



**EPIGENETICS: FUNDAMENTAL MECHANISMS,
POTENTIAL CLINICAL APPLICATIONS, AND ETHICAL ISSUES**

Epigenética: mecanismos fundamentais, potenciais aplicações clínicas e questões éticas

ISSN: 2178-7514

Vol. 17 | N°. 2 | Ano 2025

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ABSTRACT

Epigenetics, defined as the study of changes in gene expression or cellular phenotype brought about by mechanisms that do not involve alterations in the DNA sequence, introduces a layer of biological complexity 'above' that of traditional genetics. The aim of this paper is to offer a brief reflection upon the principal concepts of epigenetics, its potential clinical applications, and the ethical questions involved in this science. In contrast to DNA mutations, epigenetic modifications are generally reversible. They play an essential role in regulating gene expression and are fundamental to processes such as development and cellular differentiation, thereby allowing cells with identical genetic material to perform distinct functions. Furthermore, relevant aspects concerning the now ubiquitous convergence between epigenetics and artificial intelligence are discussed, albeit briefly. Such developments present a significant ethical challenge for humanity; after all, for whom, and in whose service, will these technologies be made available?

Keywords: Epigenetics, artificial intelligence, ethics.

RESUMO

A epigenética, definida como o estudo das mudanças na expressão gênica ou no fenótipo celular causadas por mecanismos que não envolvem alterações na sequência do DNA, adiciona uma camada de complexidade biológica "acima" da genética tradicional. O objetivo deste artigo é realizar uma breve reflexão sobre seus principais conceitos, suas possíveis aplicações clínicas e as questões éticas envolvidas nesta ciência. Diferentemente das mutações no DNA, as modificações epigenéticas são geralmente reversíveis. Elas desempenham um papel essencial na regulação da expressão gênica e são fundamentais para processos como o desenvolvimento e a diferenciação celular, permitindo que células com o mesmo material genético desempenhem funções distintas. São discutidos, mesmo que brevemente, aspectos relevantes sobre a já onipresente convergência entre a epigenética e a inteligência artificial. Tais eventos colocam um importante desafio ético para a humanidade, afinal, para quem e a serviço de quem essas tecnologias estarão disponíveis?

Palavras-chave: Epigenética, inteligência artificial, ética.

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INTRODUCTION

For a considerable period, the DNA sequence was regarded as solely responsible for the formation, function, and transmission of cellular characteristics. However, this perspective failed to elucidate phenomena such as the differences observed between identical twins or the specialization of cells possessing the same genome. Epigenetics emerged as the scientific discipline seeking to comprehend these reversible alterations in gene expression that occur without modifying the DNA nucleotide sequence. These modifications function as molecular ‘tags’ or markers that guide the cellular machinery regarding which genes should be transcribed at specific times and in particular environments. The concept of epigenetics was initially proposed by Conrad Waddington in the late 1950s to describe the events leading to the unfolding of the genetic programme for development⁽¹⁾.

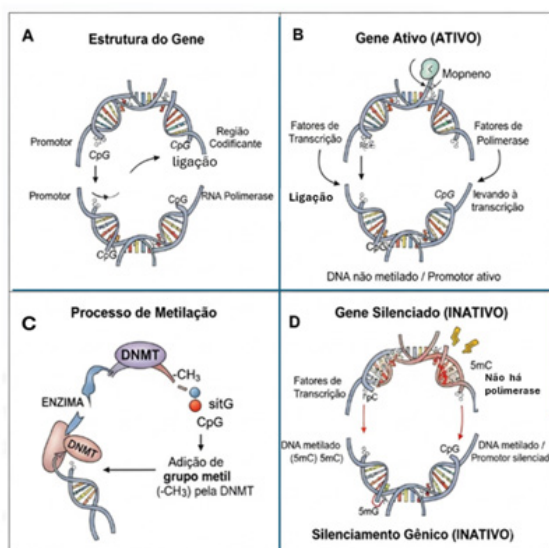
Fundamental Epigenetic Mechanisms

Epigenetic modifications entail chemical alterations to DNA or its associated proteins, which influence chromatin accessibility and, consequently, gene transcription. The principal epigenetic mechanisms described in the specialised literature are:

DNA Methylation

This is one of the primary epigenetic mechanisms; it was the first to be discovered and is arguably the most extensively studied. Figure 1 illustrates this mechanism, showing in A, the basic gene structure with the promoter and coding region. In B, the active gene, where unmethylated DNA permits the binding of transcription factors and RNA polymerase. In C, the methylation process, with the DNMT enzyme adding methyl groups. And in D, the silenced gene, where methylated DNA impedes transcription.

