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The Role of Epigenetics in Cancer: Mechanisms, Dysregulation, and Therapeutic Implications

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ABSTRACT

Changes in epigenetics are key in cancer onset, progression, and therapeutic resistance through balancing the expression of genes without mutating the DNA sequence. In contrast to the non-reversible genetic mutations, the epigenetic changes are dynamic and can possibly be reversed; thus, they offer attractive targets for clinical approaches. This phenomenon is a review of the key epigenetic events in oncogenesis, such as DNA methylation, histone changes, chromatin remodeling, and control by non-coding RNA. Another effect is the silencing of tumor suppressor genes by aberrant promoter hypermethylation and a global hypomethylation that causes genomic instability and the oncogenic activation of oncogenes. The transcriptional control is further interfered with by dysregulation of histone-modifying enzymes and chromatin remodeling complexes, which promote malignant transformation, metastasis, and avoidance of immunity. There is also an emerging body of evidence that highlights the interplay between the reprogramming of epigenetics and the tumor microenvironment, which includes hypoxia, inflammation, and metabolic stress, all of which together influence tumor behavior. Recent developments in high-throughput sequencing and single-cell epigenomics have enhanced the discovery of epigenetic biomarkers, including circulating tumor DNA methylation biomarkers and non-coding RNA biomarkers, to detect and prognose early. Epigenetic-targeted agents, such as DNA methyltransferase and histone deacetylase inhibitors, and new chromatin-modifying enzyme inhibitors have demonstrated clinical utility, at least in hematologic malignancies, and are under investigation with immunotherapy and chemotherapy.

Keywords: Epigenetics, Cancer, DNA Methylation, Histone Modifications, Epigenetic Therapy

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Introduction

The evidence that DNA was organized in a peculiar structure named "chromatin" and associated with proteins of unknown function was a very early finding. The term "chromatin" was first introduced by the German biologist Walther Flemming in the late 19th century. He observed thread-like structures within the cell nucleus during cell division and named them "chromatin" due to their ability to be stained by certain dyes. Although Flemming's observations were fundamental to the study of chromatin, the detailed structure and function were unraveled much later through the collective work of numerous scientists in genetics, biochemistry, and molecular biology [1]. By 1942, Conrad Waddington had coined the term "epigenetics" to refer to developmental processes that link genotype with phenotype. The idea became a developmental model and then a molecular discipline that involved heritable changes in gene expression that didn't involve changes in the underlying DNA sequence [2]. The modern definition of epigenetics includes modifications to DNA, histone proteins, chromatin structure, and non-coding RNA and their role in regulating gene activity and cellular identity [3]. Epigenetics is the regulation of the expression of genes in various cell types and environmental situations, whereas genetics is the DNA blueprint [4]. The existing evidence indicates that the genetic and epigenetic systems are closely intertwined and that epigenetics has important roles in cellular differentiation, developmental programming, maintaining cellular memory, and responding to environmental stimuli. Thus, epigenetics has become an indispensable tool to grasp the intricate relationship between the genome, the environment, and the phenotype [5].

Cancer is still one of the most common causes of death and disease in the world, and a public health problem. It is estimated that there were around 20 million new cases of cancer and 9.7 million cancer deaths in the world in 2022 and that this number is likely to dramatically rise over the next few decades [6][7][41]. The impact will be greatest in low- and middle-income countries, where access to screening, early diagnosis, and available and effective treatment is low, resulting in poorer outcomes [8]. In the context of cancer, epigenetic dysregulation has become a primary and ubiquitous feature associated with the initiation, progression, metastasis, recurrence, and drug resistance of tumors. Abnormal DNA methylation, histone modifications, and non-coding RNAs that regulate gene expression may lead to the abnormal expression of genes and malignant transformation [9]. Importantly, many epigenetic changes are reversible and are potential therapeutic targets. Also, the growing clinical relevance of epigenetics in oncology is evidenced by the fact that cancer-specific epigenetic signatures are now being explored as cancer diagnosis markers, prognosis markers, and markers for predicting treatment responses [10].

