



Epigenetics in Cancer Therapy

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Abstract: Epigenetics regulates parts of the genetic information accessible to cellular machinery, thus contributing to cellular diversity. Disruption of epigenetic harmonisation can lead to dysregulation of signaling pathways and contribute to diseases like cancer. Epigenetic processes are crucial in coordinating the normal growth and preservation of gene activity unique to mammal tissues. Epigenetic studies in current cancer research are vital for early detection through biomarker identification, understanding tumor heterogeneity, predicting treatment responses, and uncovering resistance mechanisms. This knowledge informs targeted therapies, enhances personalized medicine, and improves overall outcomes in cancer patients. This review comprehensively explores epigenetic processes in healthy cells, emphasizing histone modification-lysine acetylation and DNA methylation. The intricate mechanisms governing genetic expression and their dysregulation in cancer progression are also reviewed. Examining prevalent cancer types, this review stresses the pivotal role of epigenetics in understanding and potentially targeting these processes for therapeutic interventions.

Keywords: Epigenetics, histone modification, DNA methylation, malignant cells, genetic expression, prevalent cancer

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I. INTRODUCTION

The arrangement of DNA within a cell, known as chromatin structure, plays a crucial role in determining the expression of genes. This organization significantly affects the activation of genes. Epigenetics, as coined by Waddington C.H., investigates the impact of chromatin structure on gene expression. Initially centered on embryonic development, its scope has expanded to encompass diverse biological phenomena. Currently, epigenetics denotes inheritable alterations in gene activity not linked to DNA sequence changes. These modifications, established during cell differentiation and transmitted through cell division, enable cells to uphold unique identities despite sharing identical genetic content. The epigenome comprises many epigenetic alterations, including modifications to histone proteins, DNA methylation, and the organization of nucleosomes. This epigenetic landscape regulates parts of the genetic information accessible to cellular machinery, thus contributing to cellular diversity. Disruption of epigenetic harmonisation can lead to dysregulation of signaling pathways and contribute to diseases like cancer^{1,2}. Epigenetic processes play a crucial role in coordinating the normal growth and preservation of gene activity that is unique to different tissues in mammals³. They determine an individual's genetic composition that engages in response to its surroundings signals. Changes in these systems can lead to changes in genetic expression and promote tumor formation. In 2022, "nonmutational epigenetic reprogramming" emerged as a recognized hallmark of cancer, highlighting its significance in the disease process⁴. Utilizing epigenetic approaches, independently or in conjunction with conventional therapies, holds promise for cancer treatment. Cancer epigenetics study has shown significant remodeling of several parts of the epigenetic biomolecules in cancer cells. This reprogramming encompasses alterations in histone modifications, DNA methylation patterns, microRNA expression levels⁵, and nucleosome positioning. Disruptions in these epigenetic mechanisms can activate oncogenes or suppress tumor suppressor genes, contributing to the intricate bioprocess of cancer biology. Recognizing the pivotal role of epigenetics in regulating gene expression through processes like DNA methylation, histone modification, and non-coding RNA-mediated gene silencing has become indispensable in medical research. Maladaptive epigenetic alterations can impair gene function, ultimately promoting carcinogenesis. Over the past twenty years, extensive research has thoroughly examined the relationship between epigenetics and cancer. This research has provided vital clinical information on the impact of epigenetics on the advancement and treatment of cancer. This review examines fundamental epigenetic principles, the role of epigenetic changes as precursors to cancer, the evolving significance of epigenetics in understanding carcinogenesis, recent advancements in using the study of epigenetics in cancer therapy, which has reversible nature of epigenetic changes, and understanding its influenced approaches to cancer treatment. The development of cancer, which includes the processes of gene alteration, tumor genesis, development, and metastasis, occurs due to an intricate interplay of aberrant genetic and epigenetic alterations. While previous beliefs about cancer were attributed mainly to genomic anomalies⁶, it is now acknowledged that epigenetic factors also play an equally crucial role. Recent epigenetic advancements have unveiled widespread irregularities in human cancer cells, alongside numerous genetic mutations^{7,8}. These genetic and epigenetic

