Therapeutic Agents Targeting Gene Expression Modifications, Epigenetic Drugs Show Promise in Treating Diseases like Cancer and Neurological Disorders, Crucial for Precision Medicine Advancements

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Abstract

Epigenetics investigates heritable, reversible gene regulatory mechanisms beyond DNA sequence, including phosphorylation, acetylation, ubiquitination, and methylation of DNA and histones. Recent research highlights epigenetics' role in illnesses like cancer, and neurological, metabolic, and cardiovascular conditions. Reversible epigenetic changes offer therapeutic potential, with existing use of epigenetic drugs in certain neurological disorders and tumors. This survey discusses major diseases with epigenetic involvement and emerging medications for treatment.

Keywords: Epigenetics •Gene regulatory mechanisms• DNA methylation• CpG dinucleotide• DNA Methyl Transferase (DNMT) • Histones• Chromatin packaging• Ubiquitination• Histone Deacetylases (HDACs) • Cardiovascular diseases• Metabolic disorders• Atherosclerosis• Endothelial dysfunction• Nucleosome• H3K4me2• MeCP2

Introduction

The field of epigenetics investigates heritable, reversible gene regulatory mechanisms outside of DNA sequence. This control involves phosphorylation, acetylation, ubiquitination, and methylation of both DNA and histones. According to recent research, epigenetics is a major factor in a wide range of illnesses, such as cancer, neurological, metabolic, and cardiovascular conditions. Due to the reversible idea of epigenetic occasions, specialists hypothesize that restraint of epigenetic changes could be of significant restorative potential. As a matter of fact, in a few neurological sicknesses and tumors, epigenetic drugs are as of now in use. This survey will examine a portion of the significant illnesses that include epigenetic changes and the medications that are being created to treat them.

Kinds of cellular events involve epigenetics?

1. DNA Methylation: Epigenetic occasions are involved all through the whole human lifecycle, from embryogenesis to adulthood. Microorganism cells start with a degree of DNA methylation, acquired from their individual guardians. Upon preparation, a huge methylation redesign happens, in which most methylation is lost. As the zygote partitions and improvement advances, the incipient organism goes through once more methylation, restoring its unique degree of DNA methylation. Thinking about that all organic entities start as a solitary egg and that all phones in the last confounded creature contain similar qualities, epigenetics should assume a fundamental part.

DNA methylation exists essentially inside the setting of the Cytosine-Phosphate-Guanine (CpG) dinucleotide.5 All adjustments of methylation are tweaked by unambiguous catalysts. DNA Methyl Transferase (DNMT) 3a, DNMT3b, and DNMT1 are three chemically dynamic catalysts expected for the development and upkeep of DNA methylation patterns. DNMT1 goes about as a support methyl transferase, adding methyl gatherings to the methylated girl strands of recently recreated DNA. At the point when CpG deposits are methylated by DNMT1, Methyl-Restricting Space Protein (MBDP) and Histone Deacetylases (HDACs) are enrolled, hindering the record and hushing the quality. Erasure of DNMT1 brings about worldwide demethylation and early-stage lethality. DNMT3a and DNMT3b are answerable for new methylation after implantation and are profoundly communicated in creating undeveloped organisms. DNMT3a and DNMT3b layout DNA methylation during undeveloped stages and add new methyl gatherings to already un-methylated DNA.

2. Chromatin packaging (histones): Histones can undergo additional chemical modifications that change expression in addition to methylation at CpG islands in DNA. Histones encase genomic DNA to create a complex known as chromatin. A nucleosome, a unit of chromatin, is made up of 146 base pairs of DNA encircling an octamer made up of the four core histones (H_2A, H_2B, H_3, and H_4). Histones can be modified by acetylation, methylation, phosphorylation, and ubiquitination because their amino-terminal tails extend from their globular area.8 Subsequently, histone modification may have an impact on chromosomal structure, transcription, DNA replication, and repair. Histone modification can be either activating or inhibitory, in contrast to DNA methylation. Acetylation and methylation of lysine and arginine at the histone tails are frequently examined. For instance, H_3K_4 methylation stimulates the production of genes, while H3K9, H_3K_{27}, and H_3K_{20} trimethylations inhibit the same. Numerous biological processes, including as DNA repair, the cell cycle, stress responses, development, differentiation, and aging, are impacted by histone methylation. Any one of these biological processes can be affected by changes in histone methylation, which can lead to the emergence of disease. For instance, H_3K_4 me2 is down-regulated in many cancer types, such as prostate, lung, kidney, breast, and pancreatic cancer. This is frequently linked to low survival rates or a high recurrence rate. H_4K_{20}me3 downregulation is linked to lymphomas and colon cancer, while H3K27me3 is downregulated in gastric adenocarcinoma and ovarian cancer. Aging is also linked to alterations in histone methylation. For instance, $H_4K_{20}me_3$ levels rise in aged rat livers, yet $H_3K_{27}me_3$ levels fall in aged Caenorhabditis elegancy somatic tissues. These examples show how certain locations could be demethylase using small molecule histone methylase inhibitors in order to create anti-aging and anti-cancer medications.