This review will give an overview of the role of epigenetics in cancer focusing on the molecular mechanisms of epigenetic regulation and their contribution to carcinogenesis. This review focuses on the most important epigenetic pathways associated with cancer, such as DNA methylation, histone modification, chromatin remodeling and non-coding RNAs. It also highlights the role of epigenetic deregulations in the initiation and progression of tumors and investigates the relevance of epigenetic markers in the diagnosis and prognosis of cancer; it then explores the current and emerging therapeutic opportunities of epigenetic drugs in cancer treatment.

Fundamentals of Epigenetics:

Epigenetics is defined as heritable and reversible changes of gene expression that do not change the DNA sequence. It provides an account of how identical pieces of genetic information can give rise to different structures or functions in the same cells as a result of differences in stable gene activity [11]. Epigenetic changes, as opposed to mutations, can be dynamic and changing, and are affected by intrinsic and environmental factors such as age, diet, lifestyle, and external influences [12]. These modifications are important in cell differentiation, cellular identity and adaptation to changing environmental conditions [13]. Epigenetic mechanisms provide a link between the genome and phenotype and are involved in normal development and disease processes by regulating gene expression [14].

Chromatin is the main way in which genes are regulated; it is a complex of DNA and histone proteins that influences the access of the genes to the transcriptional machinery [15]. Four epigenetic mechanisms are known: DNA methylation, modification of histones, chromatin remodeling, and regulation mediated by non-coding RNA [16]. In general, DNA methylation leads to gene silencing and genomic stability, while the modifications of the histones affect the structure and activity of chromatin by processes including acetylation and methylation [17]. Chromatin remodeling complexes change nucleosome positioning to control access to DNA, and non-coding RNAs act in gene expression at both the transcriptional and post-transcriptional levels [18]. The mechanisms operate with great coordination, creating interconnected regulatory networks to regulate context-dependent gene expression, chromatin state, and cellular memory [19].

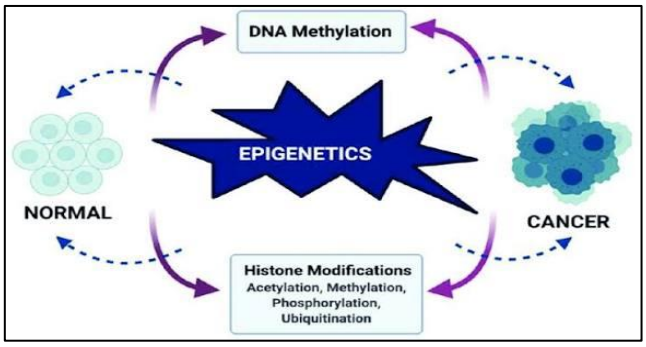

Figure 1: Role of Epigenetic Alterations in Cancer Development

This diagram shows how the epigenetic mechanisms, such as DNA methylation and histone modification (acetylation, methylation, phosphorylation, and ubiquitination), contribute to the regulation of gene expression and to the transition between normal and cancerous cellular states. Epigenetic alterations can alter the normal expression of genes, with tumor suppressor genes being silenced and oncogenes being activated, which can help drive the initiation and progression of cancer.

Epigenetic Mechanisms in Cancer:

Epigenetic changes are a characteristic of cancer and play an important role in cancer initiation, progression, and resistance to treatment [20]. Epigenetic changes do not alter the DNA sequence but are changes to the expression of the gene and include DNA methylation, histone modifications, chromatin remodeling, and non-coding RNAs [21]. These mechanisms work together to cause abnormal regulation of cells in the body, causing oncogenes to become activated and tumor suppressor genes to be silenced. Of these changes, DNA methylation is perhaps one of the most well-studied mechanisms of epigenetic change in cancer [22] [23]. Promoter hypermethylation of tumor suppressor genes is usually accompanied by the overall hypomethylation of the DNA of the cancer cells [24]. CpG island hypermethylation of genes like BRCA1, MLH1, RB1, and VHL leads to silencing of genes, whereas genome-wide hypomethylation leads to instability of the genome and activation of oncogenes. These methylation changes work together to be a key player in the process of malignant transformation and cancer progression [25].

