



Review Article

Expanding Role of Epigenetics in Human Health and Disease



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Abstract

The traditional definition of epigenetics encompasses all molecular pathways that affect how a genotype expresses itself on the way to a particular phenotype, with epigenetics serving as the interface between genotype and phenotype. Unlike genetic changes, which may have protracted, irreversible effects on health and the emergence of illnesses, epigenetic modifications are reversible and do not change the DNA sequence. However, they can affect how our bodies interpret DNA sequences. Gene expression regulated by epigenetics has emerged as a major contributing element to the etiology of many diseases over time and a crucial determinant of human health. One of the strongest arguments in support of gene expression controlled by epigenetics comes from the startling discovery that DNA methylation causes X-chromosome inactivation, which has been connected to several diseases. The intrinsic uterine environment, where the embryo and fetus grow and develop over time to become neonates is vulnerable to early epigenetic settings throughout development, affecting the offspring's long-term health as well as their predisposition for different diseases. The epigenetic settings of germ cell development are influenced by environmental factors, which can result in transgenerational epigenetic effects. Therefore, in this article, we essentially provide a summary of the present level of understanding concerning the function of epigenetics regarding critical facets of human health, including in embryonic development and adulthood, with a particular emphasis on explaining the underlying diverse epigenetic mechanisms that regulate the onset of many human diseases, as well as cutting-edge technological tools used to study the human epigenome. Finally, we talk about the state of epigenetic therapies, which might be put to use in the treatment of a range of human diseases.

Introduction

Conrad H Waddington's early 1940s definition of epigenetics states that the term's original definition encompasses all molecular pathways that affect how a genotype expresses itself on the way to a particular phenotype, with epigenetics serving as the interface between genotype and phenotype.¹ The current definition of epigenetics, which is universally accepted among biologists, is the in-depth examination of heritable alterations in gene activity during mitosis and/or meiosis, however, without ever changing the sequence of the DNA.² For instance, a wide range of progressive epigenetic changes ensures the development of a healthy individual.^{3–5} The evidence that critical epigenetic reprogramming events occur in mammals while germ cells are forming as well as dur-

ing the early stages of embryogenesis reinforces this.^{6,7} In plain language, epigenetics is the study of how environmental factors, such as diet, specific nutrients, poverty, ultraviolet radiation, *etc.*, affect how an individual's genes function.^{8,9} Contrary to genetic alterations, which may have enduring, irreversible effects on health and the onset of diseases, epigenetic modifications are changeable without altering the sequence of DNA but can affect how our bodies interpret DNA sequences.^{10,11} Even though every cell in an organism has essentially the same DNA, there are distinct differences in terms of cell types and their functions. These alterations in gene expression, which are predominantly caused by qualitative and quantitative variations, are mediated by *cis*- and *trans*-acting factors, including transcription factors (TFs) that affect cellular differentiation and development and are under epigenetic control.^{12,13} It is generally believed that epigenetic mechanisms like DNA methylation and chromatin modifications (including different RNA-mediated processes, *e.g.*, noncoding RNAs), primarily affect the expression of genes, specifically transcription as well as at post-transcriptional, translational, and/or post-translational levels; since those processes are all regulated by epigenetics, they cause cell-specific gene expression patterns and have an impact on the overall development of the organism.^{14–18}

Keywords: Epigenetic; Diseases; Public health; Chromatin; Transcription.

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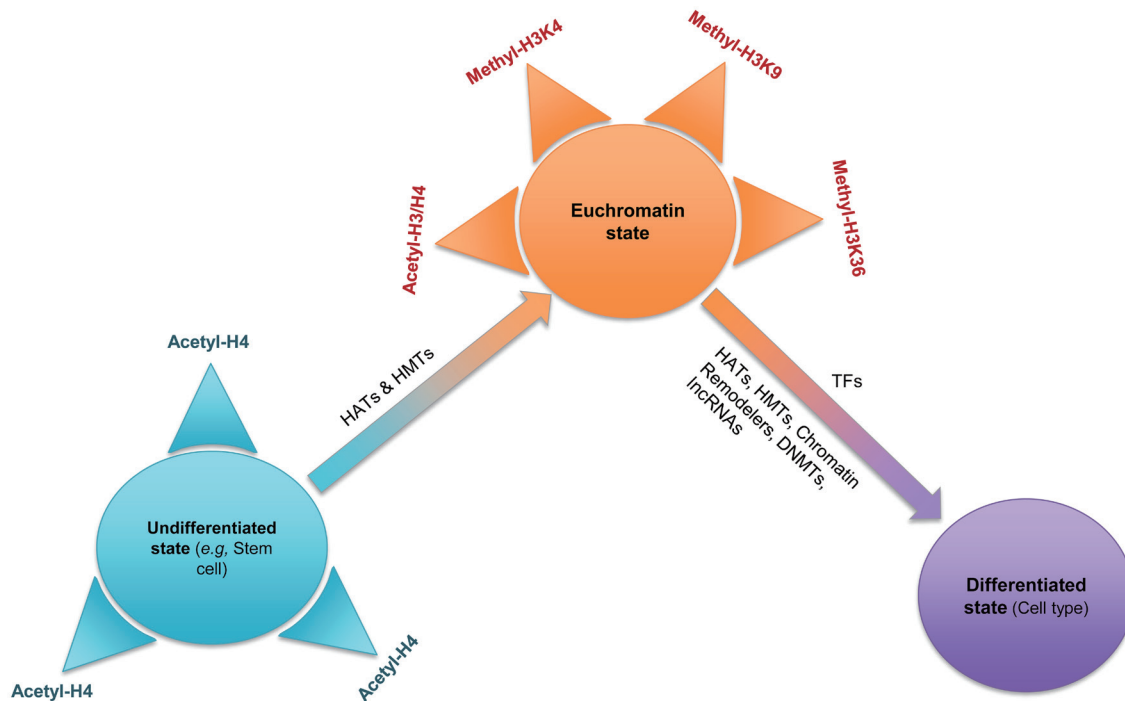


Fig. 1. Synopsis of basic epigenetic mechanisms governing the transformation of a cell type from an undifferentiated to a differentiated state. A few significant post-translational histone modifications produced by effector enzymes including chromatin remodelers, histone acetyl transferases (HATs), histone methyl transferases (HMTs), and DNA methyltransferases (DNMTs) are shown. Cell-specific transcription factors (TFs) work in tandem with epigenetic machinery to steer the course of an undifferentiated cell type during a transcriptional pause, such as the euchromatin state, in order to attain biological functions characteristic of a differentiated cell type. lncRNA, long noncoding RNA.

