAC inhibitors, as well as combination therapy and precision epigenome editing, open new treatment options. However, challenges such as target specificity, delivery, biomarker identification, and ethical issues must be resolved. Future research focusing on patient-specific epigenetic profiling and innovative therapies is essential for effective and personalized medical treatments. [21]

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