variations work in tandem across all cancer development stages, propelling the disease forward⁹. Although the genetic underpinnings of cancer are well-established, emerging research suggests that certain cancer types may be initiated by epigenetic changes¹⁰. Consequently, there is a global effort to understand the contribution of epigenetics to cancer initiation and progression¹¹. The potential reversibility of epigenetic abnormalities through epigenetic therapy distinguishes them from genetic mutations, making such interventions promising and clinically significant¹².

1.1 Epigenetic processes in healthy cells

Chromatin comprises nucleosomes, consisting of 148 base pairs of DNA wound around a central histone octamer comprising four core histone proteins: H2A, H2B, H3, and H4¹³. The control of chromatin structure involves a range of epigenetic mechanisms, including DNA methylation and histone changes. Furthermore, processes like the addition of histone variants, the rearrangement of nucleosomes, and the participation of non-coding RNAs such as microRNAs (miRNAs) play a role in this regulation¹⁴. These alterations collectively impact how the genome operates by changing the local structural characteristics of chromatin, particularly its accessibility and compactness. Together, these modifications establish an "epigenetic landscape" that shapes the function of the mammalian genome in various cellular environments, spanning different cell types, developmental stages, and disease conditions like cancer^{15,16}. Different cellular states exhibit specific patterns of these changes, acting as custodians of cellular identity. Epigenetics typically denotes a heritable alteration in gene expression during cell division, independent of DNA sequence alterations. Various chemical modifications to DNA and histones significantly influence gene expression and are replicated during cell division¹⁷. Identifying abnormal epigenetic conditions in cancerous cells, which cause the suppression of tumor suppressor genes, has prompted a widespread quest for novel medications that can restore the activity of epigenetically silenced genes. Specifically, there has been a thorough investigation for drugs that can reverse distorted patterns of DNA methylation and histone acetylation by inhibiting DNMTs and HDACs.

1.2 Histone modification-lysine acetylation

Eukaryotic cells organize their DNA into chromatin structures that are comprised of nucleosomes enveloping a histone octamer. Histone features amino acid tails that undergo various post-translational modifications (PTMs), such as methylation, acetylation, ubiquitylation, phosphorylation, ADP ribosylation, or sumoylation. Each of these modifications contributes to regulating the states of chromatin. Acetylated histones recruit regulatory factors, chromatin-remodeling complexes, and bromodomain-containing proteins. Humans have 61 bromodomains in 46 proteins, including histone methyltransferases (HMTs), histone acetyltransferases (HATs), and transcription factors. BET proteins (BRDT, BRD2, BRD3, BRD4) are implicated in malignancies¹⁸, targeted by inhibitors like IQ1 and I-BET¹⁹, which bind BET bromodomains BDI and BD2, inhibiting cancer growth via Myc reduction, JAK-STAT/NF-κB pathways, and p53 acetylation²⁰⁻²². BET inhibitors are in clinical trials for various cancers. Histones, highly conserved basic proteins, assist the hierarchical structure of the mammalian genome, influencing gene expression in tissues. Histone tails undergo multiple modifications, affecting protein

attachment and genomic stimulation/suppression. Bromo- and chromodomains attract acetylated/methylated lysine residues, modifying chromatin structure and spreading patterns. Histone alterations impact gene expression by compacting DNA around histones, hindering transcription²³. Histone methylation, mainly on lysine/arginine lateral chains, does not alter. Histone methyltransferases (HMTs) control methylation, affecting gene activation/silencing via DNA methylation.