History of epigenetics

As stated above, the British developmental biologist, embryologist, and geneticist Conrad H Waddington, who worked at Cambridge University, first introduced the phrase epigenetics in 1942.¹ Waddington did not, however, know at the time that genes existed or that they played a hereditary role. In accordance with this, a second theory concerning the existence of epigenetics, advanced by David L Nanney in 1958, pushed the field's definition and improved its comprehension to where it is today.¹⁹ Nanney postulated the presence of two systems that regulate cells. While one system primarily depends on DNA-template-driven transcription, which is genetic, the other system envisions a complementary system with vastly different operating principles that primarily regulates which data is represented in a specific cell based on epigenetic regulation. However, the conception of epigenetics by these two pioneering researchers ran counter to Muller's initial findings in 1930 from his seminal research examining deletions, inversions, translocations, and in *Drosophila melanogaster* chromosomes exposed to radiation which firmly indicated that not having any additional genetic alterations like mutational changes in the DNA or epigenetic changes; importantly, the mere gene positioning inside the genome could alone alter the expression of the gene.²⁰

Hannah, in 1951, was able to correctly interpret the variegation effect (juxtaposition of euchromatin and heterochromatin) as observed by Muller and support the crucial role of epigenetics in gene expression by claiming that specific genes in the genomic regions that are euchromatic were moved to the heterochromatic regions of the genome, altering the way the genes behaved in their

previous location.²¹ Interestingly, long before the term epigenetics was coined and recognized, Darwin and Kant's theories indicated that the surroundings played a significant part in strictly regulating the phenotypic changes of an organism, resulting in the idea of the concept of evolution.²²

The Mendel's principles, which were developed in 1865, solidified the ideas of heredity and genetics.²³ Isolation of the DNA molecule in 1869 by Friedrich Miescher, a Swiss scientist who wanted to study the chemistry of cells, also contributed.²⁴ Finally, the DNA double helix structure was determined by Watson and Crick in 1959, about a century later.²⁵ These findings collectively supported and validated the original epigenetics theory, according to which genetics can then provide the framework for epigenetics to explain how environmental factors affect the genome.

Importantly, Waddington created his iconic representation of the epigenetic landscape in 1957, demonstrating how a cell, in analogy to a ball, might take distinct routes based on the surface unevenness that effectively mirrors environmental factors inside and outside of cells.²⁶ This idea essentially demonstrates how a cell changes throughout development from an undifferentiated state to one of several distinct, individual, differentiated cell fates, which are controlled by epigenetic mechanisms (Fig. 1).

Furthermore, several research teams discovered that effective embryogenesis required the union of male and female gamete genomes. This resulted in determining imprinted genes, which are controlled in a sex-specific manner as a result of genomic imprinting potentiated by epigenetic processes, and resulted in the variable level of gene expression based on the parent from whom it came.²⁷ X-chromosome inactivation (XCI) was first observed in mammals in 1961 and is a mammalian paradigm of transgenerational

epigenetic transmission that silences genes only on the paternally inherited X chromosome; as such, it is a notable instance of epigenetics-induced imprinting on the genome.^{28,29} Both Prader-Willi and the Angelman syndromes, which map to human chromosome 15q11-q13, include alterations of the imprinted genes' expression caused by the methylation of DNA.³⁰

The characterization of the nucleosome's structure by Kornberg and Thomas in 1974 also marked a significant advance in the study of epigenetics.³¹ The identification of the double helix structure in DNA also led to the identification of other significant chromatin alterations, like DNA methylation (5-methylcytosine, 5mC) and post-translational histone modifications (PTMs). Indeed, methylation, acetylation, phosphorylation, ubiquitylation, and sumoylation of histones, and adenosine diphosphate (ADP) histone ribosylation were documented between 1962 and 1977. DNA methylation was first identified in 1965.^{32,33} It is important to note that Jenuwein and Allis' seminal work at the University of Virginia, where his team discovered the histone code in 2001, has made it easier to decipher the biological significance of these PTMs.³⁴

It is also crucial to remember that not all epigenetic alterations as described in the literature are heritable and that some of them might only be transient. The fact that monozygotic twins have similar epigenomes in their early years of life yet display significant changes in their epigenomes as they become older is proof that the epigenome is metastable and exhibits temporal variability.^{1,35-38}

Table 1 contains a timeline of important events in the development of epigenetics.^{1,16,21,26,28,31,34,39-58}

Fundamental knowledge of the epigenetic control of gene expression

Over the years, the control of gene expression by epigenetic means has become recognized as a significant essential route in the pathogenesis of numerous diseases.^{3,59-62} Also, there has been an explosion of data revealing the epigenetic mechanisms regulating health and disease.

DNA methylation

A number of physiological and pathological processes are controlled by methylation of DNA, and aberrant methylation of DNA is often linked to the emergence of many diseases as well as to adaptations like the concept of Developmental Origin of Health and Disease (DOHaD).^{1,10,12,16,17,38,42,43,63}

DNA methylation affects DNA repair processes

Genomic regions abundant in patterns made up of a cytosine nucleotide coming before a guanine nucleotide are referred to as cytosine-phosphate-guanine (CpG) islands.⁶⁴ The most common way to influence biological processes through DNA methylation is dynamic modulation concerning the CpG islands' methylation state in any particular gene's regulatory region. The specific nucleotide and location of its methylation varies between types, despite the fact that methylation of the DNA is thought to exist in every organism.⁶⁵ In humans, methylation of a cytosine nucleotide occurs when it is located directly 5' to a guanine nucleotide. Despite the fact that both methylated and unmethylated cytosines can spontaneously deaminate under physiological conditions, DNA repair mechanisms accurately repair unmethylated cytosine's conversion to uracil, maintaining the CpG dinucleotide in the island. However, when methylated cytosine is deaminated, thymine is produced, which DNA repair mechanisms cannot recognize, and cannot repair.⁶⁶ As a result, over time these defects may reduce

the frequency of the human genome's CpG dinucleotides, disrupting the islands constituted of CpGs and causing adverse effects on health, ultimately resulting in diseases.⁶⁷

