EPIGENETICS

Epigenetic Editing and Its Role in Disease Treatment

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Published November 2026

Abstract

Epigenetic control of gene expression involves regulation of gene expression without changing DNA sequence and encompasses various processes such as DNA methylation, histone modifications, chromatin remodeling and noncoding RNAs. Dysregulation of epigenetic regulation causes malfunction in gene expression leading to diseases such as cancer, neurological diseases, genetic diseases, metabolic diseases and inflammatory diseases. Epigenetic editing offers a potential therapy to specifically edit epigenetic states and regulate gene expression without directly altering DNA sequence in order to treat diseases. CRISPR/dCas9-based technology allows targeted delivery of epigenetic effector proteins to the genome site which enables targeted DNA methylation, DNA demethylation and histone modification. Such technology is capable of rescuing repressed genes, blocking deleterious gene expression and restoring physiological cell functions. However, some issues need to be addressed before epigenetic editing could become a promising therapy; off-targeting, delivery effectiveness, editing specificity, duration of epigenetic alteration, immune response and safety concerns. The development of novel molecular engineering and targeted drug delivery technologies will facilitate the use of epigenetic editing for medical purposes. Therefore, epigenetic editing is a new promising strategy for disease treatment that may contribute to the emergence of precision medicine.

Keywords: epigenetic editing; CRISPR; DNA methylation; histone modification; gene regulation; cancer; gene therapy; disease treatment

1 Introduction

1.1 Background of epigenetics

Epigenetics is heritable and reversible alteration in the regulation of gene expression without any change in the DNA sequence of the gene. The major players in epigenetics include DNA methylation, histone modifications, chromatin modifications, and noncoding RNAs. These processes control chromatin structure and transcriptional state [1, 2]. In contrast to the genetic information stored within the DNA, epigenetic regulation dictates the time and manner of gene expression.

1.2 Epigenetic dysregulation and diseases

Aberrant epigenetic regulation causes abnormal gene expression and contributes to various diseases. Aberrations in DNA methylation and histone modifications lead to cancer, while aberrant epigenetic regulation contributes to neurological, metabolic, cardiovascular, and inflammatory disorders [3, 4].

1.3 Appearance of epigenetic editing

Epigenetic editing technology allows one to alter the epigenetic state of gene regulatory elements without the actual change in the DNA sequence. The CRISPR/dCas9 system can be used for targeting epigenetic regulators to specific chromosomal loci, which would control DNA methylation, histone modifications, and gene transcription [5].

1.4 Aim and scope

The present review will cover epigenetic editing technologies and their mechanisms, applications in therapy of diseases, potential for treatment, problems, safety issues, and future directions in personalized medicine.

2 Fundamentals of epigenetic regulation

2.1 DNA methylation

DNA methylation usually occurs at CpG dinucleotides, where DNA methyltransferases (DNMTs) add methyl group to cytosines. Methylation at promoter regions is linked with chromatin condensation and gene inactivation. On the other hand, TET proteins modify 5-methylcytosine and actively participate in DNA demethylation. The alterations of DNA methylation status may impair gene transcription and be involved in a number of disorders, especially in cancer [1, 2].

2.2 Histone modifications

Histone proteins may experience different post-translational modifications such as acetylation, methylation, phosphorylation, and ubiquitination that affect chromatin organization and transcription. Histone acetyltransferases (HATs) promote transcription by increasing chromatin accessibility, while histone deacetylases (HDACs) tend to repress gene transcription. Transcription regulation by histone methyltransferases and demethylases depends on the modified residue and the specific circumstances [3].

2.3 Chromatin remodeling

The chromatin structure may have either easily accessible (euchromatin) or condensed (heterochromatin) states. ATP-dependent chromatin-remodeling complexes move nucleosomes and control access to DNA for transcription and other genetic operations [4].

2.4 Non-coding RNAs

The non-coding RNAs, especially micro-RNAs (miRNAs) and long non-coding RNAs (lncRNAs), regulate transcriptional and post-transcriptional gene

3 Epigenetic editing: concept and technologies

3.1 Definition of epigenetic editing

Epigenetic editing is an approach to control gene expression via changes in epigenetic state without genetic changes. Traditional gene editing consists in modification of genetic sequence. Therefore, the use of epigenetic editing represents a reversible tool for disease associated genes regulation [1].