Besides DNA methylation, the cancer epigenome relies on non-coding RNAs, histone modification, and chromatin remodeling. The structure of chromatin is modified by acetylation and methylation, which affect the accessibility of the genes and thus regulate transcriptional activity [26]. Dysfunctions of SWI/SNF complexes and other chromatin remodeling enzymes can cause nucleosome positioning defects and impair gene regulation, and altered histone marks can promote the expression of oncogenes or suppress the expression of tumor suppressor pathways [27]. In addition, non-coding RNAs such as microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs) play a role in epigenetic regulation and can be regulated epigenetically [28]. Abnormalities in the regulation of these RNA molecules have been linked to carcinogenesis, metastasis, metabolic reprogramming, and therapy resistance. Together, these tightly coupled epigenetic mechanisms contribute to the heterogeneity of tumors, facilitate the progression of the disease, and could be therapeutic and diagnostic targets [29][30].

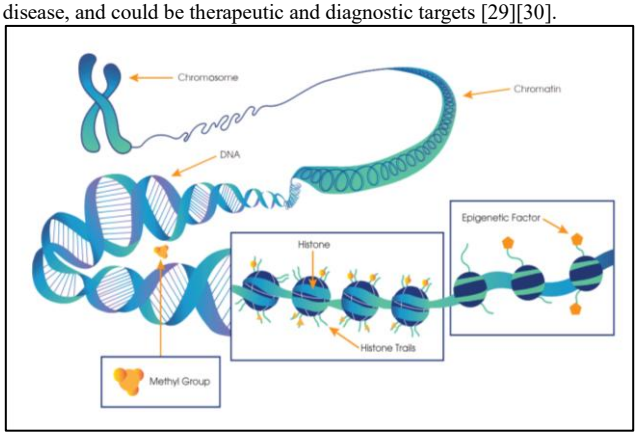

Figure 2: Overview of Epigenetic Regulation:

This diagram shows how genetic material is organized into chromatin and DNA at the molecular level and the principle of epigenetics. The DNA is coiled around the histone proteins to form a nucleosome, and these are combined to make chromatin. DNA can have chemical groups (methyl groups) attached to it, or to the histone tails, that do not change the DNA sequence but affect how the DNA is packaged.

Therapeutic Implications of Epigenetics:

Epigenetic therapy would seem to be a novel strategy in cancer treatment that targets abnormalities in the regulation of genes that are reversible [31]. Epigenetic changes are not inherited but can be reversed by therapeutic intervention, and enzymes that regulate DNA methylation, histone modification, and chromatin regulation are attractive drug targets [32]. Epigenetic drugs can be divided into four classes: DNA methyltransferase inhibitors (DNMT inhibitors), histone deacetylase inhibitors (HDAC inhibitors), histone methyltransferase inhibitors (HMT inhibitors), and bromodomain and extra-terminal domain (BET) inhibitors. Of these, the DNMT and HDAC inhibitors are the best studied and proven inhibitors [33][34]. DNMT inhibitors, including azacitidine and decitabine, restore abnormal DNA methylation and restore expression of silenced tumor suppressor genes; HDAC inhibitors, like trichostatin A, increase the acetylation of histones, hence creating a more open chromatin structure, which facilitates expression of tumor suppressor genes, apoptosis, and cell-cycle arrest. These treatments have shown the most clinical efficacy in hematological malignancies such as myelodysplastic syndromes, AML, and some lymphomas [35].

There has been a surge in progress in the epigenetic therapy field in recent years, with the emergence of more selective agents, such as histone methyltransferases and BET bromodomain proteins [36]. HMT inhibitors, including tazemetostat, inhibit the growth of tumors by blocking enzymes that are important for methylation of the histone proteins and are approved for the treatment of some types of cancer, such as follicular lymphoma and epithelioid sarcoma [37]. Another promising class that has recently been identified is the bromodomain inhibitors, which inhibit the interactions of oncogenic transcription with acetylated histones [38]. However, epigenetic monotherapies in solid tumors are not currently as effective. Thus, more and more research is now looking at combination approaches, such as administration of epigenetic drugs in combination with chemotherapy, targeted therapy, or immunotherapy [39][42][43]. These strategies are designed to increase the effectiveness of the therapy, circumvent drug resistance, and improve therapeutic success. Epigenetic therapy is an exciting and emerging area of cancer therapy that has the potential for a personalized approach to treating cancer but still needs more research to enable the optimal application in a range of cancer types [40].