1.3 The process of DNA methylation

DNA methylation is a well-acknowledged epigenetic process involving the insertion of a methyl group. This modification significantly impacts gene expression by attracting specific proteins that govern gene regulation and hindering transcription factors' binding to DNA sites. DNA promoter regions contain regulatory elements critical for controlling gene transcription. In cancer, the delicate balance between methylation and demethylation is disrupted, leading to increased methylation levels, termed hypermethylation. In the absence of prior cancer occurrences, both gene copies must undergo methylation to initiate cancer development, highlighting the increased cancer risk associated with hereditary predisposition. This underscores the pivotal role of DNA methylation in cancer initiation²⁴. Moreover, DNA methylation commonly serves as a diagnostic indicator. Methylation is particularly influential in pediatric cancers, often involving many epigenetic modifications rather than

genetic drivers. DNA methylation, a genetic process in eukaryotic cells, silences gene expression. It is distinct from histone methylation²⁵. Over recent decades, the significance of DNA methylation in various biological processes has been elucidated, including its role in embryonic development, X chromosome inactivation, and the modulation of gene expression across evolutionary stages. The gene silencing mechanism through DNA methylation involves access to promoters by specific transcription factors and other regulatory components, thereby suppressing DNA expression²⁶. Conversely, hypomethylation in these regions activates gene expression. Hypomethylation is prevalent in cancer, where it contributes to tumorigenesis by upregulating oncogene transcription and inducing genetic instability through mutations in DNA sequences. Additionally, analyzing the methylation patterns of certain genes can predict treatment response. Compared to other drugs, Zebularine's comparatively lower toxicity may be attributed to differences in uridine cytidine kinase expression between normal and cancer cells, influencing the incorporation of these aza nucleosides into nucleic acids²⁷. DNA methylation can induce gene suppression by hindering or facilitating the regulatory proteins in DNA. This mechanism impedes transcriptional activation by obstructing the access of transcription factors to their binding sites²⁸. Such methylation offers a durable method of gene silencing, which significantly influences gene expression regulation and chromatin structure in conjunction with histone alterations and other proteins associated with chromatin.

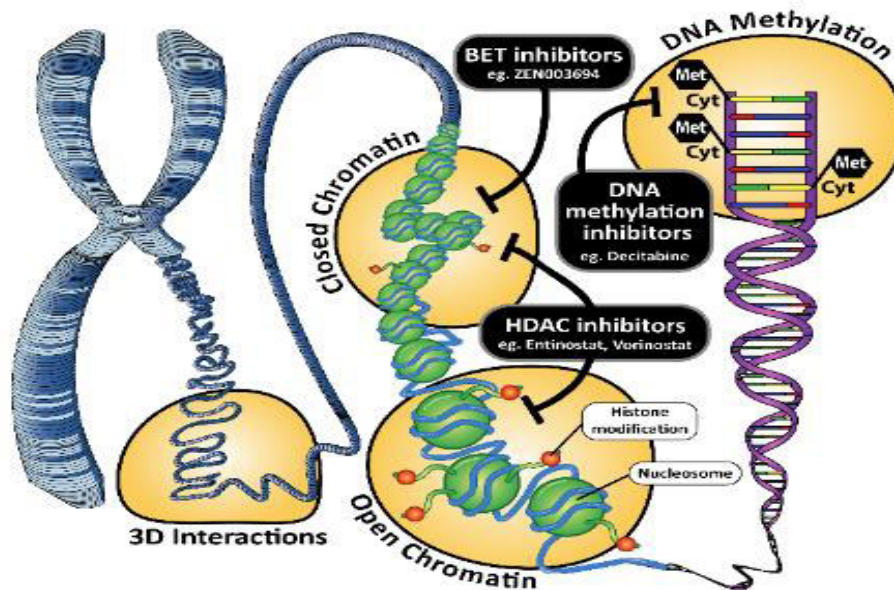


Fig 1: Epigenetic process of healthy cells²⁹ (Image usage under creative commons license 4.0)

