(Online) ISSN 2744-1636
Bioengineering Studies *Review Article*
Vol. 6, No. 1, 2025, pp.51-60
https://doi.org/10.37868/bes.v6i1.id320

Epigenetic influence on gene expression and disease development

Maida Hajdarpašić[1*]
[1] Genetic and Bioengineering, International University of Sarajevo

*Corresponding author: maida.hajdarpasic15@gmail.com

Received Jun. 1, 2025
Revised Jun. 29, 2025
Accepted Jul. 15, 2025
Online Aug. 1, 2025

Abstract

Epigenetics, the study of heritable changes in gene function that do not involve changes in the DNA sequence itself, represents a fascinating frontier in contemporary biological research. Molecular biology, genetics, and bioinformatics are integrated using epigenetic modifications and their application to gene expression. Through various epigenetic mechanisms, including DNA methylation, histone modifications, and non-coding RNA, we continue to uncover the dynamic interplay between these modifications and the regulation of gene activity. Using state-of-the-art techniques, our project aims to contribute valuable insights into the role of epigenetics in cellular processes, development, and disease. In order to develop novel therapeutic approaches and a more thorough knowledge of human health and pathology, scientists work to obtain a deeper understanding of basic biological processes. This review aims to present the latest discoveries in epigenomics, which may have implications for novel treatment approaches and personalized medical care.

Keywords: Epigenetics; Gene expression; DNA methylation; Histone modifications; Non-coding RNA; Cancer therapy,

1. Introduction

Epigenetics is a science that deals with the study of changes in the function of hereditary genes and is not the result of changes in the DNA sequence but rather changes in gene expression depending on the state of chromatin and interaction with protein complexes [1]. Each organism's genome undergoes several changes and modifications throughout life, leading to the development of various epigenetic states. The epigenome is the collection of a cell's epigenetic modifications over a specific period of time [2]. Epigenetic modification entails chemical alterations to either the DNA molecule or the proteins that it interacts with. Histone modifications, non-coding RNA molecules, and DNA methylation are common epigenetic modifications. These changes can impact on the availability of DNA to the cellular machinery involved in transcription, ultimately influencing the expression of genes.

The significance of exploring epigenetics lies within the framework of gene expression and disease development. Studying epigenetics in the context of gene expression is crucial. Important regulators of gene expression, epigenetic modifications, control whether specific genes are activated or suppressed in different cells and at different times. Histone modifications, DNA methylation, and chromatin structure changes all result

from variations in the genes that control epigenetic processes in cells. These conditions tend to promote the development of multiple types of cancer in people [1]. Those studies of DNA methylation and gene expression were the first to point out the connection between epigenetics and cancer development [3][4]. Cancer is a disease that develops from the accumulation of genetic and epigenetic modifications. It is characterized by disturbances in the expression and aberrant functions of genes, changes in the pathways related to the growth and differentiation of stem cells and altered regulation of the cell cycle [5]. Cancer cells have the ability to grow rapidly and metastasize or divide uncontrollably and then spread to different parts of the body, resulting in the formation of new tumors. As a result of their growth, they can develop into benign or malignant tumors. The potential for metastasis separates malignant from benign tumors, which explains why malignant tumors can often be more challenging to treat [2].

2. Epigenetic mechanisms

2.1. DNA methylation

DNA methylation is a biochemical process in which a methyl group is added to the DNA structure. In eukaryotic cells, methylation of genes is a common way of gene expression regulation (activation/inactivation). It is present throughout the X chromosome inactivation process, embryonic development, the silencing of gene expression, and the prompt activation of those genes at various developmental stages [6]. In mammalian cells, methylation occurs after DNA replication and during cell differentiation. Depending on the cellular conditions, changes in the methylome, i.e., sets of nucleotides methylated during a specific period can occur. Each tissue and cell possess their own unique methylome, as emphasized by Klug and W.S (2019) [2].

The addition of a methyl group to the fifth carbon atom of cytosine results in the formation of 5-methylcytosine (5mC) (see Figure 1). Because 5mC is situated within the major groove of the DNA double helix, it hinders the binding of transcription factors, leading to disruptions in gene expression. Additionally, specific methylated DNA-binding proteins further contribute to the prevention of gene expression [4]. These proteins are involved in the modifications of histones and in the alteration of chromatin structure that inhibits the expression of genes. DNA-methyltransferase (DNMT) enzymes catalyze the methylation process [7].

