Role of Epigenetics in Cancer and Targeted Therapies for Oncologic Treatments

ABSTRACT

DNA sequence has little bearing on the dynamic and heritable changes to the genome that occur in epigenetics. Both genetic and epigenetic alterations influence the development of cancer. There are several opportunities for therapeutic interventions because epigenetic modifications can be reversed. Many epigenetic drugs are currently used globally to treat conditions including leukemia and myelodysplastic syndrome. Owing to their malleability and vulnerability to outside factors, epigenetic modifiers are becoming intriguing targets for a number of cancer treatments. Recently, a large number of epi-drugs have been developed, and they may find application in clinical situations. The aforementioned initiatives to realize the potential of epigenetic medicines for efficient cancer treatment are summed up in this review. The maintenance of cell identity and the spatial and temporal regulation of gene expression depend on the proper coordination of epigenetic regulators. Both genetic and epigenetic changes contribute to cancer. The development of medications that target epigenetic regulators has advanced significantly over the past few decades, with numerous medications currently under assessment in research studies. In how they could be used to treat cancer. We also go over the preclinical and clinical outcomes of epigenetic medication combination therapies as well as other therapies including immune-based and targeted medicines.

Keywords- *Heritable modifications; Leukemia; Myelodysplastic syndrome; epigenetic modifiers; epi-drugs; Malleability.*

Abbreviations

MDS - Myelodysplastic Syndrome

CPG - Consumer Package Goods

SELEX - Systematic Evaluation of Ligands by Exponentially Enrichment

SiRNAs - Small interfering RNA

AML - Acute Myeloid Leukemia

GBM - Glioblastoma Multiforme

TME - Tumour Microenvironment

lncRNAs - long non-coding RNAs

miRNAs - MicroRNAs

HDACs - Histone deacetylase

1. INTRODUCTION

Cancer is one of the leading causes of death globally. DNA abnormalities that lead to be deregulation of pathways governing cellular processes including cell division survival apoptosis and DNA repair are the cause of cancer. Genetic changes alone cannot fully account for carcinogenesis because epigenetic

processes also play a role. Gene expression modification those are inheritable and unrelated to variations in DNA sequences are referred to as epigenetic changes. Understanding DNA structure has led to the discovery of epigenetic mechanism.[1,2]

Tumor chemosensitivity can be directly determined by epigenetic inactivation which can also impact drug resistance and post therapy clinical outcomes. DNA sequences independent covalent alteration to nucleic acid and histones which are crucial for determining cell destiny and can be passed down through cell division are the subject of epigenetics.[3]

2. HISTORY

- The term "epigenetics," first used by C.H. Waddington in 1942, refers to heritable modifications in a cell's phenotypic that are not caused by changes in the DNA sequence.
- The epigenetics of human cancer has been underappreciated in relation to the genetics of the disease ever since its discovery in 1983. However, this field has gained more attention as our knowledge of particular epigenetic mechanisms and how they relate to cancer has grown. Chromatin alteration, loss of imprinting, hypo- and hypermethylation, and so forth.
- This chronology covers the history of the field from its inception to the present.[3]
- Zebularine is an oral DNA methyltransferase inhibitor that has emerged as a highly promising medication to add to our arsenal of possible epigenetic treatment agents.
- The scope of sensitive detection technology has grown beyond mainly blood-based malignancy.
- Our collection of potentially helpful medications for epigenetic therapy is growing to include combinations of DNA methyltransferase inhibitors and histone deacetylase inhibitors.[5,6]

3. ROLE OF EPIGENETICS IN CANCER DEVELOPMENT

Epigenetics plays a significant role in the development and progression of cancer. Changes in epigenetics can affect the expression of genes related to cell division, growth, and differentiation—all processes that, when out of balance, can result in cancer. One important mechanism in the initiation and spread of cancer is epigenetic dysregulation. Without changing the underlying nucleotide sequence, epigenetic regulation is a heritable modification of DNA that modifies the structure of chromatin and the expression of genes.[18,19]

The primary method of modification involves altering the three-dimensional distribution of nucleosomes across the genome, which modifies the way DNA is packaged. Covalent labeling of amino acids on histones in the presence of nucleosomes and methylation-mediated interactions of genomic DNA at CpG sites refine this packaging process.[19,20] Histone post-translational modifications, including acetylation, methylation, and generalization, are important modulators of chromatin structure that impact gene expression in addition to DNA methylation. The function of non-coding RNAs, histone variant exchange, and chromatin remodeling are a few more processes that control the transcriptional status of genes.[21]