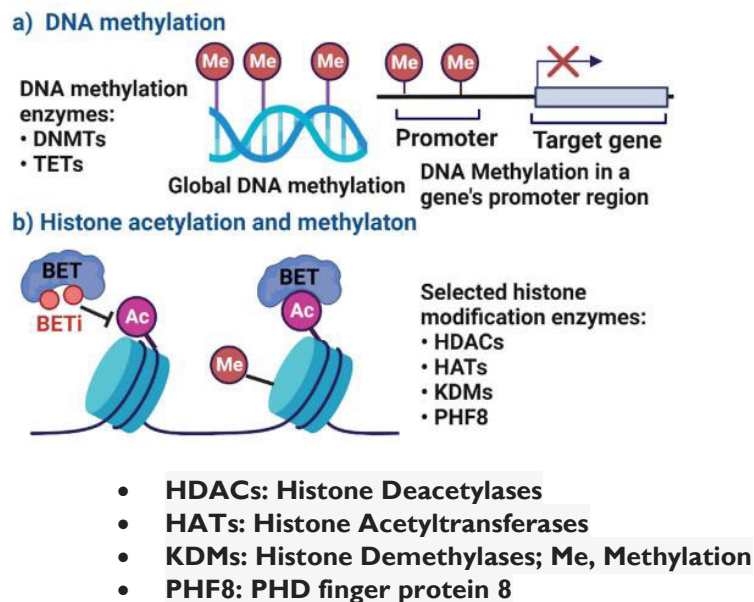


Fig 2: A schematic overview of epigenetic modifications to gene expression³⁰(Image usage under creative commons license 4.0)

1.4 Differences in epigenetic processes between normal and malignant cells

Epigenetic mechanisms oversee typical mammalian growth, development, and gene expression. These mechanisms participate in pivotal processes, including X-chromosome inactivation in females, genomic imprinting, suppression of repetitive DNA sequences, modulation of chromatin structure, and maintenance of precise genetic expression³¹. These mechanisms exert their influence by dynamically modifying the compactness and accessibility of chromatin at specific loci. Moreover, epigenetic modifications exhibit distinct properties and distribution patterns across different types of mammalian cells, collectively forming the epigenome, which significantly shapes cell fate and gene activity³². Nevertheless, variations from typical epigenetic patterns may result in distinctive heritable characteristics specific to cancer. These encompass proliferative signaling, resilience against cellular apoptosis, avoidance of growth inhibition, achievement of sustained cellular replication, initiation of inflammatory reactions, disruption of energy metabolic processes, instigation of genomic instability, encouragement of blood vessel formation, and facilitation of invasive properties, ultimately leading to metastasis³³. The cancer epigenome is characterized by widespread alterations in DNA methylation, modifications of histones, and dysregulated gene expression mediated by non-coding RNAs (ncRNAs). These alterations provide a growth advantage to tumor cells, thereby promoting cancer development³⁴. Epigenetic processes play significant roles in the development of various human diseases. While all cells in the body share the same genetic material, the epigenetic system within each cell orchestrates distinctive morphological and functional traits, enabling them to fulfill their specific functions. Diseases linked to dysfunctional epigenetic regulation include cancer, diabetes, lupus, asthma, and neurological disorders³⁵. Reduced levels of epigenetic regulation have been associated with ineffective prognoses in prostate, lung, and kidney cancers³⁶. Reversing epigenetic alterations from acute illnesses can halt disease progression to chronic stages. Advances in analytical technologies have led to a new field known as Pharmacoepigenomics, which explores epigenetic

profiles to understand molecular pathways, assess drug sensitivities in cancers, and determine optimal therapeutic strategies³⁷. Additionally, some cancer cells rely on silencing crucial tumor suppressor genes through epigenetic mechanisms. Studies have demonstrated the epigenetic extinction of numerous tumor suppressor genes in cancer, underscoring the significance of epigenetic processes in cancer development³⁸.

