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Review Article

EPIGENETICS IN MEDICAL PRACTICE IN THE TWENTY FIRST CENTURY

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Abstract

Epigenetics as a field of study is important because it tends to give answers to pertinent questions like why are identical twins behaving differently despite their possession of the same gene? Epigenetics provides a frame work for solving medical problems like mental retardation, neurodegenerative disorder, schizophrenia and social challenges like suicide and addiction. Abnormal DNA methylation pattern in epigenetics has been linked with a huge number of human cancers. However, recent research has revealed that epigenetic pharmaceuticals like vorinostat, decitabine and azacytidine could be a replacement or aid therapy for presently accepted treatment methods such as radiation and chemotherapy or may argument these current treatments. Understanding epigenetics phenomena entails the use of some research methods which include chromatin immunoprecipitation, fluorescent in-situ hybridization, methylation-sensitive restrictive enzyme and the use of bioinformatics methods. Further research work into epigenetics should be encouraged since this discipline of study has the potential to unravel lots of knowledge that will be very beneficial to managing some medical conditions.

Keywords: Deoxyribonucleic acid, DNA methylation, Epigenetics, Histone modification

Introduction

Epigenetics is defined as the study of heritable changes in gene activities which are not due to changes in Deoxyribonucleic acid (DNA) sequences. This means a change in phenotype without a change in genotype. It is also used to portray the study of stable, long standing changes in the transcriptional potential of cells that are not necessarily heritable.^{1,2} Unlike simple alterations to the DNA sequence (the genotype), the changes in gene expression of epigenetics are caused by other means- thus the use of the term epi-(Greek epi- over, outside, around) genetics.³ Gene expression can be influenced through the action of repressor proteins which are attached to silencer regions of the DNA. The term epigenetics also refers to the alterations themselves. These are functionally important alterations affecting the genome but do not cause alteration in the nucleotide sequence. Examples of mechanisms that result in such alterations are DNA methylation and histone modification each of which causes changes on how genes are expressed without effecting a change in the underlying DNA sequence.^{4,5,6} DNA methylation turns

a gene off. It leads to lack of reading the genetic information from the DNA. The removal of the methyl tag turns the gene on, resulting in the ability for the genetic information from the DNA to be read. ^{7,8} These epigenetic alterations are able to last through cell divisions for the period of the cell's life span. They are also capable of lasting for multiple generations even though there are no accompanied changes in the underlying DNA sequence of the organism; rather non-genetic factors lead to different behavior of the organism's genes.^{3,4,9} Epigenetics often denotes alterations in a chromosome that influence gene activity and expression, but is also used to explain any heritable phenotypic alterations that do not originate from modification of the genome like the prions. Such outcome on cellular and physiological phenotypic traits can be as a result of influence from external or environmental factors or may be as part of normal development programme. The normal definition of epigenetics demands these changes to be heritable either in the progeny of the cells or of the organism.^{10,11} The epigenetic changes are able to extend beyond the immediate offspring to

further generations. However, the effects are not likely to last indefinitely.¹¹ (See figure 1).



Fig.1 Representation of the chromatin structure, including histones and DNA which become available to epigenetic marks (courtesy of Wikipedia, the free Encyclopedia).

The science of epigenetics is important because it seeks to throw light towards understanding some puzzling occurrences. For instance, it seeks to explain why identical twins that possess the same gene behave unalike in personality, in behavior and even have the tendency to grow differently as they age. Identical twins overtime seem to have differences in height, weight and posture. Even if they have the same diet and lifestyle, unnoticeable cultural and environmental distinctions appear to change their phenotype.¹¹

Molecular Basis of Epigenetics

Epigenetic alterations can modify the activation of certain genes, leaving the genetic code sequence of DNA unaffected. The microstructure (not code) of the DNA or the associated chromatin proteins may be modified, resulting in activation or silencing. This mechanism allows differentiated cells in a multicellular organism to express only the genes that are essential for their own activities.^{12,13} Epigenetic changes are protected when cells divide. Many epigenetic alterations occur within an organism's life time. However, these epigenetic alterations can be transferred to the organism's offspring through transgenerational epigenetic inheritance. Moreover, if gene inactivation takes place in a sperm or egg cell that gives rise to fertilization, this epigenetic modification can as well be transferred to the next generation.^{13,14} Epigenetic changes can also be caused by DNA damage. DNA damage occurs frequently, happening on average of about 60,000 times per day per cell of the human body. These damages are grossly repaired, but at the site of a DNA repair, epigenetic alterations remain.^{15,16} A double strand break in DNA is able to cause unprogrammed epigenetic gene silencing both by causing DNA