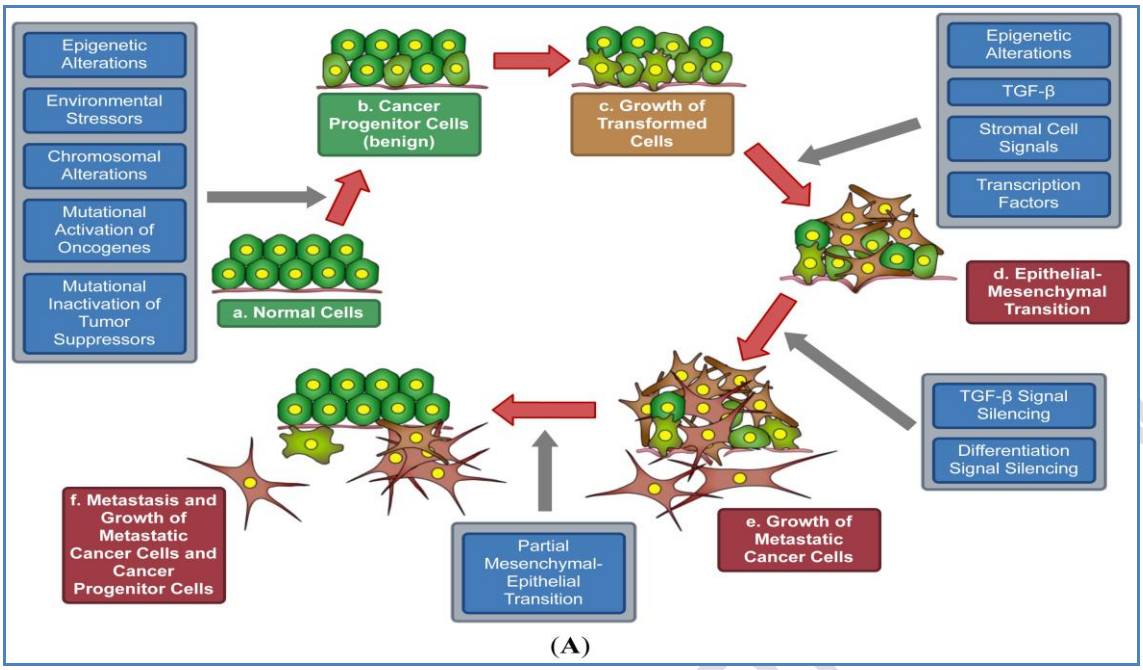

Fig.1. Epigenetic in cancer development and progression

4. IMPORTANCE OF EPIGENETICS TARGETED THERAPIES

4.1 Precision medicine - Specific epigenetic modifications apply to distinct cancer types and even subtypes within a given malignancy. Precisely addressing these modifications can result in more efficient and customized therapeutic approaches catered to the distinct epigenetic characteristics of individuals' malignancies.

4.2 Reversibility of epigenetic changes- Epigenetic alterations are reversible in contrast to hereditary mutations. Because of its reversibility, cancer cells may be able to resume their typical patterns of gene expression, which could stop or completely stop the growth of tumors.

4.3 Combination Therapy- To increase the effectiveness of conventional therapies like immunotherapy or chemotherapy, epigenetic targeted therapies can be employed in conjunction with them. These therapies can improve treatment outcomes by sensitizing cancer cells to regular treatments by correcting epigenetic changes that contribute to treatment resistance.

4.4 Reduced Toxicity- With the ability to directly target the enzymes or proteins involved in epigenetic alterations, epigenetic medications have the potential to lessen the adverse effects often associated with non-specific treatments like chemotherapy and have a more targeted effect on cancer cells.