1.5 Control of genetic expression in the advancement of cancer

Gene expression entails transcribing particular genes from DNA to mRNA, then converting mRNA into amino acids and proteins that influence the phenotype. Cancer progression is a complex process characterized by diverse molecular alterations affecting the tumor's cellular processes and surroundings. Healthy cells undergo tumorigenesis, a multifaceted molecular sequence resulting in neoplastic conversion, which may ultimately progress to malignancy, culminating in cancer³⁹. Molecular alterations frequently impact crucial genes that control cell growth, thus contributing to cancer development. Two hypotheses, namely the cancer stem cell (CSC) model and the clonal evolution model, have been proposed to elucidate the progression of tumors⁴⁰. As per the CSC model, cancerous changes originate from stem cells, whereas the clonal evolution model suggests that non-CSCs gradually acquire cancer-causing mutations. Epigenetic changes play a role in both models. It is believed that the accumulation of genetic alterations drives the progression of normal cells from hyperplasia and dysplasia to invasive cancer and, ultimately, metastatic disease⁴¹. Various progression models have been devised for different types of tumors, including colorectal, lung, breast, head and neck, and prostate cancers⁴²⁻⁴⁵, initially by correlating histopathological alterations with gene mutations. Analyzing mutations and gene expressions of well-known tumor suppressors and oncogenes during early tumorigenesis has critical roles in cancer progression⁴⁶. Molecular cytogenetic techniques have advanced gene exploration by pinpointing chromosomal segments linked to various stages and results. The extensive adoption of high-

throughput, comprehensive genome-wide methodologies, along with full sequencing of the human genome, has accelerated the detection of genes and pathways linked to cancer⁴⁷. Although genetic changes are frequently observed in tumors, alterations identified during premalignant stages are more likely to signify initial and promoting events in cancer development. These occurrences might be obscured by the intricate assortment of genetic changes typically linked with genetic instability in the later stages of the disease. Therefore, comprehensively understanding all stages of

progression is crucial for grasping the development of malignant tissue. Traditionally, genomic and proteomic research has predominantly concentrated on tumor analysis due to challenges accessing premalignant specimens and the need for substantial material quantities for genome-wide analysis. Recent advancements in cell isolation techniques and the downsizing of genomic technologies have enabled detailed molecular profiling of specific cell types and precise mapping of gene disruptions associated with distinct disease phenotypes.

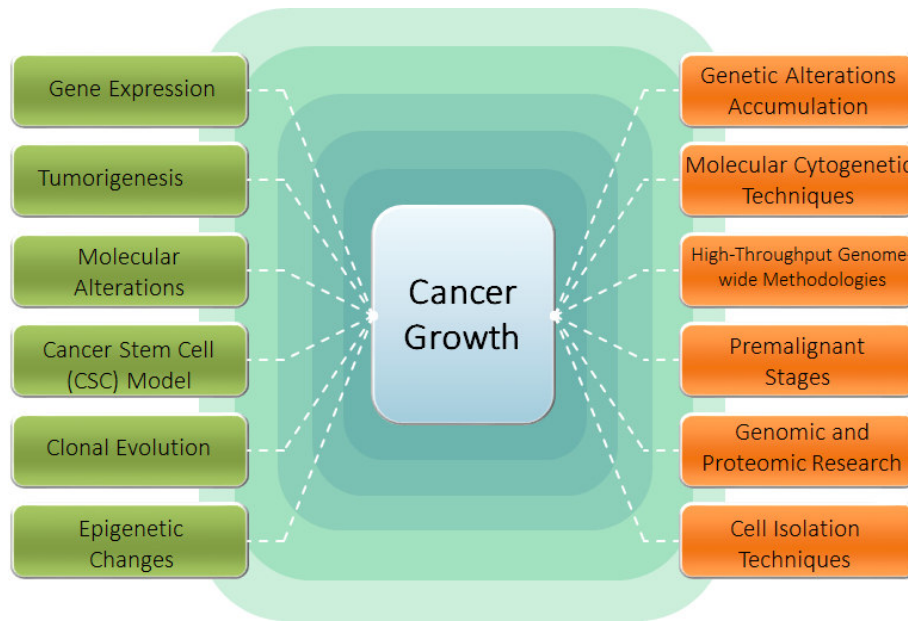


Fig 3: Genetic expression models and techniques that influence Cancer advancement