DNA methylation regulates gene transcription, controlling health and disease

When a key regulatory region of the gene such as a promoter containing CpG islands is hypermethylated, the chromatin is often compacted or closed, resulting in transcriptional inactivation of relevant genes. Due to the compacted chromatin, TFs can be inhibited from attaching to the DNA. Moreover, the proteins binding methyl-CpGs have a greater affinity for the promoter sequence, as opposed to a specific TF, when methylation occurs in a promoter region containing cytosine.⁶⁸ The binding proteins of methyl-CpG also collaborate with other proteins to form a complex that has histone deacetylase (HDAC) activity.⁶⁹ This complex then causes euchromatin (an open chromatin structure) to adopt a closed conformation, becoming heterochromatin, which prevents TFs from accessing the promoter sequence and repressing transcription of that gene. By contrast, CpG island hypomethylation causes a euchromatic state, which is frequently associated with the transcriptional activation of genes.⁷⁰⁻⁷² Additionally, CpG island hypermethylation occurs as part of regular physiological processes, such as XCI in females.²⁸ Also, while repeating sequences like satellites and long interspersed nuclear elements, *Arthrobacter luteus* infection, *etc.*, contribute to a variety of physiological processes, they can cause chromosomal instability that can be avoided by hypermethylation of repetitive DNA elements.⁷³

Key roles of DNA methyltransferases in the DNA methylation of the gene

DNA methyltransferases (DNMTs) assist in modifying cytosine in organisms, producing 5mC. Five DNMTs have been identified within the genome to date, namely DNMT-(1, 2), DNMT-(3a, 3b), and DNMT3L. The canonical DNA methyltransferases 1, 3a, and 3b directly add methyl groups to cytosine by catalysis.^{16,17,42,50-52} However, DNMT2 lacks the large N-terminal domains found in the DNMT-(1, 2, 3) families that is otherwise essential for methylating DNA and/or RNA.

Chromatin modification

Gene regulation and expression depend on chromatin structure and are accomplished by bringing in various chromatin-modifying complexes.⁷⁴⁻⁷⁶ For instance, the euchromatin state of embryonic stem cells is an illustration of the particular chromatin organization, which enables accessibility for the expression of all genes globally and makes it easier to reprogram a cell to become pluripotent.⁷⁷

Diverse types of PTMs regulate gene expression

Nucleosomes, or DNA with 146 base pairs surrounding an octamer of histone proteins made up of two molecules of each histone (H2A, H2B, H3, and H4), make up about 99% of the genome. Using data from mass spectrometry and specific antibodies, Kouzarides *et al.*⁷⁸ were able to provide a thorough discussion of a variety of chromatin alterations, such as acetylation, phosphorylation, lysine/arginine methylation, deimination, ubiquitylation, sumoylation, and ribosylation of the ADP; each of these alters the DNA-histone interactions in nucleosomes. The complex network of distinct histone residues that are methylated, demethylated, acetylated, phosphorylated, dephosphorylated, and even methylated and acetylated between each other gives rise to a histone code.³⁴

Acetylation of histones usually occurs at lysine residues that

Table 1. Timeline of significant events in the history of epigenetics

Year	Key finding
1759	Theory of epigenesis by CF Wolff. According to the epigenesis theory, structures that have not yet (pre-) developed emerge throughout development. ³⁹
1802	JB Lamarck proposed that the environment might directly and heritably alter phenotype. ⁴⁰
1879	Cytologist W Flemming coined the term chromatin to refer to the structure of the stainable cell nucleus, later referred to as chromosomes, which were visible when cells divided. ⁴¹
1898	Discovery of a nucleotide known as tuberculinic acid that is not recognized as a prerequisite to the identification of DNA methylation. ⁴²
1942	The term epigenetics was coined to clarify how genes interact with the surroundings to develop an organism's physical characteristics. ¹
1951	First isolation of 5-methylcytosine from nucleic acids. ⁴³
1957C	Waddington creates a model of the epigenetic landscape to demonstrate how cells make decisions during biological development. ²⁶
1961	For the first time, genes associated with X-chromosome inactivation were found in female mouse embryos. ²⁸
1962	Discovery of histone methylation. ¹⁶
1964	Discovery of histone acetylation. ⁴⁴
1965	Discovery of DNA methylation. ⁴²
1974	First structural resolution of a nucleosome. ⁴⁵
1975	Identification of histone phosphorylation; DNA methylation proposed as a process for the embryonic silencing of the X-chromosome; The idea that DNA methylation may regulate gene expression was proposed by Holliday and Riggs. ^{28,46,47}
1977	Discovery of histone ubiquitylation; Franklin and Zweidler used acid-urea-Triton X polyacrylamide gel electrophoresis to extract histone variants from human tissues for the first time. ^{48,49}
1981	The first proof that DNA methylation is responsible for X-chromosome silencing. ²⁸
1982	Discovery of bromodomain and prions. ^{31,50}
1985	DNA methylation takes place on particular DNA regions known as CpG islands. ⁴²
1988	Cloning of the first enzyme found in mammals that catalyzes the addition of a methyl moiety to DNA, or DNA methyltransferase, or DNMT. ⁵¹
1992	SIRT1, discovery of a NAD ⁺ -dependent deacetylase; A technique was developed to determine which particular DNA strands contain a methylated cytosine, opening the door to perform DNA methylation genome sequencing; To examine the connection between disease and methylation of DNA, the initial transgenic mouse model was developed. ^{44,47,51}
1995	The first conclusive study to show that decreased methylation of DNA resulted in the onset of cancers. ⁵²
1996	Discovery of histone acetyl transferase and histone deacetylase. ⁴⁴
1997	Discovery of RNA interference and DNMT1. ⁵¹
1999	The first demonstration in mammals is that epigenetic alterations may be propagated through generations; Colorectal cancer was linked to DNA methylation of CpG islands. ^{53,54}
2001	The first chromodomain-containing protein, heterochromatin protein 1, was reported to explain position effect variegation in <i>Drosophila</i> , a phenomenon that occurs when an active gene is translocated into the heterochromatin environment, resulting in gene suppression; A particular subclass of ncRNA called miRNA was discovered in vertebrates. ^{21,34,55}
2004	Identification of first histone demethylase. ⁵⁶
2011	Modification of histone proteins could be another method of epigenetic inheritance. ⁵⁷
2014	Most current definitions of epigenetics, according to Felsenfeld <i>et al.</i> , never make a distinction between circumstances as the modifications may be passed down during cell division, aiding in the maintenance of a particular gene expression pattern, and in circumstances where the changes are merely a component of the transcribing apparatus. ⁵⁸

CpG, cytosine-phosphate-guanine; DNMT, DNA methyltransferase; miRNA, microRNA; ncRNA, noncoding RNA; NAD, nicotinamide adenine dinucleotide; SIRT1, silent mating type information regulation 2 homolog 1.