Figure 1 – DNA Methylation



Source: the author

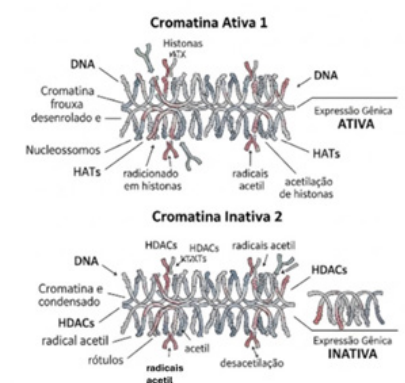
This mechanism consists of the addition of a methyl group ($-\text{CH}_3$) to the cytosine base, frequently at CpG dinucleotides. When methylation occurs in gene promoter regions, it generally impedes transcription, thereby silencing these genes. Methylation in CpG islands within the promoter region prevents RNA polymerase from binding to the DNA strand, precluding protein synthesis from that gene. Methylation is crucial for gene silencing and the maintenance of cellular identity^(1,2). It is a mechanism determined by the cell cycle or development for the proper functioning of the organism. DNA methylation leads to the recruitment of proteins that compact chromatin. The enzymes responsible for this modification are DNA methyltransferases

(DNMTs), such as DNMT1, DNMT3A, and DNMT3B. Hypomethylated (sparsely methylated) DNA is associated with active chromatin and gene expression, whilst hypermethylated (densely methylated) DNA is associated with inactive chromatin and gene silencing.

Histone Modifications

DNA, which is exceptionally long, is compacted within the cell nucleus by proteins called histones. DNA wraps around groups of histones, forming nucleosomes. Figure 2 illustrates the mechanism of histone modifications, where regions compacted into nucleosomes are generally not amenable to transcription.

Figure 2 – Histone Modifications



Source: the author

Histones possess tails where numerous epigenetic modifications occur. Histone acetylation, performed by Histone Acetyltransferases (HATs), adds an acetyl group, resulting in chromatin decondensation and permitting gene expression. Histone Deacetylases (HDACs) remove the acetyl

group, promoting compaction and inhibiting transcription. Histone methylation, carried out by Histone Methyltransferases (HMTs), can either silence or activate genes, depending on the modified amino acid residue. For instance, methylation of histone 3 lysine 9 (H3K9) causes

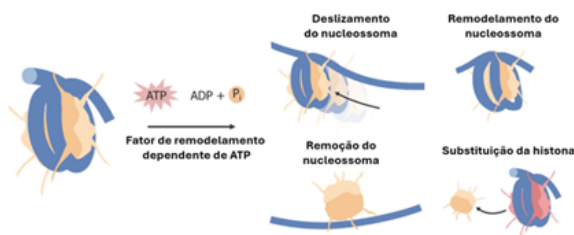
gene deactivation, whereas methylation of lysine 4 (H3K4) leads to gene expression activation, characterising the ‘histone code’^(1,2,3).

Chromatin Remodelling

Chromatin, the structure formed by DNA and histones, exists in different states of

compaction that affect gene accessibility. Figure 3 shows chromatin remodelling, highlighting nucleosome sliding along the DNA chain, nucleosome remodelling, temporary nucleosome removal, and histone replacement.

Figure 3 – Chromatin Remodelling



Source: the author

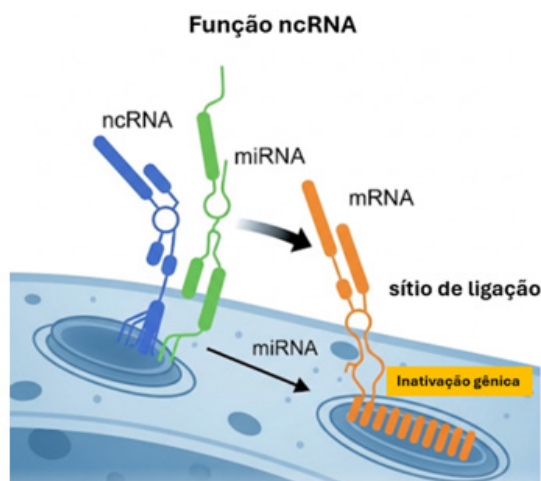
Euchromatin is less compacted, allowing access for the transcription machinery, and is associated with gene expression. Heterochromatin is highly condensed and associated with gene silencing. Chromatin remodelling, influenced by histone modifications, allows nucleosomes to slide along the DNA, altering accessibility and regulating transcription^(1,2,4).

Non-Coding RNAs (ncRNAs)

Not all portions of DNA encode proteins. Non-coding regions can be transcribed

into RNAs that exert regulatory functions without being translated. Important examples include microRNAs (miRNAs) and long non-coding RNAs (lncRNAs). The miRNAs can bind to messenger RNAs (mRNAs) and prevent their translation, thereby silencing the expression of the corresponding gene^(1,3,6). Figure 4 illustrates the mechanism of non-coding RNAs, showing microRNAs and long non-coding RNAs.