1.6 Epigenetic modifications in several prevalent types of cancer

1.6.1 Gastric cancer

Epigenetic signatures with genetic irregularities have been detected within various subsets of gastric cancer (GC). A growing body of evidence indicates that epigenetic anomalies in GC are not simply passive occurrences but actively contribute to the process of carcinogenesis⁴⁸. Gastric cancer ranks as the most prevalent form of cancer in numerous countries, with Japan notably experiencing a high incidence due to its rapidly aging population, particularly those aged over 60⁴⁹. Comparative analyses of survival rates among gastric cancer patients across different nations, based on cancer registries, indicate significantly higher survival rates in Japan. This disparity is attributed to two main factors: an increase in early-stage diagnoses and a rise in patients undergoing curative resection as their initial cancer treatment course⁵⁰. Unlike colorectal carcinoma, which typically presents a consistent histological profile of highly differentiated tubular adenocarcinoma, gastric carcinoma manifests in various histological forms, even in its early stages, with histological diversity escalating as intramural growth advances. New findings in the molecular analysis of both cancerous and precancerous stomach lesions have revealed numerous genetic and epigenetic changes responsible for the complex progression of stomach cancer⁵¹⁻⁵⁴. Specifically, different genetic pathways are involved in well-differentiated and poorly differentiated forms of gastric cancer, with certain gastric intestinal metaplasia and adenomas exhibiting genetic events akin to those observed in

well-differentiated adenocarcinoma. This understanding enables early detection of cancer or potential malignancy in stomach preneoplastic lesions through application in routine clinical practice. The process of stomach carcinogenesis is characterized by changes in oncogenes^{55,56}, tumor suppressor genes, cell cycle regulators, cell adhesion molecules, telomeres, telomerase, and genomic stability.

1.6.2 Colorectal cancer (CRC)

A range of genetic and epigenetic changes influences the development of CRC. Many patients experience chemoresistance, resulting in treatment ineffectiveness and, ultimately, high mortality rates in advanced stages of the disease. Silencing of tumor suppressor genes through abnormal promoter hypermethylation and genomic instability caused by global DNA hypomethylation contributes to the initiation and advancement of CRC⁵⁷. There is an increasing acknowledgment of the potential prognostic significance of DNA methylation in colorectal cancer (CRC). CRC is characterized by genetic modifications, primarily involving alterations in the DNA sequence such as point mutations, insertion-deletion mutations, and rearrangements, which are extensively documented⁵⁸. These mutations commonly influence gene function by changing proteins' amino acid sequence or modulating protein production levels. Instances in CRC involve point mutations occurring in particular codons of the KRAS gene, diminishing its regulatory function, and deletions impacting critical tumor suppressor genes such as p53 or SMAD4⁵⁹. In other cancer types, notable carcinogenic mechanisms involve oncogene amplifications and improper splicing of oncogene-coding sequences under highly

active promoters. While these genetic aberrations dominated early molecular biology research, recent attention has shifted towards understanding gene expression regulation alterations that don't involve DNA sequence changes, known as "epigenetic" changes. DNA methylation alterations are particularly significant in this context. However, epigenetics encompasses broader changes in gene expression via modified interactions among DNA's regulatory regions or messenger RNAs (mRNAs), independent of DNA sequence changes. Studying epigenetic changes significantly enhances our comprehension of CRC pathogenesis and pathophysiology, offering new avenues for diagnosing asymptomatic tumors, characterizing CRC variants, predicting outcomes and chemotherapy responses, and potentially developing innovative preventive or adjunctive therapies.