3. HDACs (Histone Deacetylases): In addition to acetylating and opening specific chromatin regions, deacetylating and closing other genomic regions is also necessary for correct development and function. In the cytoplasm and nucleus, HDACs are involved in the control of integrated cellular processes. The general mechanism of these enzymes is to deacetylate specific lysine residues of histones and other proteins inducing the formation of transcriptionally inactive heterochromatin. These modifications of HDACs and HATs are both reversible reactions and play a significant role in the regulation of transcription.

There are four general classes of HDACs: I, II, III, and IV.
1. Class I HDACs: This class includes HDAC1, HDAC2, HDAC3, and HDAC8. They are primarily localized to the nucleus and are involved in transcriptional repression.

2. Class II HDACs: This class is further subdivided into Class II a (HDAC4, HDAC5, HDAC7, HDAC9) and Class II b (HDAC6, HDAC10). Class II a HDACs shuttle between the nucleus and cytoplasm and are involved in regulating transcription, while Class II b HDACs are primarily cytoplasmic and regulate processes such as protein degradation, cell motility, and stress responses.

3. Class III HDACs: Also known as sit-ins, these HDACs require NAD^+ for their activity. They include SIRT1-7 and are involved in a wide range of cellular processes such as metabolism, aging, and stress responses.

4. Class IV HDAC: There is only one member in this class, HDAC11, which shares structural similarities with both Class I and II HDACs. It has been implicated in immune regulation and other biological processes.

These classes of HDACs have distinct subcellular localization, substrate specificities, and biological functions, contributing to the complexity of gene regulation and cellular processes.

Types of diseases involve epigenetic changes

1. Cardiovascular diseases: The association of epigenetic changes with cardiovascular diseases is an emerging area of research. Although the studies are not expatiated on, there are many examples that demonstrate that histone and CpG residue modifications regulate important cardiovascular functions. Although the processes are not readily understood mechanistically, many studies have shown that alteration can lead to the development of atherosclerosis and cardiovascular disease. In particular, atheroprotective estrogenic receptor genes *ESR1 and ESR2* are often hyper methylated in human atherosclerosis. These genes are usually expressed in normal vascular smooth muscle cells; however, the expression levels decrease with age, resulting in vascular damage. Folic acid deficiency also portrays an epigenetic link to endothelial dysfunction, which is related to several cardiovascular diseases. Histones can undergo additional chemical modifications that change expression in addition to methylation at CpG islands in DNA. Histones encase genomic DNA to create a complex known as chromatin. A nucleosome, a unit of chromatin, is made up of 146 base pairs of DNA encircling an octamer made up of the four core histones (H_2A, H_2B, H_3, and H_4). With amino-terminal tails extending from the globular region of the histones, they become accessible to modifications, such as acetylation, methylation, phosphorylation, and ubiquitination. Histone modification can subsequently affect DNA processes, such as transcription, DNA repair and replication, and chromosomal organization.

2. Neurological Disorders:
Considering the vast potential of epigenetic modifications, it is not surprisin that epigenetics plays a key role in development of the nervous system. In order to retain a multipotent state, many developmental and differentiation genes in neuronal precursor cells are silenced by CpG methylation. During neuronal differentiation, CpG methylation is lost and H3K4 demethylation (H_3K_4me2) is gained. Regulation of methyl CpG-binding proteins is thus very important. Mutations, duplications, and insertions of the methyl CpG-binding protein 2 (*MeCP2*) gene are known to cause Ret syndrome, an X-linked neurological disorder that eventually causes severe mental retardation. Once MeCP2 binds to DNA at CpG islands, it interacts with other proteins, including HDACs, facilitating chromosome condensation and gene silencing.

3. Metabolic disorders
The epigenome is also subject to changes caused by environmental factors. For example, although monozygotic twins are born with nearly indistinguishable epigenetic patterns, as they age, the epigenomes diverge, explaining why one twin may be more susceptible to certain diseases than the other despite having identical DNA sequences. A recent study found that mice fed a diet deficient in folic acid, L-methionine, and choline exhibited deregulation of hepatic DNMT1 and methyl CpG-binding proteins. The changes were reversible if returned to a normal diet; however, prolonged changes in DNMT1 and methyl CpG-binding protein expression led to the development of hepatic carcinoma. Because even temporary changes in diet can lead to widespread epigenetic changes, the role of epigenetics in metabolic disorders is of great importance and could serve as an invaluable tool in the treatment and prevention of metabolically linked disorders.

Although not a direct cause, several epigenetic mechanisms have been implicated in the development of type II diabetes and obesity, with differential expression of certain genes leading to differential risks of disease. This differential expression can begin in utero, with maternal nutrition status having a large impact on the epigenetic status of the fetus.

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