3.2 Epigenetic editing using CRISPR/dCas9

CRISPR-Cas9 usually works via the targeting of Cas9 to a specific DNA sequence using gRNA. Cas9 makes a cut in DNA in this sequence. Epigenetic editing includes using Cas9 which does not possess nuclease activity, but is able to target a particular sequence. It can be fused with epigenetic effector proteins and regulate locus-specific gene expression [1, 2].

3.3 DNA methylation editing

DNMT-based dCas9 allows to induce the targeted DNA methylation and gene silencing while TET-based system can induce the DNA demethylation and activate gene expression [3].

3.4 Histone modification editing

Epigenetic editing can target histone modifications, such as acetylation or methylation and others and affect transcription activity [1].

3.5 CRISPRa and CRISPRi

CRISPRa is used to activate gene expression, while CRISPRi to repress gene transcription without inducing double strand breaks. They represent useful tools for disease associated genes manipulation and target identification [2, 4].

4 Role of epigenetic editing in disease treatment

Epigenetic editing is a promising technique to treat diseases caused by deregulated gene regulation. In cancers, abnormalities in DNA methylation, histone modification, and chromatin regulation can suppress the activity of tumor-suppressor genes and activate oncogenic signaling. Hence, targeted epigenetic editing may be used to restore the activity of silenced tumor-suppressor genes, repress the activity of oncogenes, and possibly improve treatment responses or immune responses to standard therapies [1, 2].

Neurological and neurodegenerative disorders such as Alzheimer's, Parkinson's, Huntington's disease, Fragile X syndrome, and Rett syndrome also have abnormal DNA methylation and histone modification that lead to abnormal gene expression in neurons. Thus, the targeted editing technique can be applied to restore expression of genes that become silenced, although their delivery into the brain is difficult [3, 4].

For genetic diseases and rare disorders, epigenetic editing can reverse the gene expression status, activate alternative genes, or reactivate silenced gene copies without modifying the sequence of the causative DNA [1].

Epigenetics also play a role in metabolic diseases like diabetes and obesity through insulin, glucose, and lipids metabolism [5]. Moreover, epigenetics also affect vascular function, inflammation, cytokine expression, and immune cells' activities in the cardiovascular and inflammatory diseases [5, 6].

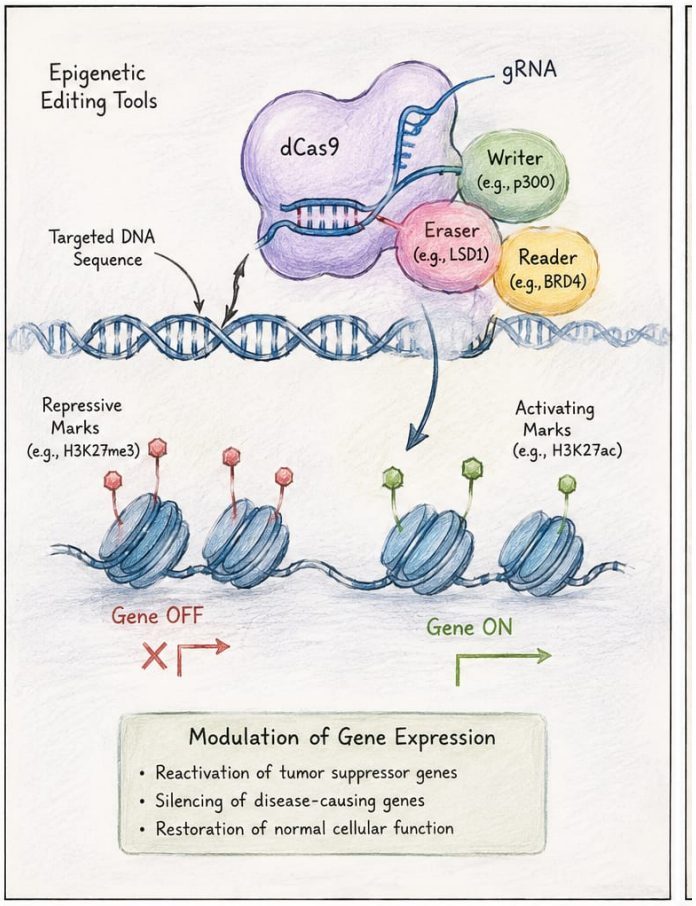


Figure 1. Epigenetic editing tools.

