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Perspective

Exploring the Complex Mechanisms and Therapeutical uses of Epigenetics

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DESCRIPTION

Epigenetics is defined as heritable changes in gene activity and expression that occur without alteration in Deoxyribose Nucleic Acid (DNA) sequence. The epigenome also alters the gene expression. Epigenome is made up of chemical compounds and proteins that can attach to DNA which controls the production of proteins in particular cells. All cells contain same genes but gene expression patterns are different in different cells.

Mechanisms

Ribonucleic Acid (RNA) interface, histone modifications and DNA methylation are all combined to alter the gene expression.

Epigenetic alterations are outside the primary sequence, but nonetheless affect the ability of gene to be expressed. DNA in most cells is packaged with histone to form nucleosome in beads on string structure. Chromatin regulation involves high order conformational changes i.e., relaxation or tightening of this thread of DNA histone complex.

Further regulation is by assembling promoter-enhancer complexes *via* long-range DNA looping i.e., can be blocked by specific DNA sequence called insulator. The core histones are subjected to diverse post-translational modifications including methylation and acetylation.

DNA methylation causes X chromosome inactivation, imprinting, heterochromatin maintenance, developmental and tissue specific expression controls in mammals.

Epigenetics in human diseases

Elevated DNA Methyl-Transferase 1 (DNMT1) levels were found in GABAergic neurons in schizophrenia and bipolar disorders. In Alzheimer's disease, significant DNA hypomethylation in the temporal neocortex has been observed. A cumulative effect of genetics (mutations in synaptic factors) has been observed in case of autism. Diabetic retinopathy is known to be associated with a number of epigenetic markers, including methylation of the Sod2 and MMP-9 genes, an increase in transcription of LSD1, a H3K4 and H3K9 demethylase, and various DNA Methyl-Transferases (DNMTs).

Imprinting disorders: During imprinting, one allele from either parent is expressed while the other is silent (imprinted). Imprinting errors are critical in numerous developmental and pediatric disorders. Epigenetic abnormalities at chromosome 15 on the paternal allele lead to Pradere Willi Syndrome (PWS). Epigenetic abnormalities at the same locus on the maternal allele of chromosome 15 cause Angelman syndrome.

In cancer: Scientists reported that microsatellites in colorectal and ovarian cancers are distorted by abnormal epigenetic modulations in the MLH-1 promoter (a DNA repair gene). Researchers reported that the loss of chromatin domains and discrete histone structures are associated with dysregulation of transcriptional control of p16 in breast cancer cells.

Epigenetics in therapy

Epigenetic modality of treatment is being experimented in the indications of diabetic retinopathy, cardiac dysfunction, schizophrenia, autoimmune disorders and oncotherapy.

Many cancer cells acquire immune evasive phenotypes that render them invisible to the immune system. Cancer cells can employ epigenetic silencing to hide from the immune system by shutting off the expression of certain cell surface molecules that play a crucial role in the efficient recognition and elimination of intruders by the immune system.

Vorinostat is approved for the treatment of Cutaneous T-cell Lymphoma (CTCL), acts on Histone Deacetylase Inhibitors (HDACs) which induce apoptosis and cell cycle arrest, as well as sensitize the cancer cells to chemotherapy. Belinostat selectively acts on class 1 and 2 HDACs and has been approved to treat Peripheral T-cell Lymphomas (PTCL). Romidepsin specifically targets class 1 HDACs and has been approved for both CTCL and PTCL patients.

CONCLUSION

Genome contains the information from the DNA sequence, while the epigenome affects regarding the reading of information. Epigenetics is relatively compared to that of

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genetics and is being experimented for futuristic methods of diagnosis, therapy and prognosis of various forms of diseases. The most commonly used method for study of epigenetic changes is bisulfide treatment. Epigenetics serve as a link between the genetic and environmental factors that activates type 1 diabetes mellitus.