DNA methyltransferase (DNMT) enzymes catalyze the reaction [8]. According to Fardi, M. [6], there are five subtypes in humans: DNMT1, DNMT2, DNMT3A, DNMT3B, and DNMT3L. While DNMT3A and 3B control new methylation, DNMT1 transfers methylation information to daughter cells [1].

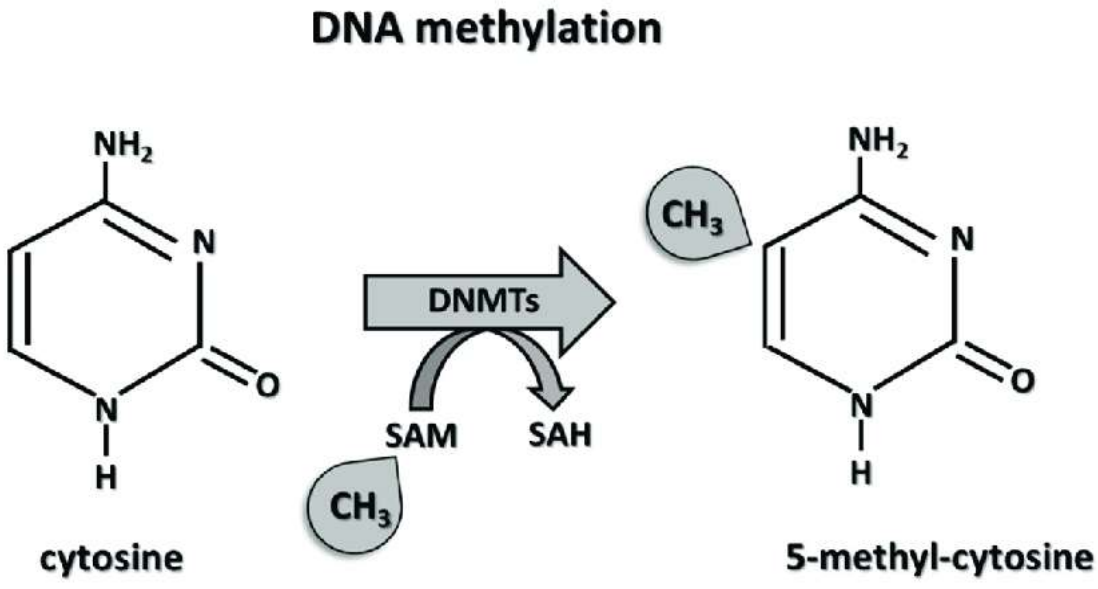

Figure 1. The process of DNA methylation is governed by DNA methyltransferases (DNMTs) [9].

Methylation of DNA occurs at the cytosine, which appears before the guanine (CpG). CpG islands, or regions where CpG dinucleotides are frequently found, are the usual targets of DNA methylation. These islands are commonly found in regions where genes are promoted [10]. Except for a few, most CpG islands are not significantly methylated: imprinted autosomal genes with completely methylated CpG islands and female X chromosome genes that have been silenced [11]. Active transcription occurs considering CpG islands, which are found in the promoter regions of housekeeping genes, genes essential to a cell's function, are not methylated in normal cells. Tumor cells demonstrate methylation of CpG islands present in gene promoters, which modifies the chromatin structure and prevents the formation of a transcription complex or mRNA synthesis. In the end, this results in the silencing of genes (Figure 2) [12].