have positive charges, loosening the bond between DNA and histones and allowing transcription by opening up the chromatin.⁷⁹ For example, transcriptional activation is associated with acetylation of H3's lysines 9 and 27, which are designated as H3K9ac and

H3K27ac, respectively.^{80,81} Methylation of a histone, by contrast, is more complex since it may entail adding 1–2 methyl groups to an arginine and 1–3 methyl groups to a lysine while maintaining the charge of the histone protein.⁸² As an illustration, lysine 27

trimethylation on H3, designated as H3K27me3, results in inhibition of transcription while lysine 4 methylation on H3, designated as H3K4me, is linked to gene activation.^{83,84} Moreover, histone phosphorylation adds a negative phosphate group to the histone tail; however, its function is largely unknown apart from its role in response to DNA damage and subsequent repair caused by H2A histone family member X phosphorylation.⁴⁷ Allis's group has shown that the H2AX variant is also phosphorylated on tyrosine (Y) 142 and that this modification is controlled in a way that depends on DNA damage.³⁴ Moreover, histone phosphorylation has also been shown to be connected with transcription regulation. For instance, regulation of transcription of epidermal growth-factor responsive genes is linked to serine phosphorylation at the 10 and 28 residues of H3 and H2B's serine 32.⁸⁵ In addition, a large ubiquitin molecule can be inserted into the lysine residues on histones. Examples of ubiquitylated histones are H2AK119ub, which is associated with gene silencing, and H2BK123ub, which is connected to transcription activation.^{86,87} Also, PTMs on histone proteins can be conjugated to small ubiquitin-like modifiers that dynamically alter chromatin structure and gene expression. Even though it was originally believed to only suppress gene transcription, recent evidence seems to point to diverse roles for histone sumoylation in cotranscription mechanisms, namely chromatin reorganization, extension of transcription, and avoiding cryptic transcription.^{88,89} Also, ADP-ribosylation of histones has been demonstrated in studies to be associated with histone acetylation, methylation, and phosphorylation, and to have important roles in DNA repair, replication, transcription, and cell proliferation.⁹⁰⁻⁹²

Energy-dependent chromatin remodeling complexes alter chromatin function

Cells are equipped with additional highly regulated epigenetic mechanisms that are mediated by chromatin remodeling complexes that use adenosine triphosphate (ATP) for their activity.^{75,76} The majority of evidence for the four families of chromatin remodeling complexes that use ATP-SWI/chorizo nonfermentable, imitation SWI/Sucrose Non-Fermentable, INO80, and chromodomain-helicase-DNA binding has come from their structural similarities. Chromatin remodelers can catalyze a wide variety of chromatin structural changes, such as nucleosome sliding, which causes histone variant exchange.⁹³ As an illustration, it has been demonstrated that the ATP-reliant chromatin remodeling complexes' nucleosome remodeling factor SWI2/Sucrose Non-Fermentable 2-related 1 chromatin remodeling complex catalyzes the transfer of the H2A variant H2AZ and the histone octamer sliding along the DNA, respectively, to promote transcription.⁹⁴

Noncoding RNAs control human health and disease

The largest number of transcripts in the human genome that are highly transcribed are noncoding RNAs (ncRNAs), which represent the greatest majority of transcripts.⁹⁵ Three distinct ncRNAs form [microRNAs (miRNAs), long noncoding RNAs (lncRNAs), and circular RNAs (circRNAs)] have a significant impact on human health as well as the development of diseases.^{96,97}

MiRNAs control chromatin activity by interacting with the methylation process of DNA and histone alteration

Small ncRNAs known as miRNAs, which range in length from 18 to 25 nucleotides, are becoming increasingly recognized as one of the main epigenetic regulators in eukaryotes.⁹⁸ The global miRNA database, miRbase, currently lists references for more than 2,500 miRNAs. MiRNAs produced by Drosha and Dicer in two sequen-

tial cleavage steps from defective hairpin conformations are seen in precursors of lengthy ncRNAs or intronic segments of DNA of coding or noncoding genes.⁹⁹ Although the precise mechanism by which miRNAs downregulate protein translation is still unknown, it may include degradation of mRNA, inhibition of translation, or a blending of these processes together. Furthermore, epigenetic changes such as methylation of DNA, modification of RNA, and modification of histones can affect how miRNAs are expressed.¹⁰⁰ Also, an miRNA-epigenetic feedback loop that promotes reciprocal communication can be established by miRNAs targeting epigenetic modifier enzymes involved in epigenetic modifications. For instance, miR-9 is a notable miRNA that is regulated by epigenetic mechanisms. Its regulation has been linked to hypermethylation of a CpG island across the miR-9 locus. Many cancers, including solid tumors in the breast, colon, and other organs, along with hematological malignancies like acute lymphoblastic leukemia, exhibit miR-9 hypermethylation.^{101,102}

The structure and function of chromatin are regulated by lncRNAs

RNAs that exceed 200 nucleotides in length but do not encode proteins are known as lncRNA transcripts. Given the multitude of ways that lncRNAs might work, one way to group them involves the way that they operate, *i.e.* as a signal, decoy, guide, scaffold, enhancer, or sponge lncRNAs.¹⁰³

Signal lncRNAs

In general, signal lncRNAs respond to particular physiological and environmental cues to modulate downstream genes and exhibit expression according to cell type, either on their own or in conjunction with specific TFs, PTMs, and histone-modifying enzymes.¹⁰³⁻¹⁰⁵ For instance, XCI is assisted by the well-known lncRNA X-inactive specific transcript in a biological process by which one of the two X-chromosomes in female cells becomes inactivated to balance the genes' expressions in mammalian males and females.¹⁰⁶ Additionally, signal lncRNAs have the ability to control chromatin dynamics because their negative changes can balance out positively charged histone tails, causing chromatin to decompact (go from heterochromatin to euchromatin) and potentiating gene activation.¹⁰⁷

Decoy lncRNAs

lncRNAs have the potential to function as a kind of chromatin decoy by, among other things, preventing some chromatin modifiers from interacting with the promoters of target genes.¹⁰⁸ For instance, the lncRNA lncPRESS1 sequesters the HDAC sirtuin 6, a deacetylase that causes gene repression, away from the promoters of several pluripotency genes, allowing human embryonic stem cells to retain their pluripotency and become transcriptionally poised towards cellular factors.¹⁰⁹