4.5 Overcoming Resistance- Treatment resistance in cancer may be influenced by epigenetic modifications. Epigenetic medicines can assist overcome resistance mechanisms and increase responsiveness to traditional treatments by focusing on these alterations, which will ultimately improve patient outcomes.[16,17]

5. EPIGENETICS TARGETED APTAMERS IN CANCER THERAPY

Aptamers are single-stranded DNA or RNA molecules with unique tertiary structures that enable preferential binding to certain molecular targets. Targets ranging from tiny chemicals to biomacromolecules, infected cells, stem cells, and cancer are frequently used in aptamer screening procedures. Systematic Evolution of Ligands by Exponential Enrichment (SELEX) is the term for this

procedure. Advances in the field of nucleic acid chemistry have resulted in the development of versatile tools for bioconjugation and chemical modification.[22]

By, among other things, increasing the variety of libraries available for aptamer screening, greatly enhancing the biostability of nucleic acid aptamers, decreasing the rate at which aptamers separate from target molecules and thus raising their binding affinities, tagging aptamers with radioisotope or fluorogenic reporters, and conjugating aptamers with medicinal substances for targeted medication administration, these tools have further strengthened the potential of aptamers as molecular theranostic agent candidates.[21] The following main ideas emphasize how crucial it is to use epigenetics-targeted aptamers in cancer therapy:

5.1 Specificity- Histone modification enzymes, DNA methyltransferases, and other epigenetic markers are examples of epigenetic targets to which aptamers can be precisely tailored to bind. This selectivity protects healthy cells while enabling accurate targeting of cancer cells with abnormal epigenetic patterns.

5.2 Multifunctionality- Aptamers can be engineered to transport medications, siRNAs, or imaging agents, enabling a multimodal strategy in the treatment of cancer. This adaptability allows for tailored therapy while keeping an eye on the effectiveness of the treatment or supplying more therapeutic substances.

5.3 Synergistic effect- When combined with other therapeutic methods like immunotherapy, radiation therapy, or chemotherapy, epigenetic-targeted aptamers can have synergistic effects that improve cancer patients' overall treatment outcomes.

5.4 Emerging research- Even though the field of using epigenetics-targeted aptamers in cancer therapy is still in its infancy, aptamers are being investigated further for their potential as novel agents to influence epigenetic changes in cancer cells. Promising results from early preclinical investigations indicate that epigenetic-targeted aptamers may find use in clinical settings in the future. [22]

Because they particularly interfere with faulty epigenetic pathways in cancer cells, epigenetics-targeted aptamers show promise as a focused and efficient method in cancer therapy.

6. MECHANISM OF EPIGENETICS MODIFICATION

Epigenetic cancer therapy stops tumor growth by focusing on the aberrant epigenetic modifications that cancer cells experience and restores normal gene expression patterns. [6]