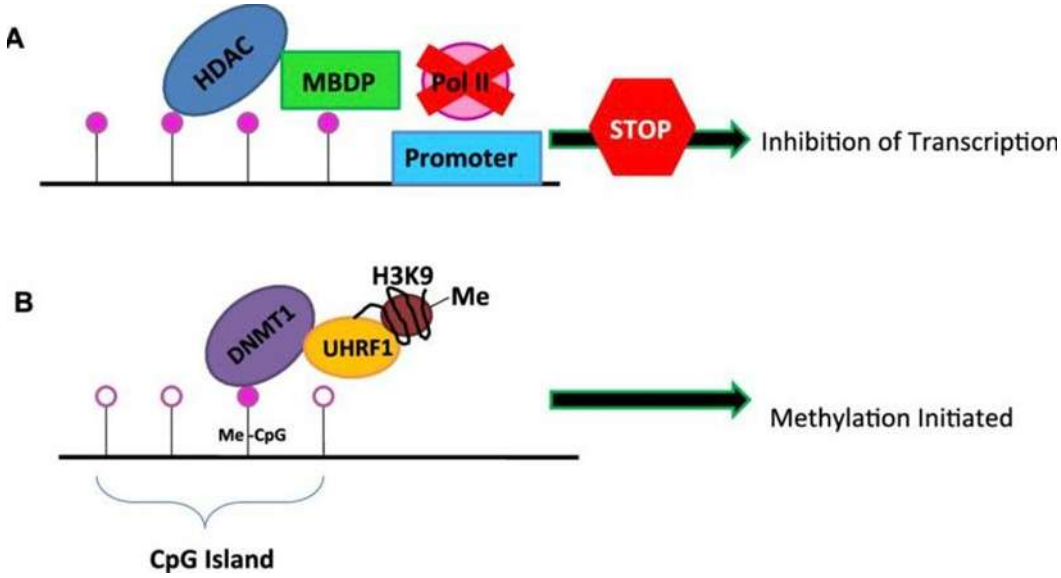

Figure 2. Model of how the methylation process of CpG islands in gene promoter regions inhibits transcription [13].

2.2. Histone modifications

Histone modifications are one of the main actors of epigenetic regulation because they influence chromatin structure and, in turn, gene expression [6]. Histone modifications and chromatin configuration changes that regulate DNA transcription by allowing or preventing access to specific proteins. In cells, DNA is arranged into chromosomes and chromatin by further condensation and coiling after wrapping around octameric histone cores, which form nucleosomes. This formation of the structure prevents transcription from beginning [2]. Heterochromatin and euchromatin are two different types of chromatin. Heterochromatin is a more condensed form of chromatin that primarily consists of inactive genes, while euchromatin is composed of less condensed chromatin that contains active genes [1].

Four histones make up histone octameric cores: H2A, H2B, H3, and H4. A tetramer of two histones, H2A and H2B, and two dimers, H3 and H4, make up one core [14]. At the N-terminal end of each histone is an amino acid tail that is located outside the nucleosome's structure [2]. The locations of post-translational modifications are the globular C-terminal end and the histone tail. Acetylation, methylation, citrullination, ADP ribosylation, biotinylation, and SUMOylation are some of these modifications that are applied to particular amino acids. The most researched modifications on histones H3 and H4 are lysine acetylation and methylation [7]. Histone acetylation and methylation influence several nuclear functions, including gene transcription, DNA replication and repair, and chromosomal organization [15]

2.3. Histone Acetylation

The process of adding an acetyl group to a protein is known as acetylation of histone proteins. Histone acetyltransferases (HATs) are enzymes that catalyze the acetylation of histones, the proteins that encompass

DNA. In order to create an open chromatin conformation that promotes gene transcription, acetyl groups are added to lysine residues on histones in this process [16]. The positive charge of lysine is neutralized by binding the acetyl group, which reduces its interaction with the negatively charged DNA and causes unwinding and a permissive chromatin structure [7].

Tumor formation and incorrect gene expression are caused by the unstable activity of enzymes involved in acetylation and deacetylation [7]. The precise control of gene expression depends on the dynamic balance between histone acetylation and deacetylation, which is mediated by histone deacetylases (HDACs). When proteins containing bromodomains bind to acetylated histones, they can attract transcriptional machinery and ultimately activate genes[17].

2.4. Histone Methylation

One important regulatory mechanism controlling chromatin organization and gene expression in cells is epigenetic histone methylation. Proline-arginine-methyl-transferases (PRMT) and lysine-methyl-transferases (KMT) add a methyl group to lysine (K) and arginine (L) residues to methylate histones H3 and H4 [18]. Lysine can have up to three methyl groups attached to it, while arginine can only have up to two. Methylation modifies the affinity for transcription factors but does not change the charge of the histone, unlike phosphorylation and acetylation. Methylation can either activate or inhibit gene transcription, depending on the amino acid residue it occurs on [19]. The accurate target histone residue and the degree of methylation determine how histone methylation affects gene expression. For example, methylation of lysine on histone H3, that is, methylation of H3K9, H3K27, and H4K20, inhibits transcription, and methylation of H3K4, H3K36, and H3K79 activates transcription. Different transcriptional activities are also influenced by variations in the number of methylations; for instance, transcription of H3K9 is impossible with triple methylation but possible with single methylation [20]. H3K4 methylation is an additional example. Triple-methylated lysine (H3K4me3) is present at active or paused transcription start sites, while single-methylated lysine (H3K4me1) is present at active gene enhancers [1].