Figure 4 – Non-coding RNAs (ncRNAs)



Source: the author

Some studies suggest that 30% to 60% of protein-coding genes may be regulated by microRNAs. LncRNAs can bind to the DNA strand, blocking the transcription of a series of genes. RNA-mediated regulation is still a relatively recent area of study, with significant potential for advancements in epigenetics.

The so-called 'Epigenetic Clock' refers to an estimation of biological age based on DNA methylation patterns, which is crucial in the ageing process. Deviations in this clock may indicate a predisposition to age-related diseases. Epigenetic therapies face the challenge of the potential reversibility of methylation status, representing an important area for the refinement of therapeutic interventions^(3,4,8).

Epigenetics and Diseases

The dysfunction of epigenetic mechanisms can lead to the development of

various diseases. For instance, epigenetics is intimately linked to oncogenesis. Anomalies such as hypermethylation, which can silence important genes like tumour suppressor genes, and hypomethylation, which can activate oncogenes and cause genomic instability, are widely associated with diverse types of cancer. The tumour microenvironment can also affect normal epigenetic patterns, contributing to the emergence of neoplasms. Well-documented examples in the specialized literature include colorectal cancer, with hypermethylation of the MLH1 gene (a DNA repair gene), associated with Lynch Syndrome and many sporadic cases. In breast cancer, hypermethylation of the BRCA1 gene (a tumour suppressor gene) and hypermethylation of the ESR1 gene (the oestrogen receptor gene) are observed. In prostate cancer, hypermethylation of the GSTP1 gene (a detoxification gene) occurs. In lung

cancer, hypermethylation of the CDKN2A (p16) gene (a tumour suppressor gene) is noted. In leukaemias and lymphomas, atypical patterns are used to classify subtypes and predict treatment response. Furthermore, histone modifications, such as the acetylation of lysine 16 on histone H4 (H4K16ac) and trimethylation of lysine 20 on histone H4 (H4K20me3), are common in many types of cancer. The marker EZH2 (a Histone Methyltransferase) is frequently overexpressed in prostate and breast cancer, leading to an increase in H3K27me3 (trimethylation of lysine 27 on histone H3), silencing tumour suppressor genes. Other markers, such as miR-21 (an onco-miR), are usually overexpressed in many cancers, including breast, lung, colorectal, and glioblastoma, acting as an inhibitor of tumour suppressor genes^(3,7,8).

Alterations in DNA methylation patterns, primarily hypermethylation, have been associated with conditions such as Alzheimer's disease (AD), Parkinson's disease, autism, schizophrenia, bipolar disorder, depression, epilepsy, and borderline personality disorder. For example, AD is characterized by the accumulation of beta-amyloid plaques and neurofibrillary tangles of tau protein in the brain. Studies have shown both global DNA hypomethylation (decrease) and hypermethylation (increase) at different stages and in various brain regions of AD patients. For specific genes like APP (Amyloid Precursor Protein), changes in methylation can influence beta-amyloid production. Mutations in PSEN1 (Presenilin 1) are causal in familial forms of

AD, and its expression can also be modulated epigenetically. Hypermethylation of BDNF (Brain-Derived Neurotrophic Factor) can lead to its reduced expression, which has been associated with diminished neuroprotection and synaptic plasticity. Dysregulation of enzymes that add or remove acetylation marks (HATs and HDACs) and methylation on histones has been implicated in AD. For instance, reduced histone acetylation (such as H3K9ac and H4K12ac) can lead to chromatin condensation and repression of genes important for cognitive function^(3,7,8,5).

Parkinson's disease (PD) is characterized by the loss of dopaminergic neurons in the substantia nigra and the accumulation of alpha-synuclein protein. Alterations in the methylation of this gene, particularly hypomethylation in certain regions, can lead to its increased expression and, consequently, to alpha-synuclein accumulation. Genes related to mitochondrial function and oxidative stress are implicated, as mitochondrial dysfunction is a determinant of PD, and genes involved in these pathways can undergo epigenetic alterations. Mutations in LRRK2 (Leucine-Rich Repeat Kinase 2) are the most common cause of familial PD, and its expression can be influenced by methylation^(3,7,5). Alterations in histone acetylation and methylation in dopaminergic neurons have been observed. For example, changes in the levels of H3K4me3 (an activating mark) and H3K27me3 (a repressive mark). The enzyme SIRT1 (an HDAC) has been implicated in regulating the expression of genes related to PD and neuroprotection.