Key epigenetic modifications in cancer development and progression

1. DNA methylation
2. Histone Modification
3. Non- coding RNA coding
4. Chromatin remodeling

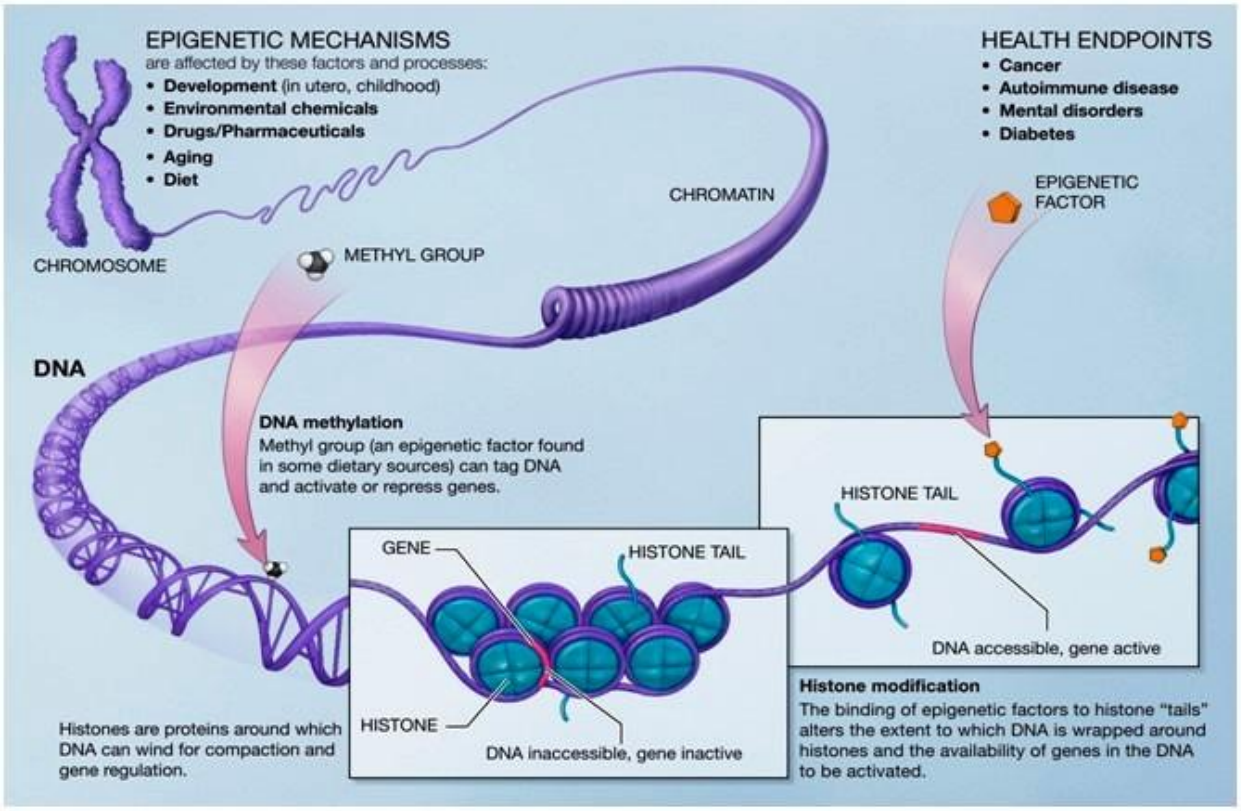

Fig.2. Mechanism of epigenetic modification

6.1 DNA methylation: The process of adding methyl groups to the DNA molecule is known as DNA methylation.[26] By encouraging or inhibiting the transcription of particular genes, this alteration can control the expression of genes. Numerous biological processes, such as X-chromosome inactivation, genomic imprinting, embryonic development, and gene expression regulation, depend critically on DNA methylation. Variations in DNA methylation patterns have been linked to a number of illnesses, such as neurological conditions and cancer.[6] Two key types can be distinguished among the recurrently mutant epigenetic regulators in AML according to their main mode of activity. Including extra sex combs-like 1 (AXSL1), enhancer of zeste homologue 2 (EZH2), and mixed-lineage leukemia (MLL), the first group influences post-translational histone modifications. Ten-eleven translocation 2 (TET2) and DNA methyltransferase 3A (DNMT3A) are two members of the second group, which controls DNA methylation of cytosines in the setting of CpG dinucleotides. Both histone modifications and DNA methylation have been demonstrated to be impacted by mutations in isocitrate dehydrogenase 1 (IDH1) and IDH2. Here, we evaluate the state of knowledge on the function of DNMT3A, TET2, and IDH1/2 mutations in human pre-LSCs, their impact on hematopoiesis, and therapeutic approaches to target this population.[27]

6.2 Histone Modification Inhibitors: Histone modification inhibitors are chemicals that target enzymes that change histone proteins, which are key components of chromatin that regulate gene expression. Histone changes including acetylation, methylation, phosphorylation, and ubiquitination can influence the accessibility of DNA to transcription factors and RNA polymerase, regulating gene expression.[9] Histone modification inhibitors have been investigated for possible therapeutic applications in a variety of disorders, including cancer, where abnormal histone modifications are widespread. Some histone modification inhibitors have been approved for the treatment of specific forms of cancer, while others are still being studied in preclinical and clinical trials. These inhibitors represent a promising field of study for the creation of new targeted medicines for cancer and other disorders.[8]

6.3 Non- coding RNA Targeting: Targeting Non-Coding RNAs: Long non-coding RNAs (lncRNAs) and microRNAs (miRNAs) are examples of non-coding RNAs that influence gene expression and can become

dysregulated in cancer. Certain epigenetic treatments aim to suppress carcinogenic pathways or restore normal gene expression patterns by targeting these non-coding RNAs.[8]

6.4 Chromatin Remodeling: The accessibility of DNA to transcription factors and other regulatory proteins is controlled by chromatin remodeling complexes. One factor that may contribute to abnormal gene expression in cancer is the dysregulation of chromatin remodeling complexes. In order to restore normal chromatin structure and gene expression patterns, certain epigenetic therapies specifically target these complexes.[11]

7. EPIGENETICS THERAPY IN DIFFERENT CANCER TYPES

Numerous cancer types have showed promise for improvement using epigenetic therapy. Several prevalent cancer forms that have been studied with epigenetic treatments include:

7.1 Hematological Malignancies: Acute myeloid leukemia (AML), Myelodysplastic syndrome (MDS), and cutaneous T-cell lymphoma are among the hematological malignancies for which epigenetic medications, such as DNA methyltransferase inhibitors (Azacitidine, Decitabine) and histone deacetylase inhibitors (Vorinostat, Romidepsin), have been approved for use in treatment.[23-24]

7.2 Solid Tumors: Additionally, epigenetic treatments are being researched for a variety of solid tumors, such as prostate, lung, breast, and colorectal cancers. Specifically, inhibitors of histone deacetylase have demonstrated promise in the management of solid malignancies.

7.3 Brain Tumors: Glioblastoma multiforme (GBM) and other brain cancers frequently exhibit epigenetic changes. The therapeutic potential of epigenetic medicines targeting DNA methylation and histone alterations has been studied in relation to brain cancers.

7.4 Ovarian Cancer: In ovarian cancer, where abnormal DNA methylation patterns and histone changes contribute to the growth of the tumor, epigenetic therapies have been investigated. Among the epigenetic medications being researched for ovarian cancer are histone deacetylase inhibitors and DNA methyltransferase inhibitors. [13, 14]

8. CLINICAL APPLICATIONS FOR EPIGENETIC CANCER THERAPY

8.1 Diagnosis and Prognosis: Changes in epigenetics may function as biomarkers for the diagnosis and prognosis of cancer. To help in cancer detection, categorization, and patient outcome prediction, tumor tissues or liquid samples can be examined for DNA methylation patterns, histone modifications, and non-coding RNA expression profiles.

8.2 Targeted Therapy Selection: By identifying certain epigenetic changes that drive carcinogenesis, epigenetic profiling of tumors can aid in the guidance of therapy decisions. Based on the unique tumor profile of each patient, targeted therapy, such as DNA methylation inhibitors or histone modification inhibitors, can be chosen based on likelihood of effectiveness.

8.3 Personalized Treatment Approaches: Personalized therapy strategies that are adapted to the distinct biological features of every patient's cancer are made possible by epigenetic profiling.

8.4 Combination Therapy: To increase therapeutic efficacy, epigenetic therapies can be used in conjunction with other forms of treatment including immunotherapy, targeted therapy, or chemotherapy.

8.5 Clinical Trials and Drug Development: To further advance the field of epigenetic cancer therapy, clinical trials assessing the safety and effectiveness of these treatments are necessary. These trials assist in defining patient populations most likely to benefit from epigenetic-targeted medicines, identifying potential drugs, and optimizing treatment regimens. [15]

9. CHALLENGES AND FUTURE DIRECTIONS

- Finding predictive biomarkers: Biomarkers may be particular epigenetic modifications, patterns of gene expression, or other molecular traits of cancers.[25]
- Treatment regimen optimization: To increase the effectiveness of epigenetic cancer treatments, treatment regimen optimization, including dose, scheduling, and combination therapy, is crucial.
- Treatment resistance management: Just as with other cancer therapy, resistance to epigenetic treatments may gradually arise. Improving long-term treatment outcomes requires an understanding of resistance mechanisms and the development of techniques to overcome them.
- Minimization of Off-target effects: Improving the safety profile of epigenetic treatments and reducing off-target effects depend on the development of more focused inhibitors that precisely target epigenetic changes linked to cancer while protecting healthy cells.[28]
- Patient Stratification and tailored Medicine: Future directions in epigenetic cancer treatment will involve developing tailored treatment plans based on unique patient attributes, such as epigenetic profiles.[15]

10. CONCLUSION

One effective treatment approach is epigenetic therapy. However, in order to increase efficacy, a number of obstacles and typical limit must be removed. One notable drawback of epigenetic medicines has been there relative ineffectiveness against solid tumors, despite their greatest success against haematological malignancies. A unique epigenetic profile characterized by DNA hypermethylation and hypoxia-induced decreased acetyl-CoA levels lead to a global reduction in histone acetylation, which in turn promotes heterochromatin formation, are contributing factors. These components are associated with the core TME. A deeper understanding of cancer epigenetics will be crucial to achieving the ultimate objective of finding safe, efficient treatments as well as drugs to both prevent and facilitate early identification of cancer.

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