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Exploring the Role of Epigenetics in Drug Development

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ABSTRACT:

Scientists have long attempted to characterize illnesses only in terms of hereditary or environmental variables. Nonetheless, research on the function of epigenetics in human illnesses began to be conducted fifty years ago. Over the past ten years, there has been a lot of interest in this topic, particularly in relation to complex disorders like addiction, cancer, autoimmune diseases, behavior plasticity, memory, and neurodegenerative and psychological disorders. This overview first discusses the taxonomy and history of epigenetic changes. It then goes on to discuss the function of epigenetics in biology and the relationship between epigenetics and environment. Additionally, the function of epigenetics in human diseases is examined by concentrating on a few diseases with a few complex traits, and we conclude by outlining the field's future prospects. Disease is known to be influenced by epigenetics, which are heritable variations in gene expression without alterations in DNA sequence. Aberrant methylation patterns of DNA and chromatin modifications involving histones are two significant epigenetic alterations that are known to be associated with disease. This article discusses a recent advancement in pharmacology called "epigenetic therapy," which aims to reverse these modifications. Two categories of medications are being developed at this time. One suppresses DNA methyltransferases (DNMTs), which suppresses DNA methylation. These medications may be helpful in the treatment of cancer since it is known that hypermethylation of tumor suppressor genes silences those genes. | Normal cellular phenotypes are established by the dynamic and reversible process of epigenetic control of gene expression, which also plays a role in human illnesses. Histones and other DNA-packaging proteins, as well as DNA itself, undergo hierarchical covalent alteration as part of the molecular process of epigenetic control.

Keywords: DNA methylation, Demethylation, Histone modification, molecular aspects of epigenetic, non-histone modification**.**

Introduction:

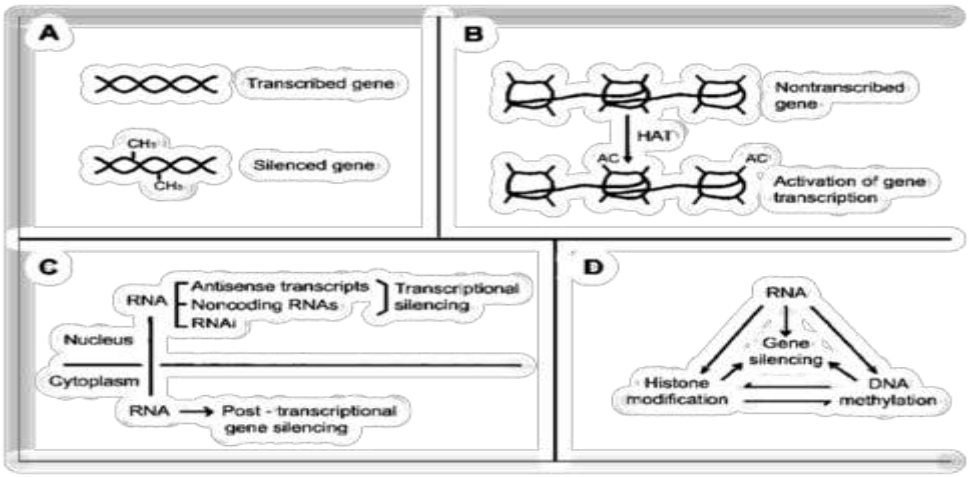
Epigenetics is like a control panel for our genes. It is about how certain factors can switch genes on or off without changing the actual genetic code. These changes can affect properties of cell but without causing change in the DNA sequence[1.] Also, epigenetics impacts on areas which includes developmental biology, somatic gene therapy, cloning and genomic imprinting[2.] Epigenetics was first detected in humans in 1983 by Feinberg and Vogelstein[3]. It plays major role in pathogenesis and multifactorial disorders[4]. The mechanism of epigenetic impact the gene activity at transcriptional and post-transcriptional level. Such mechanism results in varieties of cell differentiations, morphogenesis and adaptability of an organism which is affected by genetic and environmental factors[5]. Also, this mechanism is important, they play role in diseases related to lifestyle, early life experience, and exposure to toxins[6]. Other mechanism contributes to chromatin remodelling via ATP-dependent processes and they exchange the histones variants, covalent modification of histones, DNA is regulated by non-coding RNAs, methylation and other modifications related to it[7]. Nucleosome is the basic building block of chromatin which is octamer of histone proteins contains around 147 base pairs of DNA[8.] Multicellular organisms have different mechanism that each type of cell in body has unique pattern of gene activity and specific expression of gene[9]. The epigenetic state of the cell is dynamic and its response to environmental factors both during the development of foetal and adults[10]. The overall state of the cell's genome is called as epigenome[11]. Epigenetic alterations can be caused by nutritional change as well as oxidative stress level which lead to change in internal and external environment of biological system[12]. A genotype of organism is capable to convert into phenotype due to majority of environmental factors this is called as plasticity[13]. The history of epigenetics in 1879 by Thomas hunt morgan described about a genetic linkage between drosophila genes and X chromosome[14].