Challenges and Future Perspectives:

Although great strides have been made in understanding of cancer epigenetics, several factors remain to restrict the use of epigenetic diagnostics and therapies in the clinic. A major difficulty is the complexity and heterogeneity of epigenetic modifications across various types of cancer and even within cancer patients with the same tumor type. This diversity complicates the search for biomarker signatures and/or generalized therapeutic approaches. Further, most of the epigenetic drugs available now are non-target specific, which can have off-target effects and toxicities. Another challenge is the development of resistance to epigenetic therapies, especially when short- or long-term treatment is required. Additionally, although epigenetic therapies have shown significant promise in hematological malignancies, their efficacy has yet to be seen in solid cancers due to tumor heterogeneity, tumor microenvironment complexity, and lack of drug delivery.

Conclusion:

Epigenetic changes are key players in the initiation, progression, metastasis of cancer, and resistance to therapy. Epigenetic changes affect the expression of genes without changing the DNA sequence, through various mechanisms like DNA methylation, histone modifications, chromatin remodeling, and non-coding RNA regulation. These changes are essential for all aspects of carcinogenesis—activation of oncogenes, silencing of tumour suppressor genes, genomic instability, and tumor heterogeneity. Epigenetic modifications are reversible, providing novel opportunities for cancer diagnosis, prognosis, and treatment. While challenges still exist, especially in the areas of treatment resistance, toxicity, and limited therapeutic effects in solid tumors, continued progress in epigenomic technologies and precision medicine should drive the progress of epigenetic discoveries into clinical practice. Epigenetics is a field of rapidly advancing research and could prove to be a valuable tool in cancer management and for developing more personalized and effective cancer treatments.

References

[1] Farsetti A, Illi B, Gaetano C. How epigenetics impacts human diseases. European journal of internal medicine. 2023 Aug 1;114:15-22.

[2] Spitschak A, Casalegno Garduño R, Pützer BM. Cancer in transition: discovery of tumor-intrinsic transcriptional programs shaping the immune and microenvironmental landscape. Biomarker Research. 2026 Apr 16.

[3] Recillas-Targa F. Cancer epigenetics: an overview. Archives of Medical Research. 2022 Dec 1;53(8):732-40.

[4] Singla N, Thapa R, Kulshrestha R, Bhat AA, Gupta S, Purohit M, Singh SK, Gupta G. Introduction to epigenetics. InTargeting epigenetics in inflammatory lung diseases 2023 Dec 21 (pp. 17-41). Singapore: Springer Nature Singapore.

[5] Lamka GF, Harder AM, Sundaram M, Schwartz TS, Christie MR, DeWoody JA, Willoughby JR. Epigenetics in ecology, evolution, and conservation. Frontiers in Ecology and Evolution. 2022 Apr 11;10:871791.

[6] Deo SV, Sharma J, Kumar S. GLOBOCAN 2020 Report on Global Cancer Burden: Challenges and Opportunities for Surgical Oncologists: SVS Deo et al. Annals of surgical oncology. 2022 Oct;29(11):6497-500.

[7] Morgan E, Arnold M, Gini A, Lorenzoni V, Cabasag CJ, Laversanne M, Vignat J, Ferlay J, Murphy N, Bray F. Global burden of colorectal cancer in 2020 and 2040: incidence and mortality estimates from GLOBOCAN. Gut. 2023 Feb 1;72(2):338-44.

[8] Afzal MA, Shahzadi N, Ijaz M, Ali MA, Saadat S. Sustainable transformation road map to improved global food and nutrition security: a narrative review. Frontier in Medical and Health Research. 2025;3(6):844-53.

[9] Karami Fath M, Azargoonjahromi A, Kiani A, Jalalifar F, Osati P, Akbari Oryani M, Shakeri F, Nasirzadeh F, Khalesi B, Nabi-Afjadi M, Zalpoor H. The role of epigenetic modifications in drug resistance and treatment of breast cancer. Cellular & Molecular Biology Letters. 2022 Dec;27(1):52.

[10] Oura K, Morishita A, Hamaya S, Fujita K, Masaki T. The roles of epigenetic regulation and the tumor microenvironment in the mechanism of resistance to systemic therapy in hepatocellular carcinoma. International journal of molecular sciences. 2023 Feb 1;24(3):2805.

[11] Han H, Luo RH, Long XY, Wang LQ, Zhu Q, Tang XY, Zhu R, Ma YC, Zheng YT, Zou CG. Transcriptional regulation of SARS-CoV-2 receptor ACE2 by SP1. Elife. 2024 Feb 20;13:e85985.