A lysine methyltransferase called EZH2 is necessary for stem cell maintenance and differentiation. H3K27 is triple methylated by EZH2 to produce H3K27me3. During gene silencing associated with stem cell differentiation and general cell development, H3K27me3 is present [21]. In healthy cells, EZH2 regulates methylation and functions as a dual regulator of pluripotency and differentiation via interactions with DNA methyltransferases; in cancer cells, on the other hand, H3K27me3 suppresses the expression of specific genes, no matter the level of methylation present in their promoters [22]. Many cancers contain higher expression of EZH2 [23]. Tumor suppressor genes become silenced as a result of this activity [6]. Many diseases are connected to variations in histone methylation and EZH2 activity. The intricate relationships among histone methylation and other epigenetic mechanisms play a major role in the development, differentiation, and response of cells to stimuli from outside. Histone methylation dysregulation has been linked to several illnesses, indicating its critical role in maintaining genomic stability and healthy cellular function.

2.5. Histone phosphorylation

The dynamic field of epigenetics is further complicated by histone phosphorylation, a crucial post-translational modification that is caused by the action of kinases and phosphatases that add or remove phosphate groups from threonine, serine, and tyrosine on histone tails. Histones acquire an increased negative charge upon the addition of a phosphate group. The chromatin structure is affected by the resulting charge. The precise function of this modification is unknown, so this article explores the complexities of histone phosphorylation, demonstrating its mechanisms, functional importance, and effects on the larger topic of epigenetic regulation.

3. Non-coding RNAs:

Non-coding RNAs, also known as ncRNAs, are RNA sequences produced by DNA transcription that are not translated into proteins but still have a significant impact on the formation of heterochromatin, DNA

methylation, epigenetic regulatory pathways, gene silencing, and histone modifications [24]. Over 80% of the human genome is composed of these regulatory sequences, which are divided into two categories in accordance with the number of nucleotides: long (more than 200 nucleotides) and short (less than 200 nucleotides) [25].

Long noncoding RNAs, or lncRNAs, due to their absence of an open reading frame, do not translate from mRNA into polypeptides and are structurally similar to mRNA molecules. There are antisense, bidirectional, intergenic, and intronic lncRNA loci, depending on the adjacent gene [26]. The behavior of lncRNAs within the genome is explained by a number of different mechanisms. When lncRNA binds to a transcription factor, the factor and its target gene are unable to interact. Moreover, by binding several proteins together, lncRNAs can create RNA-protein complexes. IncRNA may influence enzyme complexes that contribute to gene silencing by modifying chromatin structure, leading these complexes to the target alleles [27]. By interacting with specific enzymes, they modify chromatin structure, which in turn affects gene expression. They are active during the regulation of gene expression during transcription, but also post-transcriptionally.Piwi-interacting RNAs (piRNAs), small interfering RNAs (siRNAs), and microRNAs (miRNAs) are subtypes of short non-coding RNAs (sncRNAs). In germline cells, piRNA functions as a gene repressor along with siRNA and miRNA, blocking the formation of RNA-protein complexes. They are produced by a process that starts with a precursor that is 70–100 nucleotides long and ends with 20–25 ribonucleotides [25]. The group of sncRNAs that includes miRNAs is a well-characterized subset of non-coding RNAs. They carry a 20-nucleotide sequence that is highly conserved. They regulate a large number of genes that code for proteins in humans. They function as tumor suppressors or onco-miRNAs, depending on the targeted gene, by binding to the 3'-end of the targeted mRNA and preventing translation and protein synthesis [7]. miRNA expression is usually highly controlled and plays a critical role in differentiation, proliferation, and apoptosis. It was found that the expression of miRNA varied between tumor and healthy tissues.

The oncogenic miRNA miR-101 is one type. Increased expression of EZH2 has been linked to reduced expression of miR-101 in some cancers. As a result, EZH2 expression increases the risk of cancer by contributing to methylations within tumor-suppressor genes (such as H3K27me3 methylation) [28]. The opposite happens when miR-101 expression increases, i.e., cancer cell growth is stopped. miRNA molecules have the potential to serve as biomarkers for the diagnosis of cancer, prognostication, and understanding of the treatment response and its impact on the patient's body.

4. Epigenetic mechanisms in carcinogenesis

Cancer is characterized by epigenetic dysregulation, which includes abnormal genome modifications that support uncontrolled proliferation of cells, tumor initiation, and progression. The most common way to characterize tumors is plastic and heterogeneous. Two models are used to explain their development. According to Lu, Y. (2020) [7], there are two models; the first model involves cancer stem cells and is thought to be the origin of oncogenic changes, and the second model, known as a clonal model, involves the reduced acquisition of oncogenic changes in cells that are not cancer stem cells.