Guide lncRNAs

Guide lncRNAs direct regulatory proteins to their target sites in subcellular locations where they attach to them to form ribonucleoprotein molecules, causing expression or silencing of the target genomic regions.⁹⁵ This could entail chromatin-modifying enzymes being recruited, which then alter the state of the chromatin by forming intricate complexes among RNAs, RNA-DNA hybrid molecules, and effector proteins-RNA-DNA. As an illustration, the polycomb repressor complex 2 attaches to the lncRNA HOX transcript antisense RNA 5'-domain, which then triggers DNA methylation and gene silencing. On the other hand, the 3'-domain interacts with the complex of lysine demethylase/RE1 silencing

transcription factor and causes the removal of methylation marks from the gene, which activates transcription.¹¹⁰

Scaffold lncRNAs

Scaffold lncRNAs have a range of binding sites that allow them to form functional complexes with additional proteins that mediate transcriptional activation or repression. A well-known example of a scaffold lncRNA is the telomeric repeat-containing RNA, an element of telomeric heterochromatin that interacts with telomerase RNA to suppress telomerase activity.^{95,111} As a result, lncRNA telomeric repeat-containing RNA-expressing cells are accelerated toward an early stage of senescence.

Enhancer lncRNAs

Enhancer lncRNAs function *in cis* to control target gene expression by bringing remote enhancers close to the promoter region containing the basal transcriptional machinery by binding, as a result of facilitated long-distance communication between the enhancer and promoter.¹¹² An enhancer lncRNA called lncRNA enhances endothelial nitric oxide synthase (eNOS) expression, which increases endothelial nitric oxide synthase (commonly known as eNOS) level, can aid in RNA polymerase II recruitment to the eNOS promoter, which augments the transcription of eNOS precursor RNA.¹¹³

Sponge lncRNAs

There is growing evidence that lncRNAs can perform as miRNA sponges and face off against protein-coding transcripts for miRNA binding. Because sponge lncRNAs and miRNAs have complementary sequences, they can bind to each other and restrict the amount of miRNAs that transcription machinery can access to control the transcription of target genes.¹¹⁴ For instance, the sponge lncRNA phosphatase 1 nuclear targeting subunit has seven sequences that are complementary to miRNA-205, decreasing the capacity of miRNA-205 to attach and repress the mRNAs of the zinc finger E-box-binding homeobox 1 and zinc finger E-box-binding homeobox 2.¹¹⁵

CircRNAs

Single-stranded nucleotide molecules with covalent encapsulation that lack 3' poly A tails or 5' caps, unlike mRNAs, are known as circRNAs.^{95,103} The size of the spliced circle molecule might range from less than 100 nucleotides to more than 4 kb. Similar to lncRNAs, sponging miRNAs represent one process whereby circRNAs regulate post-transcriptional gene expression in the cytoplasm of a cell. However, very few research studies have revealed that circRNAs function by means of interacting with proteins. In addition to the several other potential methods of action, circRNAs can recruit TFs, chromatin-modifying enzymes, and enzymes that modify DNA or histones to alter gene expression, either activating or inhibiting it.¹¹⁶

Importance of epigenetics in embryonic development and adulthood

Despite the long-held belief that an individual's phenotype is primarily determined by means of their parents' genetic code, more acceptance is coming forth for the idea that genetic code-determined phenotypes can be further modulated by a variety of epigenomes that arise during development as a result of epigenetic plasticity established during the initial stages of embryogenesis.¹¹⁷ The intrinsic uterine surroundings, wherein the embryo, fetus, and

neonate develop over time, are susceptible to the early epigenetic settings throughout development, affecting the long-term health of the offspring as well as their propensity for various disorders.¹¹⁸ In fact, environmental factors that affect the epigenetic setting of germ cell development may cause some of these modifications to be passed down through generations. They all work together to explain DOHaD.¹¹⁹⁻¹²²

Epigenetic processes direct embryo development

The process of rapid cell proliferation causing embryo growth begins with the formation of a single-cell embryo (zygote) produced by the fertilization of an ovum by a sperm.¹²³ The cells that are produced initially all possess the unique ability known as totipotency, which allows them to develop into every kind of specialized cell found in the embryo, membranes outside the embryo, and the placenta. While an embryo's cell population grows, it gradually starts to differentiate, giving rise to distinct cell populations (pluripotency to multipotency).¹²⁴ Each of these groups exhibits an increasingly narrower variety of developmental results, primarily mediated through a range of epigenetic mechanisms, which when combined give rise to permanent gene expression patterns that are unique to a particular lineage.¹²⁵ At about the 5th-day mark after fertilization the human embryo, which has between 50 and 150 cells and is made up of the trophoblast and an inner cell mass, transforms into a blastocyst.¹²⁶ Trophoblast cells have a very limited capacity to differentiate because they can only become the various cell types seen in the placenta. As a result, they are regarded as multipotent cells. On the other hand, the inner cell mass has a rich collection of pluripotent stem cells that are embryonic in nature, able to develop into a variety of genuine fetal cell types since they have unconstrained developmental potential. Implantation is the process of the blastocyst embedding into the endometrial lining of the uterus, which generally occurs in week 2 of development.¹²⁷ Typically, the human blastocyst implants in the endometrium. Early implantation begins with the blastocyst adhering to the uterine wall, which is known as apposition. Next, the blastocyst attaches to the receptive endometrium, which is known as adhesion, and finally, the attached blastocyst invades the endometrial stroma by crossing through the endometrial epithelial basement membrane, a process known as invasion.¹²⁸

Impact of epigenetic changes on preimplantation embryo development

While early literature focused solely on the substrates and culture conditions required for embryonic development, particularly in the context of *in vitro* fertilization, more recent findings suggest that the epigenome can be changed by the surrounding environment, which can then influence developmental competence by affecting embryo metabolism, *etc.*¹²⁹ Aside from the metabolic effect, epigenetic reprogramming and modification provide critical molecular functions during embryonic development, primarily by regulating expression of genes that determine cell fate by influencing cellular differentiation and stabilizing monoallelic gene expression at critical loci.¹²⁰ CpG methylation has had its function studied in epigenetic reprogramming among numerous species, and new research is unraveling the collaborative roles among CpG methylation, chromatin changes, and ncRNAs when altering the early epigenetic landscape during embryonic development.¹³⁰ Zygotic genome activation (ZGA) occurs after zygote formation in initial embryonic growth and is another important aspect of preimplantation embryonic development, which is controlled by epigenetic processes.¹³⁰ Histone alterations not only help to establish totipo-

tency but are also important in ZGA. During ZGA, gene activation markers like trimethylated H3 lysine 4 are more prevalent among humans, whereas gene inactivation markers like H3 lysine 27 (H3K27me3) are less prevalent.¹³¹