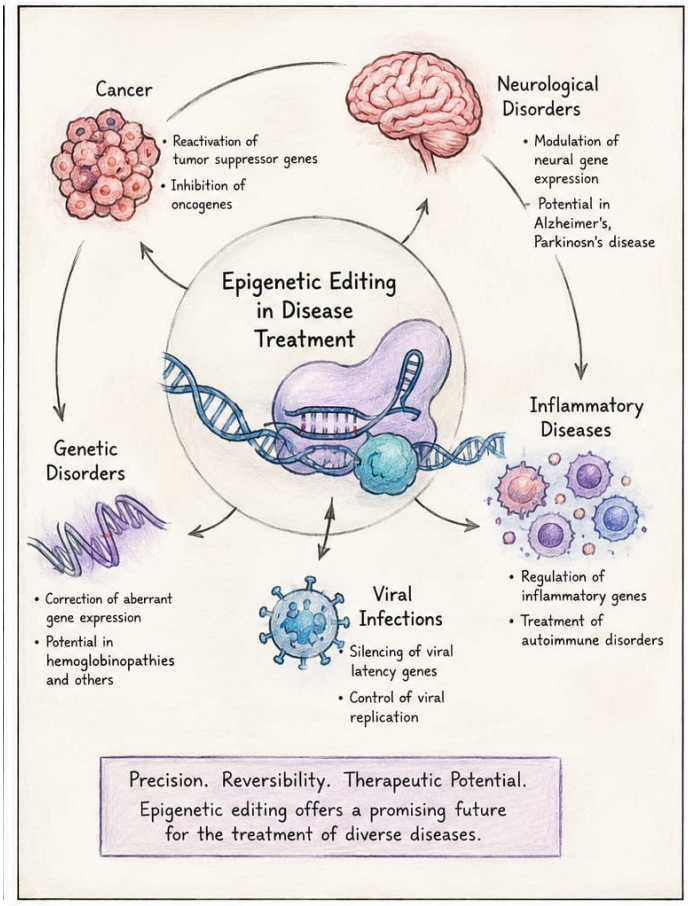


Figure 2. Epigenetic editing in disease treatment.

Table 1. Disease and epigenetic editing-based treatment.

Disease	Epigenetic editing-based treatment
Cancer	Reactivation of silenced tumor-suppressor genes and repression of oncogenes using targeted DNA methylation/demethylation and histone modification
Fragile X syndrome	Targeted demethylation of the *FMR1* promoter to restore gene expression
Rett syndrome	Targeted epigenetic activation to restore *MECP2* expression
Angelman syndrome	Epigenetic repression of *UBE3A-ATS* to reactivate the paternal *UBE3A* allele
Alzheimer's disease	Targeted modulation of neuronal genes through DNA methylation and histone modification
Parkinson's disease	Epigenetic regulation of neuroprotective and disease-associated genes
Sickle-cell disease / β-thalassemia	Epigenetic activation of fetal hemoglobin (HbF) production
HIV infection	Targeted epigenetic activation of latent viral genes or durable epigenetic silencing
Inflammatory diseases	Targeted repression of pro-inflammatory genes
Metabolic disorders	Correction of abnormal epigenetic regulation of metabolic genes

5 Advantages of epigenetic editing over conventional approaches

There are some benefits of epigenetic editing when compared to conventional gene-editing techniques. While conventional genome editing usually entails alteration of the DNA sequence, epigenetic editing involves modulation of the gene expression without any change in the DNA sequence itself. CRISPR epigenome editing utilizes DNA-targeting systems in order to induce changes in regulatory states without causing any double-strand break in DNA [1, 2].

One of the major benefits of epigenetic editing is a possibility of creating a reversible and programmable regulation of gene expression. By changing DNA methylation, histone modification and/or transcriptional states, epigenetic editors could activate or repress certain genes related to diseases without affecting the genetic sequence [1]. Moreover, epigenetic editing might enable a targeted manipulation of regulatory regions, which could provide a new method for gene expression restoration or blocking.

The other major benefit of epigenetic editing is its usage in personalized medicine. According to the recent findings, it becomes possible to target epigenetic abnormalities caused by particular diseases according to the molecular characteristics of individuals [3]. Durable gene silencing without DNA cleavage is already achieved [3]. However, specificity, delivery, durability and unwanted epigenetic side-effects should be considered [1, 4].