The cancer stem cell model indicates that a tumor contains both proliferating and non-proliferating cells. Cancer stem cells are tumor cells that divide [29]. They are characterized as a specific group of cells that can differentiate, self-renew, and initiate new tumor growth within a tumor. Tumor-suppressor gene suppression and oncogene activation are processes that occur due to epigenetic modifications linked to methylation in cells at the beginning of cancer (Figure 3). Most often, CpG islands in the promoters of tumor suppressor genes are hypermethylated. Some examples include the tumor suppressor genes CDKN2 and PTEN, hypermethylated in melanoma, the SIX3 gene in glioblastoma, and the RASSF10 gene, whose hypermethylation causes kidney cancer. There are multiple sites of hypermethylation in prostate cancer.

The genes TIMPS, DAPK, and CDKN2A, which regulate cell metastasis, apoptosis, and the cell cycle, are hypermethylated, as is the promoter of the GSTP1 gene, which codes for glutathione S-transferase pi [30].

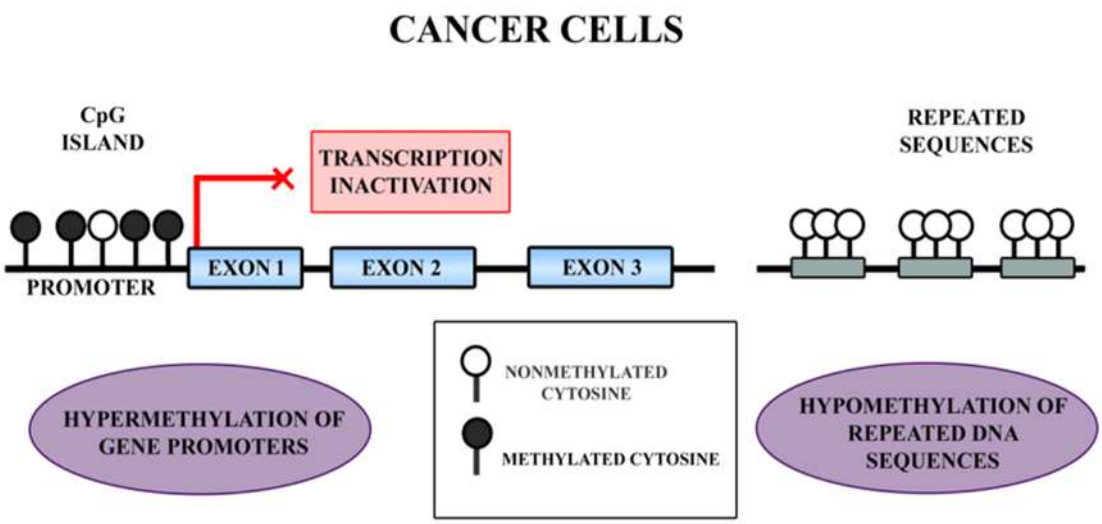

Figure 3. Cancer cells are characterized by global hypomethylation and hypermethylation of CpG islands [31].

Numerous malignancies have also been linked to aberrant miRNAs. Tumor-suppressor miRNAs prevent the expression of oncogenes, whereas onco-miRNAs silence tumor-suppressor genes and tend to be overexpressed [32]. In addition, some miRNAs carry out both functions even as the cancer is developing. One such example is miR-181, whose variable expression in cancers has led to the hypothesis that it functions similarly to onco-miRNAs and miRNAs as a tumor-suppressor. Since the miR-181 group's genes are found on different chromosome regions and are subject to various epigenetic modifications, it is thought that epigenetic changes can generally alter miRNA biogenesis. The four members of the miR-181 group are miR-181a, miR-181b, miR-181c, and miR-181d. In accordance with Braicu, C. (2018) [33], miR-181a-1 and miR-181b-1 are found on chromosome 1, miR-181a-2 and miR-181b-2 are found on chromosome 9, and miR-181c and miR-181d are found on chromosome 19. Cancers often have dysregulated N6-methyladenosine (m6A) modification in mRNA processing and miRNA primary transcript (pri-miRNA). Increased amounts of writers METT3 and METT14 have been detected in some cancer types. These writers allow the translation of specific mRNAs through m6A modification. When lncRNAs or circRNAs (circular RNAs) bind to miRNAs, their function may be terminated [34] .