Embryo implantation is dependent on epigenetic regulation of the endometrium

The endometrium and the embryo that is implanting communicate with one another throughout the highly regulated process of implantation; this is necessary for establishing and maintaining the pregnancy and is highly reliant on endometrial receptivity.¹²⁷ For instance, the endometrium's regenerative capacity is extraordinary in that it thickens to a depth of 5–7 mm within a cycle, up from 0.5–1 mm following menstruation.¹³² As a result, the endometrium necessitates the active engagement of mechanisms like angiogenesis, as controlled by TFs along with epigenetic processes such as methylation of DNA and chromatin modifications.¹³³

Adult development is linked to epigenetic processes

Recent studies appear to support the idea that epigenetics related to age is more significant than genetics in deciding which body genes express themselves, which in turn influences a person's vulnerability to specific diseases.⁵ For instance, age-related changes in methylation of DNA patterns have been noted. In addition, variations in histone modifications with aging can affect the genomic stability needed to maintain physiologically appropriate processes. Recent studies have also revealed that human classical CD14+CD16 monocytes age regularly, with H3K27me3 declining and H3K27me1 increasing; this is yet another example of how epigenetics has a major impact on controlling the physiological fitness of health as people age.¹³⁴

Methods of analyzing chromatin's DNA methylation patterns

DNA methylation involves the addition of a methyl group to a certain base pair by chemical means. Conversion based on bisulfite, enrichment based on affinity, and together with approaches based on restriction enzymes can all be used to evaluate DNA methylation across the entire genome. The term whole-genome bisulfite sequencing refers to the process that entails sequencing the entire DNA sample following bisulfite treatment. In contrast, reduced representation of bisulfite sequencing enriches between 1% and 5% of the genome with rich CpG density using restriction enzymes, bisulfite conversion, and size selection.¹³⁵ Enriched genomic interest regions by targeted sequencing utilizing special bisulfite padlock probes or hybridization capture probes such as TruSeq Methyl Capture EPIC made by Illumina Corporation (San Diego, CA, USA) is a more versatile but also more expensive method. Additionally, the Pacific Biosciences (Menlo Park, CA, USA) platform has developed long-read sequencing, which enables direct detection of DNA base modifications like cytosine during sequencing.¹³⁵ Moreover, nanopore sequencing is another innovative sequencing method that has the ability to distinguish between methylation and unmethylated cytosines. Affinity enrichment, on the other hand, uses a binding protein against methylcytosine or antibodies directed against 5 mC followed by sequencing as a substitute for converting DNA methylation status by bisulfite conversion.^{135,136}

Chromatin immunoprecipitation (ChIP) methods to examine DNA-protein interactions

ChIP is a widely used method to examine DNA-protein interactions, including histone modifications. This technique makes use

of antibodies with a particular affinity for binding to desired histone modifications. ChIP, subsequent to sequencing, in the method known as ChIP-seq, is the principal approach for evaluating the epigenome's overall state of histone marks.^{92,137,138} ChIP-exo is an improvement over ChIP-seq that enables binding site resolution to be increased to a single base from hundreds of base pairs. Although more expensive, ChIP-nexus is essentially an enhanced edition of ChIP-exo that uses an intramolecular ligation approach for library preparation that is more effective. ChIPmentation is a method that immediately tags ChIP fragments with Tn5 transposase and is then followed by sequencing; this approach lowers the cost and input requirements of regular ChIP-sequencing. Also, cleavage under targets and release using a nuclease is a different approach for histone profiling that has lately grown in favor because it requires less sample DNA input. In contrast, cleavage under targets and tagmentation with Tn5 (a fusion protein of protein A and transposase) involves loading with sequencing adapters to address some of the drawbacks of cleavage under targets and release using a nuclease. The latter typically results in DNA loss caused by micrococcal nuclease digestion.

Methods of analyzing chromatin structural patterns

Genomic regions vary regarding nucleosome occupancy and the DNA's accessibility to proteins. To quantify these traits across the genome, numerous techniques have been devised. Sequencing targeting DNase I hypersensitive sites and deep sequencing using micrococcal nuclease digestion were the first of these techniques to be established.¹³⁹ Another comparable test that considers genomic DNA within a euchromatic state specifically vulnerable to sonication-assisted shearing is the identification of regulatory elements by using formaldehyde subsequent to sequencing. Additionally, the transposase-accessible chromatin using sequencing (ATAC-seq) technique is the most recent method to examine chromatin accessibility.¹⁴⁰ By using tagmentation, ATAC-seq is the fastest and highest sensitivity among all existing techniques and significantly decreases the amount of input DNA required.

Chromatin conformation capture methods to investigate long-distance genomic sequence interactions

Moreover, across the genome, regulatory elements engage in long-distance interactions. Different crosslinking and ligation-based approaches with differing degrees of coverage and specificity have been developed to detect and characterize them across the entire genome. For instance, chromatin conformation capture is an innovative approach that relies on ligating and crosslinking physically interconnected chromosomal areas.¹⁴¹ Reversal of the crosslinking produces fragments of linear DNA. The characterization of interconnecting domains from various chromosomes can then be carried out downstream using a variety of techniques. Hi-C is a whole-genome implementation of chromatin conformation capture, which exploits next-generation sequencing for high-throughput measurement among every chromatin interaction. In addition, techniques like HiChIP, which combines Hi-C with ChIP, and analysis of chromatin interactions via a method known as paired-end tag sequencing are also used to explore the long-distance interactions of specific chromatin regions.¹⁴²

Multomics assays to investigate epigenetic alterations

Recent years have observed the growth of a number of multiomics assays for the simultaneous characterization of numerous epigenomic levels across the genome.¹⁴³ For instance, measurement of both DNA methylation and chromatin accessibility can be per-

formed simultaneously in the same sample using a technique known as nucleosome occupancy methylome sequencing. EpiMethylTag is a different technique that combines ATAC-seq or ChIP-seq, known as M-ATAC or M-ChIP, respectively with bisulfite conversion. This also enables the simultaneous analysis looking at the changes in methylation patterns along with histone modifications on identical DNA molecules. Another approach is known as ATAC-Me resembling EpiMethylTag and it combines ATAC-seq and bisulfite sequencing. In addition, researchers have recently developed high-resolution epigenomic methods at the single-cell level by utilizing breakthroughs in single-cell sequencing methods.^{144,145}