6 Challenges and safety concerns

However, despite the promising therapeutic applications of epigenetic editing, there exist certain barriers that should be overcome prior to the use of the method in the clinic. Epigenetic editors or the effectors domains of the editors can cause off-target effects and affect the expression of genes in unintended genomic locations [1]. Another important barrier to the application of the approach is the delivery problem since the editors have to be delivered to particular target organs and cells. Non-viral methods, such as viral vectors and lipid nanoparticles (LNPs), among others, are considered; however, the problems of delivering editors into particular tissues and their size pose additional problems [1, 2].

Another important characteristic of epigenetic editing is the persistence of epigenetic changes. Certain epigenetic changes are transient, while other changes can last through cell division and result in gene regulation lasting for a long time. Current research indicates that targeted epigenetic gene silencing can be persistent in vivo, which is important for the development of potential therapies [3]. Long-lasting changes can create epigenetic memory.

Also, since the various tissues have different epigenetic landscapes, the task of targeting the cell is difficult. An immune response to the Cas protein or the delivery vehicle can pose limitations to treatment [2]. In the case of safety issues, the long-term ones include improper gene regulation, cell behavior and differentiation, and tumor generation [1, 3].

7 Current clinical translation and future perspectives

Epigenetic editing is making advances from the lab stage to preclinical stage, but most targeted epigenome editing technologies are still in experimental phases. Some recent innovations in the field of CRISPR-mediated techniques have shown the ability to modulate certain genes without altering their DNA sequences; thus, their use as therapeutics in the future seems promising [1, 2]. However,

there is still need for validation of efficacy, delivery, specificity, longevity, and safety of epigenetic editing technology.

One important area of future research in epigenetics is personalizing epigenetic therapies by designing therapy based on genetic and epigenetic profile of an individual, disease subtype, and molecular markers. This would allow targeted manipulation of the disease-specific regulatory elements [1].

Use of combination therapies may also enhance the efficacy of epigenetic treatments. Epigenetic editing could potentially be used in combination with chemotherapy, immunotherapy, traditional targeted drugs, currently available epigenetic drugs, or gene therapy [3].

Advances in future technologies will help to enhance the efficacy of epigenetic editing via CRISPR editors, multiplex epigenetic control, better delivery systems, artificial intelligence in the targeting process, and single-cell epigenomics [1, 2]. Epigenetic editing tailored to individual patients will help in precision medicine as it will enable specific correction of aberrant gene regulation states without causing any harm.

8 Conclusion

Epigenetic mechanisms play an important role in the regulation of gene expression, cell differentiation, development, and function of tissues. Abnormal DNA methylation, histone modifications, chromatin remodeling, and non-coding RNA regulation lead to the pathogenesis of various diseases, including cancer, neurological, metabolic, cardiovascular, and inflammatory diseases [1, 2]. Therefore, epigenetic editing is a promising tool that allows for selective manipulation of gene regulatory states associated with diseases without altering DNA sequence.

Among existing technologies, CRISPR/dCas9 technology provides a possibility to specifically target certain loci of the genome and recruit epigenetic modifiers for gene activation or repression. This technology offers several benefits over the permanent alteration of the DNA sequence and may allow for a more precise control of the disease-associated genes [1, 3]. Diseases that are linked with gene silencing or activation are good targets for such therapy.

However, some difficulties still need to be addressed, such as efficient tissue targeting, off-target effects, durability of epigenetic modifications, cell type specificity, immune responses, and long-term safety [1, 3]. Future developments in CRISPR technologies, delivery methods, single cell epigenomics, and precision medicine may solve all these problems. In general, epigenetic editing has high potential to become a crucial part of disease treatment in the future.

References

[1] McCutcheon SR, Rohm D, Iglesias N, et al. Epigenome editing technologies for discovery and medicine. *Nature Biotechnology*. 2024;42:1199–1217.

[2] Thakore PI, Black JB, Hilton IB, et al. Editing the epigenome: technologies for programmable transcription and epigenetic modulation. *Nature Methods*. 2016;13:127–137.

[3] Portela A, Esteller M. Epigenetic modifications and human disease. *Nature Biotechnology*. 2010;28:1057–1068.

[4] Robertson KD. DNA methylation and human disease. *Nature Reviews Genetics*. 2005;6:597–610.

[5] Zhao S, Allis CD, Wang GG. The language of chromatin modification in human cancers. *Nature Reviews Cancer*. 2021;21:413–430.

[6] Smith ZD, Hetzel S, Meissner A. *DNA methylation in mammalian development and disease*. Nature Reviews Genetics. 2025.