Histone modifications that are out of balance are another contributing factor to cancer. Non-coding RNAs, aberrant activation of proto-oncogenes through DNA methylation, and even additional histone modifications are linked to histone modifications. For instance, elevated methylation of H3K36me2 results in elevated acetylation of H3K27ac in multiple myeloma. The expression of the genes encoding the enzymes acetylase, methyltransferase, deacetylase, and demethylase is disrupted in cancer cells. There are also modifications in the control of the reader, writer, and eraser enzymes. Histone deacetylation is one of the initial steps in a cell's transformation into a tumor. Histone deacetylase complexes are drawn to the region of tumor-suppressor genes by mutated DNA-binding proteins; there, chromatin is more strongly condensed, inhibiting transcription and promoting the growth of malignant tumor cells [35]. Histone deacetylases (HDAC) from groups I (1, 2, 3, 8) and II (4, 5, 6, 7, 9) have been found to be involved in the development of tumors. Certain mutations and translocations observed in solid tumors and hematological malignancies are linked to A-HAT-type enzymes. Hat-1 expression is frequently elevated in leiomyoma and leiomyosarcoma, and this is also linked to a lower prognosis for patients with these cancers. Many cancers have elevated expression of the demethylase LSD1. It functions by blocking the transcription of H3K4me1/2 that has been demethylated. In addition, increased expression of the PRMT enzyme is often seen in carcinomas. For example, the enzyme PRMT5 (protein arginine N-methyltransferase 5) is overexpressed in leukemia, glioblastoma, prostate cancer, and lymphomas. It does this by activating oncogenic transcription factors, such as c-Myc. Epigenetic modifications are possible due to

various factors such as being exposed to radiation, heavy metals, stress, hormones, analogs of bases, and smoking [36] .

4.1. Epigenetics in breast cancer

One of the most common cancers in women to be diagnosed with is breast cancer. Even with improvements in care, a high mortality rate continues to rise. Histone modifications and DNA methylation are the main targets of epigenetic drugs. Breast cancer cells have a variety of modified gene methylation patterns. LDH, LIMD2, SEPTIN7, and TRIM27 are hypomethylated genes linked to disease metastasis, proliferation, and spread [5]. Tumor suppressor genes SFN, APC, GSTP1, RARB, and DAPK, as well as the cell cycle regulators CCND2 and p16ink4A/CDKN2A, are frequently methylated. When their activity is reduced, and hypermethylation appears, the tumor-suppressor genes BRCA1, BCL2, and RAS encourage cell transformation. One of the primary processes that converts mesenchymal cells into tumor cells is the disrupted regulation of DNA methylation, which is also crucial for the development of diverse properties in cancer stem cells. Clusters of circulating tumor cells are turned on by dysregulation of methylation at the binding sites of specific transcription factors, including SIN3A, OCT4, SOX2, and NANOG. This kind of behavior encourages cancer to spread and progress [37].

Drug resistance is one of the main obstacles to treating more advanced cases of breast cancer. Genome instability, heterogeneity, growth factors, cytokines, epigenetic modifications and mutations, regenerative cancer stem cells, and the tumor microenvironment all impact signaling pathways, alter metabolism, and have an impact on how well a treatment works. Promising results have been found in the treatment of breast cancer through the use of epigenetic modifiers in conjunction with immunotherapy, chemotherapy, or endocrine therapy. As of now, epigenetic therapy for breast cancer is not in clinical use and is still in the early stages of development [5].

5. Epigenetic cancer therapy

The advancement of improved chemotherapy and radiotherapy faces challenges attributed to the adaptability and diversity of cancer. Due to these variations, advancements in the conventional treatment of cancer patients remain constrained, necessitating the creation of personalized therapeutic approaches. Epigenetic alterations, being reversible and responsive to external influences, offer a promising avenue for novel cancer treatments. Potential drugs, such as inhibitors targeting DNMT, HDAC, histone methyltransferase, and demethylase enzymes, emerge as viable options [38]. miRNA-based drugs, including miRNA analogs and anti-miRNAs, are also under investigation as potential therapeutic modalities. In clinical research, the combined use of various epigenetic drugs or their integration with immunotherapy and chemotherapy has shown progress in suppressing tumors. However, the development of certain epigenetic drugs poses challenges, as they may not exclusively target specific sites and can lead to unintended modifications [39].

6. Conclusion

Malignant tumors result from abnormalities in the enzymes that control epigenetic mechanisms and their effects on somatic cells. Change of healthy cells into tumor cells is caused by processes that include non-coding RNA activity, histone modification, and DNA methylation. As a result of their reversibility, mutations have been considered as potential candidates for novel forms of therapy. Many reversible epigenetic modifications that impact the expression of different genes interact to determine the possibility of cancer. The changes that occur result in modifications to DNA and chromatin structure. The effective emergence and continued progression of cancer are largely dependent on the expression of proto-oncogenes, the silencing of tumor-suppressor genes, and the creation of an appropriate microenvironment. The combination of drugs for the treatment of solid tumors is still not well researched, and further research is needed. However, there is a lot of potential for a novel approach to cancer treatment that utilizes epigenetic medicines in conjunction with currently available medical treatments.