[12] Borrego-Ruiz A, Borrego JJ. Epigenetic mechanisms in aging: Extrinsic factors and gut microbiome. Genes. 2024 Dec 14;15(12):1599.

[13] Wu YL, Lin ZJ, Li CC, Lin X, Shan SK, Guo B, Zheng MH, Li F, Yuan LQ, Li ZH. Epigenetic regulation in metabolic diseases: mechanisms and advances in clinical study. Signal Transduction and Targeted Therapy. 2023 Mar 2;8(1):98.

[14] la Torre A, Lo Vecchio F, Greco A. Epigenetic mechanisms of aging and aging-associated diseases. Cells. 2023 Apr 14;12(8):1163.

[15] Mishra J, Chakraborty S, Niharika, Roy A, Manna S, Baral T, Nandi P, Patra SK. Mechanotransduction and epigenetic modulations of chromatin: Role of mechanical signals in gene regulation. Journal of Cellular Biochemistry. 2024 Mar;125(3):e30531.

[16] Bure IV, Nemtsova MV, Kuznetsova EB. Histone modifications and non-coding RNAs: mutual epigenetic regulation and role in pathogenesis. International Journal of Molecular Sciences. 2022 May 22;23(10):5801.

[17] Ali S, Tang Y. Noncoding RNA-mediated regulation of DNA methylation: Insights into plant epigenetic mechanisms. Journal of Plant Growth Regulation. 2025 Feb;44(2):373-88. ‘

[18] Gagnidze K, Pfaff DW. Epigenetic mechanisms: DNA methylation and histone protein modification. InNeuroscience in the 21st century: from basic to clinical 2022 Oct 18 (pp. 2677-2716). Cham: Springer International Publishing.

[19] Sum H, Brewer AC. Epigenetic modifications as therapeutic targets in atherosclerosis: a focus on DNA methylation and non-coding RNAs. Frontiers in Cardiovascular Medicine. 2023 May 25;10:1183181.

[20] Karami Fath M, Azargoonjahromi A, Kiani A, Jalalifar F, Osati P, Akbari Oryani M, Shakeri F, Nasirzadeh F, Khalesi B, Nabi-Afjadi M, Zalpoor H. The role of epigenetic modifications in drug resistance and treatment of breast cancer. Cellular & Molecular Biology Letters. 2022 Dec;27(1):52.

[21] Song J, Yang P, Chen C, Ding W, Tillement O, Bai H, Zhang S. Targeting epigenetic regulators as a promising avenue to overcome cancer therapy resistance. Signal transduction and targeted therapy. 2025 Jul 18;10(1):219.

[22] Wang N, Ma T, Yu B. Targeting epigenetic regulators to overcome drug resistance in cancers. Signal transduction and targeted therapy. 2023 Feb 17;8(1):69.

[23] Wang D, Zhang Y, Li Q, Li Y, Li W, Zhang A, Xu J, Meng J, Tang L, Lyu S. Epigenetics: Mechanisms, potential roles, and therapeutic strategies in cancer progression. Genes & diseases. 2024 Sep 1;11(5):101020.

[24] Alshammari E, Zhang Y, Sobota J, Yang Z. Aberrant DNA methylation of tumor suppressor genes and oncogenes as cancer biomarkers. Genomic and Epigenomic Biomarkers of Toxicology and Disease: Clinical and Therapeutic Actions. 2022 Apr 27:251-71.

[25] De Marco K, Sanese P, Simone C, Grossi V. Histone and DNA methylation as epigenetic regulators of DNA damage repair in gastric cancer and emerging therapeutic opportunities. Cancers. 2023 Oct 13;15(20):4976.

[26] Zhao P, Malik S. The phosphorylation to acetylation/methylation cascade in transcriptional regulation: how kinases regulate transcriptional activities of DNA/histone-modifying enzymes. Cell & Bioscience. 2022 Jun 3;12(1):83.

[27] Kim J, Lee H, Yi SJ, Kim K. Gene regulation by histone-modifying enzymes under hypoxic conditions: a focus on histone methylation and acetylation. Experimental & Molecular Medicine. 2022 Jul;54(7):878-89.