[7] Wu X, Zhang Y. TET-mediated active DNA demethylation: mechanism, function and beyond. *Nature Reviews Genetics*. 2017;18:517–534.

[8] Millán-Zambrano G, et al. Histone post-translational modifications—cause and consequence of genome function. *Nature Reviews Genetics*. 2022;23:563–580.

[9] Li E. Chromatin modification and epigenetic reprogramming in mammalian development. *Nature Reviews Genetics*. 2002;3:662–673.

[10] Hananya N, Koren S, Muir TW. Interrogating epigenetic mechanisms with chemically customized chromatin. *Nature Reviews Genetics*. 2024;25:255–271.

[11] McCutcheon SR, Rohm D, Iglesias N, et al. Epigenome editing technologies for discovery and medicine. *Nature Biotechnology*. 2024;42:1199–1217.

[12] Villiger L, Joung J, Koblan L, et al. CRISPR technologies for genome, epigenome and transcriptome editing. *Nature Reviews Molecular Cell Biology*. 2024;25:464–487.

[13] Epigenome editing for targeted DNA (de)methylation: a new perspective in modulating gene expression. 2024.

[14] Goell JH, Hilton IB. CRISPR/Cas-based epigenome editing: advances, applications, and clinical utility. *Trends in Biotechnology*. 2021;39:678–691.

[15] McCutcheon SR, et al. Epigenome editing technologies for discovery and medicine. *Nature Biotechnology*. 2024;42:1199–1217.

[16] Mabe NW, et al. Pharmacological targeting of the cancer epigenome. *Nature Cancer*. 2024;5:844–865.

[17] Sharma R, et al. The role of epigenetic mechanisms in autoimmune, neurodegenerative, cardiovascular, and imprinting disorders. *Mini-Reviews in Medicinal Chemistry*. 2022;22:1977–2011.

[18] Grodzka O, et al. *Diagnostic and prognostic value of epigenetic markers in neurological diseases*. Cellular and Molecular Neurobiology. 2026.

[19] Keating ST, El-Osta A. Metaboloepigenetics in cancer, immunity, and cardiovascular disease. *Cardiovascular Research*. 2023;119:357–370.

[20] Epigenetic regulation and molecular mechanisms in cardiovascular diseases: a review of recent advances and therapeutic implications. 2026.

[21] McCutcheon SR, Rohm D, Iglesias N, et al. Epigenome editing technologies for discovery and medicine. *Nature Biotechnology*. 2024;42:1199–1217.

[22] Villiger L, Joung J, Koblan L, et al. CRISPR technologies for genome, epigenome and transcriptome editing. *Nature Reviews Molecular Cell Biology*. 2024;25:464–487.

[23] Cappelluti MA, et al. Durable and efficient gene silencing in vivo by hit-and-run epigenome editing. *Nature*. 2024;627:416–423.

[24] Minton K. Epigenetic editing works like a CHARM. *Nature Reviews Genetics*. 2024;25:600.

[25] McCutcheon SR, Rohm D, Iglesias N, et al. Epigenome editing technologies for discovery and medicine. *Nature Biotechnology*. 2024;42:1199–1217.

[26] Madigan V, Zhang F, Dahlman JE. Drug delivery systems for CRISPR-based genome editors. *Nature Reviews Drug Discovery*. 2023;22:875–894.

[27] Cappelluti MA, et al. Durable and efficient gene silencing in vivo by hit-and-run epigenome editing. *Nature*. 2024;627:416–423.

[28] McCutcheon SR, Rohm D, Iglesias N, et al. Epigenome editing technologies for discovery and medicine. *Nature Biotechnology*. 2024;42:1199–1217.

[29] Villiger L, Joung J, Koblan L, et al. CRISPR technologies for genome, epigenome and transcriptome editing. *Nature Reviews Molecular Cell Biology*. 2024;25:464–487.

[30] Mabe NW, et al. Pharmacological targeting of the cancer epigenome. *Nature Cancer*. 2024;5:844–865.

[31] McCutcheon SR, Rohm D, Iglesias N, et al. Epigenome editing technologies for discovery and medicine. *Nature Biotechnology*. 2024;42:1199–1217.

[32] Portela A, Esteller M. Epigenetic modifications and human disease. *Nature Biotechnology*. 2010;28:1057–1068.

[33] Villiger L, Joung J, Koblan L, et al. CRISPR technologies for genome, epigenome and transcriptome editing. *Nature Reviews Molecular Cell Biology*. 2024;25:464–487.