Epigenetic pathways control the emergence of human diseases

The role epigenetics plays in human illnesses has increased recently, and academics from all around the world are becoming increasingly interested in this area of research. Abnormal epigenetic alterations are linked to a variety of diseases, such as oncogenesis, neural problems, type 2 diabetes, cardiovascular diseases, infectious diseases, *etc.*

The link between epigenetics and cancer

Oncological outcomes are significantly influenced by epigenetic changes.¹⁴⁶⁻¹⁴⁸ One way to inactivate several tumor suppressor functions is to hypermethylate tumor suppressor gene promoter regions.¹⁴⁹ Besides, additional genes participating in the vast array of essential physiological properties have also shown hypermethylation, which leads to oncogenesis. It is interesting to note that ncRNAs have been widely researched for their function in the epigenetic regulation of breast cancer.¹⁵⁰ Due to CpG hypermethylation in miRNA genes or deregulation of miRNA biosynthetic processes, miRNAs aberrantly control genes in cancer.¹⁵¹ Additionally, the activation of glioblastoma multiforme (GBM)-related genes and oncogenesis have been linked to the extent of arginine methylation of histone that is protein arginine methyltransferase-dependent at particular genomic locations.¹⁵² Additionally, an extensive DNA hypomethylation across the genome has been identified by whole-genome analysis as the most notable and early known alteration in DNA methylation patterns of neoplastic cells.¹⁵³ It is likely DNA demethylation may have a role in aneuploidy and genomic instability, two prominent characteristics of cancer.¹⁵⁴ DNA methylation loss may result in transcriptional activation, allowing gene expression of repeated sequences, transposable elements, and cancer-causing genes.¹⁵³⁻¹⁵⁵ Also, the histone acetylation pattern is altered in GBM cells and has been linked to tumor aggressiveness, as shown by the findings that HDAC1, 2, and 3 are critical for the etiology of gliomas.¹⁵⁶

Taken together, the onset and prognosis of cancer, which was once thought to be a genetic disease, is now understood to require both genetic changes and anomalies in the epigenome. Current development in the rapidly progressing research in the field of cancer epigenetics has shown extensive dysregulation of every part of the cancer's epigenetic machinery.^{151,157} However, this article's breadth does not allow for a thorough description of the role of epigenetics in oncogenesis.

Epigenetic changes cause neurological disorders

The fundamental premise that the basis of neurogenesis depends on the epigenetic mechanisms governing developmental outcomes in a healthy individual strongly supports the deep effects of their deregulation on the etiology of many neural diseases, such as Alzheimer's disease (AD) and Parkinson's disease (PD), *etc.*¹⁵⁸⁻¹⁶⁰

For instance, DNA methylation in multiple genes linked to AD such as amyloid precursor protein, ankirin, and apolipoprotein E, is changed.¹⁶¹ Moreover, in AD patients' brains as well as AD mice with transgenes, histone acetylation levels were found to be significantly lower.^{162,163} Particularly significant is that postmortem examination of brain tissue from AD patients revealed H3 acetylation enrichment along lysine 27 in genomic regions regulating tubulin-associated unit (tau) and pathology dependent on β -amyloid formation, inducing concurrent hyperexpression among the important genes found there; namely, these are precursor protein for amyloid, presenilin 1 and 2, and protein tau associated with microtubules that regulate tau and β -amyloid formation in the brain.¹⁶⁴

On the other hand, hypomethylation has been found throughout the genome and is not confined to the gene that encodes α -synuclein, leading to hyperexpression and protein buildup in Lewy bodies in PD neurons.¹⁶⁵ Additionally, a recent study looked at the PTMs of genes in the substantia nigra of two PD patients, which showed that the synuclein alpha promoter region is associated with two substantial histone methylations, namely H3K4me3 and H3K27me3. M3k4me3 is increased and enhances transcription initiation in PD patients' brains. H3K27me3, on the other hand, is related to the snuffing out of the *SNCA* gene's expression.¹⁶⁶ Moreover, epigenetic modifications (primarily aberrant histone modifications) have been seen in Huntington's disease.^{167,168} Complex gene-environment interactions are believed to cause the onset and development of multiple sclerosis, a persistent inflammatory state having an impact on the brain, even though epigenome modifications may also be involved.¹⁶⁹ Finally, human and animal hippocampus specimens with epilepsy have shown evidence of global hypermethylation, which alters processes including neuron development and remodeling.¹⁶⁵

How epigenetics participates in the development of CVDs

Epigenetic changes have been associated with CVDs, such as atherosclerosis and hypertension.¹⁷⁰⁻¹⁷⁴ DNA methylation has frequently been seen as a significant etiologic factor in disorders of the cardiovascular system.¹⁷¹ However, despite their biological importance in other diseases, there is limited evidence to support the activities of DNA methylating and demethylating enzymes in CVDs, to date. Nonetheless, there has been evidence of large-scale DNA hypomethylation in some atherosclerotic lesions while DNA hypermethylation is found in genes that protect against atherosclerosis.¹⁷⁵ While DNA methylation might not be enough by itself to influence CVD development per se, covalent changes on histone tails collaborate with subtle DNA modifications to influence chromatin structure and gene expression that have been implicated in CVD progression. For instance, HDAC5 and HDAC9 from the HDAC Class IIa family offer protection against hypertrophic remodeling. HDAC5 and HDAC9 binding inhibits Mef2C, a TF that activates prohypertrophy genes.¹⁷⁶ Thus, the dysregulated expression of HDACs can lead to a range of heart abnormalities, such as dilated cardiomyopathy, cardiac hypertrophy, atherosclerosis, and stroke.¹⁷⁷

The connection between T2D and chromatin changes

The initial indications of T2D epigenetic regulation were only identified 10 years ago, when it was demonstrated that various DNA methylation patterns were present in particular genes or areas of the genomes in diabetic mouse and human adipose and muscle tissues.¹⁷⁸⁻¹⁸¹ Furthermore, T2D peripheral blood mononuclear cells exhibit lysine 4 H3 methylation in the chromosomal segment regulating the expression of nuclear factor kappa-B, a TF

that modulates inflammatory reactions.¹⁸² Additionally, a significant role in epigenetics exists in the emergence of T2DM micro- and macrovascular problems.¹⁸³ Importantly, insulin's metabolic function and impaired insulin release from the pancreatic beta cells are two key factors that contribute to developing T2D.¹⁸⁴ The DNA methylation of several genes, including *IRS1*, *PPARG*, *KCNQ1*, and *TCF7L2*, which are implicated in the effects of insulin in locations like the skeletal muscle, fat tissue, and liver, have been shown to be altered.¹⁸⁵ Also, *HDAC7* upregulation has been linked to a reduction in glucose-stimulated insulin production in human pancreatic cells of people with T2D.¹⁸⁶ Additionally, acetylation of the *FOXO1* gene, which controls *PDX1*, a critical TF that activates the insulin gene, affects the development of insulin-producing beta cells in the pancreas and glucose homeostasis.^{187,188}