1.6.3 Mammary Carcinoma

The understanding of the epigenetic landscape of breast cancer is comprehensive and plays a pivotal role in the progression of the disease. Early epigenetic changes, such as DNA methylation and alterations in chromatin states, are key drivers in breast cancer initiation⁶⁰. Utilizing epigenetic profiling of tumors and circulating DNA holds promise for prognostic assessment, particularly through the measurement of DNA methylation. However, despite these advancements, only a few epigenetic markers have transitioned to clinical applications or trials to guide cancer therapy⁶¹. Breast tumors commonly exhibit reduced methylation across their genome, but the number of genes displaying decreased methylation, especially those with potential therapeutic implications, remains limited. Elevated estrogen levels are linked to increased susceptibility to breast and endometrial cancers, impacting tumor progression and patient prognosis. Initially, most breast cancers test positive for estrogen receptors (ER), suggesting their growth is either fueled by estrogens or inhibited by antiestrogens. DNA methylation in the promoters of *ESR1* and *PGR* genes is suggested as a mechanism contributing to the development of ER-negative tumors. Ongoing research involving over 25,000 cancer genomes aims to explore oncogenic alterations at genomic, epigenomic, and transcriptomic levels to identify clinically relevant cancer subtypes for prognosis and treatment strategies. The International Cancer Genome Consortium (ICGC) oversees three breast cancer initiatives, collectively analyzing at least 1500 tumors using advanced sequencing technologies to study their genetic, transcriptomic, and epigenetic characteristics⁶².

1.6.4 Prostate cancer(PsC)

Epigenetic dysregulation, involving modifications in DNA methylation, histone alterations, and nucleosome restructuring, is a consistent feature in the progression of PsC. These changes hinder tumor-suppressor genes, activate oncogenic factors, and foster therapy resistance. Exploring epigenetic pathways as a therapeutic avenue shows promise in managing PsC. These genes govern numerous cellular functions, such as regulating the cell cycle, apoptosis⁶³, responding to hormones, repairing and preventing DNA damage, transmitting signals, and influencing tumor invasion and suppression. In the development of PsC, epigenetic modifications occur at an earlier stage and with greater frequency than genetic mutations. These modifications result in the functional silencing of various genes, providing

potential molecular indicators for PsC and a deeper understanding of its root causes. PsC cells frequently employ promoter hypermethylation to suppress genes, facilitating the progression and maintenance of the cancerous characteristics⁶⁴. This silencing affects a range of tumor-suppressor genes related to hormone signaling, DNA repair, cell adhesion, cell-cycle control, and programmed cell death⁶⁵. PsC evolves through a series of genetic and epigenetic abnormalities. The relationship between DNA methylation and histone acetylation is intricate, suggesting that changes in one may affect the other globally. Emerging evidence strongly suggests that the entire epigenome undergoes fundamental disturbances during PsC development, making it a promising target for therapeutic interventions. Changes in DNA methylation, fluctuations in chromatin protein levels, and histone configuration adjustments can be used as markers to identify and classify PsC. The reversible characteristics of DNA methylation provide a foundation for potential epigenetic treatments in cancer management.