Declaration of Competing Interest

The authors declare that they have no known financial or non-financial competing interests in any material discussed in this paper.

Funding information

No funding was received from any financial organization to conduct this research.

References

[1] R. L. Bennett and J. D. Licht, "Targeting Epigenetics in Cancer," 2018. doi: 10.1146/annurev-pharmtox-010716-105106.

[2] W. S. Klug, M. R. Cummings, C. A. Spencer, M. A. Palladino, and D. Killian, "Concepts of Genetics, Global Edition," *Person, str*, 2019.

[3] M. A. Dawson and T. Kouzarides, "Cancer epigenetics: From mechanism to therapy," 2012. doi: 10.1016/j.cell.2012.06.013.

[4] S. Virani, S. Virani, J. A. Colacino, J. H. Kim, and L. S. Rozek, "Cancer epigenetics: a brief review," 2012. doi: 10.1093/ilar.53.3-4.359.

[5] G. Sher *et al.*, "Epigenetic and breast cancer therapy: Promising diagnostic and therapeutic applications," 2022. doi: 10.1016/j.semcancer.2020.08.009.

[6] M. Fardi, S. Solali, and M. Farshdousti Hagh, "Epigenetic mechanisms as a new approach in cancer treatment: An updated review," 2018. doi: 10.1016/j.gendis.2018.06.003.

[7] Y. Lu, Y. T. Chan, H. Y. Tan, S. Li, N. Wang, and Y. Feng, "Epigenetic regulation in human cancer: The potential role of epi-drug in cancer therapy," 2020. doi: 10.1186/s12943-020-01197-3.

[8] M. Singh *et al.*, "Current paradigms in epigenetic anticancer therapeutics and future challenges," 2022. doi: 10.1016/j.semcancer.2021.03.013.

[9] M. Ciechomska, L. Roszkowski, and W. Maslinski, "DNA methylation as a future therapeutic and diagnostic target in rheumatoid arthritis," 2019. doi: 10.3390/cells8090953.

[10] H. K. Long, H. W. King, R. K. Patient, D. T. Odom, and R. J. Klose, "Protection of CpG islands from DNA methylation is DNA-encoded and evolutionarily conserved," *Nucleic Acids Res.*, vol. 44, no. 14, 2016, doi: 10.1093/nar/gkw258.

[11] Y. Yasukochi *et al.*, "X chromosome-wide analyses of genomic DNA methylation states and gene expression in male and female neutrophils," *Proc. Natl. Acad. Sci. U. S. A.*, vol. 107, no. 8, 2010, doi: 10.1073/pnas.0914812107.

[12] D. Han *et al.*, "Lysine methylation of transcription factors in cancer," 2019. doi: 10.1038/s41419-019-1524-2.

[13] S. Sarkar *et al.*, "Cancer development, progression, and therapy: An epigenetic overview," 2013. doi: 10.3390/ijms141021087.

[14] S. Saha, "Histone modifications and other facets of epigenetic regulation in trypanosomatids: Leaving their mark," *mBio*, vol. 11, no. 5, 2020, doi: 10.1128/mBio.01079-20.

[15] A. Mushtaq *et al.*, "Role of histone methylation in maintenance of genome integrity," 2021. doi: 10.3390/genes12071000.

[16] R. Kriswiastiny, Radiyati Umi Partan, Hermansyah, Surya Darma, and Muhammad Reagan, "The Role of Histone Deacetylase and Histone Deacetylase Inhibitors in Rheumatoid Arthritis," *Bioscientia Medicina : Journal of Biomedicine and Translational Research*, vol. 5, no. 11, 2021, doi: 10.32539/bsm.v5i11.423.

[17] T. Narita, B. T. Weinert, and C. Choudhary, "Functions and mechanisms of non-histone protein acetylation," 2019. doi: 10.1038/s41580-018-0081-3.

[18] K. P. Bhat, H. Ümit Kaniskan, J. Jin, and O. Gozani, "Epigenetics and beyond: targeting writers of protein lysine methylation to treat disease," 2021. doi: 10.1038/s41573-020-00108-x.

[19] M. Han, L. Jia, W. Lv, L. Wang, and W. Cui, "Epigenetic enzyme mutations: Role in tumorigenesis and molecular inhibitors," 2019. doi: 10.3389/fonc.2019.00194.