[28] Fadaei S, Zarepour F, Parvaresh M, Motamedzadeh A, Tamehri Zadeh SS, Sheida A, Shabani M, Hamblin MR, Rezaee M, Zarei M, Mirzaei H. Epigenetic regulation in myocardial infarction: Non-coding RNAs and exosomal non-coding RNAs. Frontiers in Cardiovascular Medicine. 2022 Nov 10;9:1014961.

[29] Prabhakaran R, Thamarai R, Sivasamy S, Dhandayuthapani S, Batra J, Kamaraj C, Karthik K, Shah MA, Mallik S. Epigenetic frontiers: miRNAs, long non-coding RNAs and nanomaterials are pioneering to cancer therapy. Epigenetics & Chromatin. 2024 Oct 16;17(1):31.

[30] Manna I, Fortunato F, De Benedittis S, Sammarra I, Bertoli G, Labate A, Gambardella A. Non-coding RNAs: new biomarkers and therapeutic targets for temporal lobe epilepsy. International Journal of Molecular Sciences. 2022 Mar 11;23(6):3063.

[31] Sahafnejad Z, Ramazi S, Allahverdi A. An update of epigenetic drugs for the treatment of cancers and brain diseases: a comprehensive review. Genes. 2023 Apr 6;14(4):873.

[32] Li T, Chen Y, Li S. The advances in the development of epigenetic modifications and therapeutic drug delivery systems. International Journal of Nanomedicine. 2024 Dec 31:10623-37.

[33] Suraweera A, O’Byrne KJ, Richard DJ. Epigenetic drugs in cancer therapy. Cancer and Metastasis Reviews. 2025 Mar;44(1):37.

[34] Hussain A, Tebyaniyan H, Khayatan D. The role of epigenetic in dental and oral regenerative medicine by different types of dental stem cells: a comprehensive overview. Stem cells international. 2022;2022(1):5304860.

[35] Bouyahya A, Mechchate H, Oumeslakht L, Zeouk I, Aboulaghras S, Balahbib A, Zengin G, Kamal MA, Gallo M, Montesano D, El Omari N. The role of epigenetic modifications in human cancers and the use of natural compounds as epidrugs: mechanistic pathways and pharmacodynamic actions. Biomolecules. 2022 Feb 25;12(3):367.

[36] Gold S, Shilatifard A. Therapeutic targeting of BET bromodomain and other epigenetic acetylrecognition domain–containing factors. Current Opinion in Genetics & Development. 2024 Jun 1;86:102181.

[37] Marzochi LL, Cuzziol CI, Do Nascimento Filho CH, Dos Santos JA, Castanhole-Nunes MM, Pavarino ÉC, Guerra EN, Goloni-Bertollo EM. Use of histone methyltransferase inhibitors in cancer treatment: A systematic review. European journal of pharmacology. 2023 Apr 5;944:175590.

[38] Mondello P, Ansell SM. Tazemetostat: a treatment option for relapsed/refractory follicular lymphoma. Expert opinion on pharmacotherapy. 2022 Feb 11;23(3):295-301.

[39] Rosenthal AC, Munoz JL, Villasboas JC. Clinical advances in epigenetic therapies for lymphoma. Clinical Epigenetics. 2023 Mar 4;15(1):39.

[40] Zhao R, Cernak TA. Tazemetostat (Tazverik): An EZH2 Inhibitor for Treatment of Epithelioid Sarcoma and Follicular Lymphoma. Chemistry and Pharmacology of Drug Discovery. 2024 Aug 20:199.

[41] Ashraf MA, Afzal MA, Ijaz M, Arshad A, Zafar MN, Ukkasha SM, Zahid I. Financial impact of nutrition on non-communicable diseases in hospital or other healthcare settings. Biological Times. 2025 Sep 4;4(9):20-1.

[42] Arshad A, Noor M, Amjad A, Noor M, Seemab R, Siddique U. CRISPR Gene Editing Technology in Treating Hereditary Diseases. Biological Times. 2025 Aug 4;8:19-23.

[43] Afzal MA, Shahzadi N, Saadat S, Seemab R, Sajjad I, Tariq N, Ashraf SR, Tahir S, Kharl HA. CRISPR-Cas9 genome-editing technology: a transformative tool for curing human disorders. Journal of Medical & Health Sciences Review. 2025 Jul 29;2(3).