1.6.5 Lung cancer

Lung cancer involves intricate genetic and epigenetic transformations in the respiratory epithelium. While somatic mutations and genetic variations are known factors, epigenetic changes are particularly common among lung cancer patients. Recent progress in comprehending epigenetics has illuminated the mechanisms underlying carcinogenesis, notably DNA hypermethylation, which frequently arises early in the disease⁶⁶. These epigenetic adjustments substantially influence critical cancer-related functions like cell proliferation, invasion, metastasis, apoptosis, and cell cycle regulation⁶⁷. One notable epigenetic modification in cancer involves the methylation of CpG dinucleotide in gene promoters, leading to transcriptional silencing and affecting tumor suppression or growth regulation genes. This presents an alternative mechanism to the classic two-hit model proposed by Knudson⁶⁸. Research, including studies on mice exposed to cigarette smoke, has demonstrated that both genetic mutations and epigenetic modifications play roles in lung cancer development⁶⁸, with similarities observed between mouse and human lung cancers⁶⁹. Various studies have also identified somatic DNA methylation alterations in genes associated with lung cancer. In a previous study, methylation-specific PCR was used to assess gene promoter methylation in 107 surgically removed non-small cell lung cancer (NSCLC) patients, along with matching normal lung tissue samples^{70,71}. Laboratory and animal model research suggests that reactivating genes suppressed by methylation in lung cancer could inhibit tumor development by halting cell division, inducing programmed cell death, and preventing new blood vessel formation⁷². Future clinical treatments targeting epigenetic pathways in lung cancer may involve addressing formulation stability issues with nucleoside analogue demethylating agents⁷³, refining dosing schedules for optimal demethylation effects with minimal side effects, exploring therapeutic assessing the promise of non-nucleoside methylation inhibitors such as epigallocatechin-3-gallate and selenium compounds, as well as investigating the effectiveness of emerging demethylating agents like psammoplins, small molecule methyltransferase inhibitors, and oligonucleotides⁷⁴.

2. CHALLENGES AND PROSPECTS

Epigenetic modifications represent one of the initial anomalies in cancer progression. The effectiveness of addressing these alterations in combating cancer has been well-documented. However, despite the evident clinical benefits of using drugs targeting epigenetic changes in cancer therapy, there exist several challenges that demand attention and resolution. Extensive research underscores the significant clinical responses attained through epigenetic therapies in hematologic malignancies. However, the effectiveness and practicality of therapy have been significantly impeded by inadequate patient selection based on transcriptional or epigenetic markers. Our ability to modify epigenetic patterns within the human genome is constrained by our incomplete understanding of the epigenome and the key regulators of epigenetic regulation. While some epigenetic therapies have shown promising results in treating blood cancers and have received regulatory approval, effectively treating and maintaining therapeutic efficacy in solid tumors remains a significant challenge. Improving patient selection, optimizing trial design, and refining dosing regimens can enhance clinical outcomes. However, the most promising approach to improving clinical responses in solid tumors appears to be combining epigenetic medications with other treatment modalities, such as targeted or immune-based therapies. In summary, the complex nature of cancer presents substantial challenges in its identification and management. While further research is essential to elucidate more precise mechanisms, it is widely acknowledged that epigenetic processes play crucial roles in both normal biochemical pathways and tumor development, with significant alterations observed during cancer initiation. Consequently, epigenome targeted therapy emerges as a promising avenue for cancer treatment. The recent

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epigenetic advancements in biology have significantly challenged the conventional belief that the genetic code solely dictates cellular gene function and is the primary culprit behind human diseases. In cancer epigenetics, progress has revealed that genome packaging could be as critical as the genome in governing vital cellular processes and contributing to conditions such as cancer. These insights offer potential strategies to enhance the sensitivity of cancer cells, particularly cancer stem cells, which often resist conventional chemotherapy.

3. CONCLUSION

A deeper comprehension of cancer stem cells and developing more targeted epigenetic medications hold promise in effectively resetting the aberrant cancer epigenome. Several crucial stages must be completed to achieve effective epigenetic therapy. Initially, acquiring a deeper understanding of the various molecular mechanisms underlying existing epigenetic drugs is essential. This enhanced comprehension can be a roadmap for identifying biomarkers to forecast treatment response. Certain epigenetic alterations could hold significant promise as biomarkers for this objective.

4. AUTHORS CONTRIBUTION STATEMENT

Dr. Abikesh Prasada Kumar Mahapatra, Vinod S. Mule wrote the initial draft. Dr Avula Naveen and Dr. Somenath Ghosh contributed to critical revision and supervision. All authors reviewed the manuscript.

5. CONFLICT OF INTEREST

Conflict of interest declared none.

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