Molecular aspects of epigenetics:

Epimutations is heritable defect in expression of genes, this does not involve changes in DNA sequence[15]. Epigenetics changes occur due to environmental factors so this change lead to inheritance of daughter cells during cell division which also influence the germline[16]. Epigenetics is rapidly evolving based on molecular aspects , three molecular mechanism like DNA methylation, histone modification, and RNA associated silencing which interact with each other[17]. This therapy is very useful form because this is easily reversible with pharmacological intervention when compared to genetic defects[18].

DNA methylation and demethylation:

DNA methylation has much high stability which throughout the periods of cell cycle serves as a special epigenetic memory of cells[19]. Throughout the entire human lifecycle epigenetic events occurs from embryogenesis to adulthood. As there is division of zygote the embryo undergoes de-Novo methylation, and again new level of DNA methylation occurs[20]. The existence of DNA methylation primarily occurs with cytosine-phosphate-guanine(CpG) dinucleotide [21]. For the formation and maintaining the DNA methylation patterns three catalytic active enzyme are required like DNMT3a, DNMT3b, DNMT3c,[22].



Methylation of DNA occurs at site of cytosine by adding a methyl group, using S-adenosylmethionine as a source of methyl group[23]. DNMT1 is considered to be maintenance methyltransferase that copies DNA methylation patterns of parenteral strand to newly replicated strand during cell division and DNMT3a and DNMT3b as De-novo methyltransferases[24]. DNA methylation has many functions such as silencing of transposable elements against viral sequence and repression of certain gene[25]. Histones can be modified by number of ways like acetylation, methylation and phosphorylation[26]. Acetylation of histones occurs at lysine and catalysed by HATs associated with activation of gene transcription. Histones is decatalysed by HDACs[27].

Histone and non-histone modifications:

Gene regulation is way through which histone modification occur through including acetylation, methylation, phosphorylation, ribosylation, sumoylation and citrullination[28]. Non-histone is the another mechanism of structural inheritance[29].

Mitotic gene bookmarking:

The mitosis gene bookmarking is the important issue in epigenetic interpreting[30]. Transcription agents and RNA polymerase are the most excluded from mitotic chromatin and is transcriptionally inactive[31].

Types of Diseases Involve Epigenetic Changes:

Cardiovascular diseases: these genes occur in normal vascular smooth muscle cells, due the age there is decrease in expression level which lead to vascular damage[32].

Neurological disorders: epigenetic play a vast role in nervous system. During neuronal differentiation CpG is lost in methylation and H3K4 demethylation is gained[33]. Hence it is important to bind CpG protein in methyl regulation. Mutations and duplication of CpG methyl binding protein gene cause Rett syndrome which lead to mental retardation[34].

Metabolic disorders: epigenetic changes occurs due to temporary changes in diet, though it serves as invaluable tool in prevention and treatment of disorders which are metabolically linked[35].

Cancer: it is the uncontrolled growth of cell with metastatic potential[36]. This involve changes in both DNA methylation and histone modification at residues of CpG. Oncogenes like ras and src becomes active by methylation[37]. In upstream regions methylation is caused by regulation of DNMT1 and is mostly observed in cancer cells apart from normal [38].

Autoimmune diseases: it include studies in both monozygotic and dizygotic twins as have role for epigenetics[39]. The frequency of occurrence is more in females due to female sex hormones[40].

Addiction: opioids estimation of people in worldwide is about 13.5 out of which 9.2 is heroin[41]. The responses of organism for environmental condition is changed through alterations and epigenetic changes which are corelated with learning and memory[42].

Regenerative medicine: it play a role in embryonic stem cell and differentiation and reprograming. The epigenetic proteins shows utility in regenerative medicine particularly in embryonic stem and formation of pluripotent stem cells[43].

Drugging the epigenome:

HDACs: HDACs , this are divided into five different phylogenetic types[44].

Class 1 include- HDAC1, HDAC2, HDAC3 and HDAC8

Class 2 include-HDAC4, HDAC5, HDAC7 and HDAC9

Class 2(b) include- HDAC6 and HDAC10

Class 3 include- sirtuins SIRT1-SIRT7

Class 4 include- HDAC11.

This all the classes from 1- 4 requires a divalent metal ion for catalysis[45].

Sirtuines are the enzymes dependent on NAD^+ which deacetylase the protein and ADP include ribosylase activity. This are structurally and biochemically unrelated to other classes[46]. Substrate like histone and non-histone deacetylase by HDACs [47]. Increased acetylation of histone and non-histone substrates mediated by drugs are linked to arrest tumour cell growth, apoptosis and anti-angiogenesis[48.]

Epigenetic regulation of ADME genes:

There are approximately 300 genes involved in absorption, distribution, metabolism and excretion. Approximately 60 genes participate in regulation of DNA methylation and histone modification[49]. CYP1A2, is an enzyme abundant in liver which is involved in metabolism of several drugs[50]. CpG island of exon2 consist of 17 CpG dinucleotides which is in corelation with differences in CYP1A2 mRNA levels[51]. In the cancer cell lines , there is promoter of ABCB1 gene which codes for MDR1 transporter[52]. Irinotecan is a first line treatment for metastatic corectal cancer. SN-38 is an active metabolite which is inactivated by glucuronidation mediated by UGT1A1 enzyme[53]. The gene which codes for folate carrier is SLC19A1. This is responsible for uptake of reduces folate and for antifolate drugs which include methotrexate[54].

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