[20] D. Husmann and O. Gozani, "Histone lysine methyltransferases in biology and disease," 2019. doi: 10.1038/s41594-019-0298-7.

[21] R. French and S. Pauklin, "Epigenetic regulation of cancer stem cell formation and maintenance," 2021. doi: 10.1002/ijc.33398.

[22] J. Zhang, C. Yang, C. Wu, W. Cui, and L. Wang, "DNA methyltransferases in cancer: Biology, paradox, aberrations, and targeted therapy," 2020. doi: 10.3390/cancers12082123.

[23] M. L. Eich, M. Athar, J. E. Ferguson, and S. Varambally, "EZH2-targeted therapies in cancer: Hype or a reality," *Cancer Res.*, vol. 80, no. 24, 2020, doi: 10.1158/0008-5472.CAN-20-2147.

[24] X. Zhang *et al.*, "Mechanisms and functions of long non-coding RNAs at multiple regulatory levels," 2019. doi: 10.3390/ijms20225573.

[25] M. Kazimierczyk and J. Wrzesinski, "Long non-coding rna epigenetics," 2021. doi: 10.3390/ijms22116166.

[26] A. Luisa Pedroso Ayub, D. D'Angelo Papaiz, R. da Silva Soares, and M. Galvonas Jasiulionis, "The Function of lncRNAs as Epigenetic Regulators," in *Non-Coding RNAs*, 2020. doi: 10.5772/intechopen.88071.

[27] K. Mishra and C. Kanduri, "Understanding long noncoding RNA and chromatin interactions: What we know so far," 2019. doi: 10.3390/ncrna5040054.

[28] J. Tiffen *et al.*, "EZH2 Cooperates with DNA Methylation to Downregulate Key Tumor Suppressors and IFN Gene Signatures in Melanoma," *Journal of Investigative Dermatology*, vol. 140, no. 12, 2020, doi: 10.1016/j.jid.2020.02.042.

[29] S. Ghasemi *et al.*, "Epigenetic targeting of cancer stem cells by polyphenols (cancer stem cells targeting)," 2021. doi: 10.1002/ptr.7059.

[30] E. Bouras, M. Karakioulaki, K. I. Bougioukas, M. Aivaliotis, G. Tzimagiorgis, and M. Chourdakis, "Gene promoter methylation and cancer: An umbrella review," 2019. doi: 10.1016/j.gene.2019.06.023.

[31] N. Zmarzły, E. Wojdas, A. Skubis, B. Sikora, and U. Mazurek, "DNA methylation: gene expression regulation," *Acta Universitatis Lodziensis. Folia Biologica et Oecologica*, vol. 12, 2016, doi: 10.1515/fobio-2016-0001.

[32] C. S. Bhol *et al.*, "Epigenetic modifications of autophagy in cancer and cancer therapeutics," 2020. doi: 10.1016/j.semcancer.2019.05.020.

[33] C. Braicu *et al.*, "miR-181a/b therapy in lung cancer: reality or myth?," 2019. doi: 10.1002/1878-0261.12420.

[34] W. J. Wang, L. Y. Li, and J. W. Cui, "Chromosome structural variation in tumorigenesis: mechanisms of formation and carcinogenesis," 2020. doi: 10.1186/s13072-020-00371-7.

[35] M. Wang, V. Ngo, and W. Wang, "Deciphering the genetic code of DNA methylation," *Brief. Bioinform.*, vol. 22, no. 5, 2021, doi: 10.1093/bib/bbaa424.

[36] J. J. Han, X. Q. Wang, and X. A. Zhang, "Functional Interactions Between lncRNAs/circRNAs and miRNAs: Insights Into Rheumatoid Arthritis," Feb. 07, 2022, *Frontiers Media S.A.* doi: 10.3389/fimmu.2022.810317.

[37] H. Farah *et al.*, "Epigenetic regulation of circulating tumor cells in precision oncology," *Pathol. Res. Pract.*, vol. 276, p. 156282, Dec. 2025, doi: 10.1016/j.prp.2025.156282.

[38] K. K. Wong, "DNMT1: A key drug target in triple-negative breast cancer," 2021. doi: 10.1016/j.semcancer.2020.05.010.

[39] N. L. Mangang, S. K. Gargasz, S. G. Murugan, M. Kumar, G. C. Shukla, and S. Vijayaraghavalu, "MicroRNAs Modulating Cancer Immunotherapy Mechanisms and Therapeutic Synergies," Dec. 01, 2025, *Multidisciplinary Digital Publishing Institute (MDPI)*. doi: 10.3390/cancers17243978.