The connection between infection and epigenetics

Interactions between hosts and pathogens are greatly influenced by epigenetic factors.^{189–191} These serve to increase the host genome's accessibility so that a virus can alter histones unique to a host. The host, instead, might methylate the DNA to inactivate the expression of the viral genome integrated into the host genome, thereby inhibiting viral replication. DNA methylation controls the immune reaction of the host to bacterial infections in addition to its function in viral infection pathogenesis.¹⁹² Practically all viruses exploit host epigenetic reprogramming, which is a crucial component of their host immune evasion routes.¹⁹³ Also, pathogen-associated molecular patterns found in microorganisms (bacteria, fungi, viruses, and protozoa) that are engaged in the detection of pathogens may change the host immune cell's epigenetic environment. It has been shown by Ramendra *et al.*¹⁹⁴ that the strong pathogen-associated molecular patterns of 1,3-D-glucan from fungus were able to modify the epigenetic landscape and chromatin accessibility of monocytes.¹⁹⁵ On the other hand, the HBV-encoded oncogene X protein of the hepatitis B virus can alter host miRNA patterns, which then modifies the viral burden and strengthens persistence.

Current state of epigenetic therapeutics for treating human disease

Typically, epigenetic drugs or “epidrugs” are pharmacological substances that treat DNA and histone PTMs that are abnormal in a diseased condition. Inhibitors of DNA methyltransferase, histone methyltransferase, histone demethylase, histone acetyltransferase, and histone deacetylase are the five classes into which epigenetic medications are typically divided.¹⁹⁶ Many of these different types of inhibitors have been reviewed elsewhere.^{197,198} Despite the fact that the majority of these inhibitors have shown efficacy when used alone, there are powerful complementary actions of inhibitors of histone modification and DNA methylation, and such is projected to considerably boost the potential efficacy.¹⁹⁹

Development of therapeutics based on epigenome editing

Since epigenetics research has advanced over the years, it is now possible to use epigenome editing to treat a variety of disorders. Technologies for altering the genome, like clustered regulatory interspaced short palindromic repeat (CRISPR)-associated protein (Cas) (CRISPR-Cas), transcription activator-like effector (TALE) nuclease, zinc finger nuclease, and others are rapidly developing and may be adapted for altering epigenomes.^{200,201} Early investigations used zinc finger and TALE domains, which were initially utilized to develop enzymes that can edit the epigenome with selectiv-

ity for a target sequence. They can combine the binding domain for DNA that finds the intended sequence with the enzyme-containing EpiEffector molecule that consists of a group of enzymes that alter DNA and histone proteins in an epigenetic manner but they do not attach to particular DNA sequences.²⁰² In addition to the TALE and zinc finger systems, CRISPR systems developed employing Cas proteins which are dead (which fail to break DNA since the endonuclease activity of the Cas protein has been lost) still have DNA binding capability that is programmable.^[200,201] Despite being in its early stages, this technology has already shown its potential in a number of experiments.

Challenges and future directions

Despite the importance of comprehending how epigenetic mechanisms operate in health and disease to develop novel therapeutic approaches in the treatment of human diseases, there are numerous difficulties associated with instigating targeted epigenetic modifications that aim to restore the epigenetic landscape to a normal physiological state from a diseased state. Hence, the synthesis of drugs targeting epigenetic modifications may be severely hampered by these issues, which must be resolved. For instance, because epigenetic alterations occur at numerous locations throughout the genome, it is difficult to target particular genes without impacting others. For epigenetic drugs to be effective, gene-specific targeting and reducing off-target effects are essential.¹⁹⁸ Also, toxicity is a common feature of epigenetic drugs, which restricts the dose and time they can be administered. For the development of safer and more efficient treatments, measures to improve drug selectivity and lower side effects are crucial. Epigenetic drugs that target certain epigenomic-modifying enzymes have significant side effects on the patient because they impede all of the enzyme's actions, which affects the complete genome. However, compared to the irreversible DNA sequence changes brought on by genomic editing, the reversible effects of epigenome editing provide a benefit.

It is imperative to take into account a number of important factors, including the unwanted genomic mutations brought on by the epigenome editing treatment, particularly with CRISPR/dead Cas-mediated epigenome editing, a thorough understanding of the nuclear structure, and how it changes during undifferentiated and differentiated cell states, cell types, and method of administration. For example, epigenome editing in differentiated cells is not only challenging but also less effective therapeutically than in undifferentiated stem and progenitor cells, making it unsustainable.^{200,201} Moreover, understanding and overcoming resistance pathways are necessary for the long-term efficacy of any epigenetic therapy. Also, to increase therapeutic selectivity and lower toxicity, researchers are currently investigating cutting-edge drug delivery technologies, such as nanoparticles and targeted approaches.²⁰³ Moreover, notwithstanding the challenges in using assay systems to study epigenetics in clinical settings, there are ongoing efforts that focus on translating these basic research methodologies, with a focus on the possibilities of microfluidic tools, including CRISPR-based detection systems, and epigenetic biomarkers employed as biosensors with particular reference to point-of-care use in future-generation diagnostic platforms.²⁰⁴ Lastly, thanks to the development of technologies for large-scale epigenome mapping and drug sensitivity testing, together with drug screening of a particular cell populace from patients identified using these technologies, it is now possible to provide a customized treatment for each patient while minimizing side effects.

Conclusions

The advanced developments in epigenetics have led to the creation of a number of technologies that have improved our understanding of the biological functions of epigenetic regulation. This includes more precisely interpreting the vast amounts of data from epigenomic mapping. Therefore, drugs that target abnormal DNA methylation, histone acetylation, or other epigenetic processes may be effective in treating a range of disorders. By lessening the toxicity of epigenetic drugs, epigenome-editing can also help with better therapeutic approaches. The effectiveness of cancer treatment can be improved by combining epidrugs with other treatments like immunotherapy or traditional chemotherapy.

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Conflict of interest

The authors declare having no conflicts of interest in relation to this study.

Author contributions

Wrote the manuscript (SKC), and reviewed and edited the manuscript (SKC and DC).

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