Major Depressive Disorder (MDD), also referred to as Profound Depression, is a mood disorder characterized by persistent sadness, loss of interest, and other emotional and physical symptoms. Several epigenetic mechanisms are associated with this disorder. Notably, hypermethylation of BDNF, especially in response to chronic stress, leads to its reduced expression in the hippocampus and other brain areas. Alterations in the methylation of the SLC6A4 gene (Serotonin Transporter, SERT) typically affect serotonin availability, a key neurotransmitter in mood regulation. Hypermethylation of the NR3C1 gene (Glucocorticoid Receptor), particularly in individuals with a history of childhood trauma or stress, can lead to dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, which is frequently present in severe depressive states. Markers of depression are also found in alterations to histone acetylation and methylation in brain regions such as the prefrontal cortex and hippocampus^(1,3,7). For example, reduced histone H3 acetylation and H3K4 methylation at the BDNF promoter have been associated with depression. Indeed, epigenetic research has already identified tens of thousands of markers associated with different diseases.

Environmental Influence and Epigenetic Inheritance

Epigenetics allows an organism to adjust gene expression in response to the environment

without altering the genome sequence. External factors and lifestyle, such as diet, stress, famine, emotional trauma, and treatments, can influence epigenetic patterns. More notably, epigenetic modifications can be transmitted across generations, a phenomenon known as epigenetic inheritance. Epidemiological studies, such as that of the Dutch Hunger Winter cohort, have revealed correlations between the food availability for grandparents and an increased risk of diabetes and cardiovascular diseases in their grandchildren. The transmission of H3K27me3 marks (a histone modification associated with gene repression) from mother to embryo in fruit flies has been demonstrated to be important for embryonic development. It is important, however, to be cautious about exaggerated conclusions regarding the epigenetic inheritance of trauma or ‘miracle diets’, as epigenetics is a complex field, and the term is sometimes overused in biology ^(3,7,8).

A New Era: Epigenetics and Artificial Intelligence

Artificial Intelligence (AI) has been revolutionizing epigenetics by empowering researchers to manage the immense complexity and volume of data generated by epigenomic studies. Machine learning algorithms, a subfield of AI, are particularly adept at identifying subtle patterns and correlations within these vast datasets (Big Data), permitting the discovery of new epigenetic signatures and the understanding of how they govern gene expression in states of health and disease.

One of the most significant contributions of AI lies in the prediction and identification of epigenetic markers. Machine learning models can be trained to predict sites of epigenetic modifications, such as DNA methylation regions or specific histone modification sites, with high accuracy, precision, and specificity, even in regions of the genome that are still poorly explored. Furthermore, AI is crucial in associating these markers with specific phenotypes, such as the risk of developing cancer, neurodegenerative diseases, chronic diseases, or the response to treatments, thereby accelerating the discovery of biomarkers for early diagnosis, prognosis, and therapeutic monitoring. The capacity to integrate epigenomic data with other layers of biological information (genomics, transcriptomics, proteomics) is also enhanced by AI, offering a more systemic view of cellular processes. The synergy between AI and epigenetics promises to drive the development of precision medicine and the discovery of new therapies. AI can assist in identifying new therapeutic targets within the epigenome and in designing drugs capable of specifically modulating these dysregulated epigenetic marks in diseases. Moreover, by modelling complex epigenetic interaction networks, AI contributes to a more profound understanding of the fundamental mechanisms by which environmental factors and lifestyle influence gene expression throughout life, opening new avenues for preventive and personalized interventions.

Final Considerations or The Ethical Dilemma Intrinsic to Epigenetics

As with the maturation process of any technology possessing disruptive potential, epigenetics, its applications, and availability highlight a significant ethical and humanitarian challenge. In a world governed by the principle that those with the most financial capital hold the most value – even if they are corrupt politicians, rapists, or drug traffickers – it becomes clear that the chasm of material inequality may be less profound than that of ethical and moral disparities. Human beings are by nature simultaneously good and evil, angel and demon. Will epigenetics and its spectacular promises merely repeat the age-old litany of exclusion, segregation, and prejudice? Perhaps the great ‘ethical famine’ we are experiencing might produce ‘epi-ethical’ markers in all of us, such that one day we may learn to value others, animals, and all ecosystems as we value our own mothers, fathers, and children. Perhaps the perception that few currently hold is that epigenetics is a biological time bomb, one that will eventually explode into a generalized imbalance within our bodies. Certain types of cancer, a neurological disease, another cardiovascular, a renal condition; the menu of our ultimate afflictions is vast. Yes, epigenetics may prolong our state of equilibrium and a healthy life, but as Marx said, “all that is solid melts into air.” All of us, without a single exception, will return to cosmic dust.

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Observação: os/(as) autores/(as) declaram não existir conflitos de interesses de qualquer natureza.