methylation in addition to promoting silencing types of histone modifications (chromatin remodeling).¹⁷ Also the enzyme Parp 1 (Poly (ADP)-ribose polymerase) and its product poly (ADP)-ribose (PAR) accumulate at sites of DNA damage as part of a repair process. This accumulation directs recruitment and activation of the chromatin remodeling protein ALC 1 that is able to cause nucleosome remodeling.^{17,18,19} Nucleosome remodeling causes epigenetic silencing of the DNA repair gene, MLH 1.^{12,20} DNA damage chemicals which include benzene, hydroquinone, styrene, carbon tetrachloride and trichloroethylene cause significant hypomethylation of DNA with some occurring through the activation of oxidative stress pathway.²⁰

Techniques used to Study Epigenetics

Epigenetic research utilizes a wide range of molecular biological methods to understand epigenetic phenomena. These include chromatin immunoprecipitation (together with its large scale variants, (chlp-on-and chlp-seq), fluorescent in-situ methylation-sensitive hybridization, restriction enzymes, DNA adenine methvltransferase identification (DamlD) and bisulfate sequencing. In addition, the use of bioinformatics methods plays a role especially in computational epigenetics.²¹

Behavioral Epigenetics

Behavioral epigenetics is the science which explains the way signals from the surrounding lead to molecular biological changes which modify what happens in the brain cells. It is the field of study which explains how everything that happens during the life span of an individual (like social experience, diet and exposure to toxins) molds biological hereditary.²² Behavioral epigenetics tends to proffer a solution for understanding how the expression of genes is affected by experiences and the environment resulting in individual differences in behavior. cognition, personality and mental health.²³ This science provides a framework for solving medical problems like mental retardation, neurodegenerative disorders, schizophrenia, autism and even social challenges like suicide, aging, addiction and child abuse and neglect.^{23,24} The first recorded example of epigenetics influencing behavior was provided by Michael Szyf et al, in 2004. They found out that the type and amount of nurturing a mother rat gives in the

early weeks of the rat's infancy determines the way the rat will respond to stress later in life.²⁵ This stress sensitivity was connected to a down-regulation in the expression of the glucocorticoid receptor in the brain. Consequently, this down regulation was identified to be a result of the extent of methylation in the promoter region of the glucocorticoid receptor gene.²⁶ Soon after birth it was noticed that methyl groups suppress the glucocorticoid receptor gene in all the young rats, causing the gene not to unwind from the histone to allow for its transcription, resulting in a reduced stress response. The nurturing behaviors from the mother rat were noted to stimulate activation of stress signaling pathways that removed methyl groups from the DNA. This released the tightly wound gene exposing it for transcription. The glucocorticoid gene was activated, causing a lowered stress response. The young rats that received relatively less nurturing upbringing were more sensitive to stress throughout their life span. This pioneering research work in rats has been difficult to duplicate in human being due to lack of availability of human brain tissue for evaluation of epigenetic changes.^{24, 26}

Pyschopathology and Mental Health in Epigenetics

Epigenetics and environmental influences appear to work together to increase the risk of addiction.²⁷ For instance, environmental stress has been revealed to raise the risk of substance abuse.²⁸ In order to cope with stress, alcohol and drugs may be used as an escape.²⁹ Once the abuse of a substance begins, epigenetic changes may further worsen the biological and behavioral changes that accompany addiction. The abuse of a substance for a short time can generate long lasting epigenetic changes in the brain of rodents through DNA methylation histone and modification.^{6,27} It has been observed that epigenetic changes alter gene expression that raises the susceptibility of a person to engage in repeated overdose of a substance in the future. The consumption of alcohol has been revealed to generate epigenetic alterations that contribute to increased alcohol.^{27,30} desire of Therefore, epigenetic modifications may play a role in the progression from the controlled intake to the loss of ability to contain alcohol consumption.³¹ These alterations may be long term as is seen in smokers who still possess nicotine related epigenetic changes ten years after they had stopped smoking.³²

Epigenetics of Schizophrenia

Epigenetic alterations including hypomethylation of glutamatergic genes (i.e NMDA-receptor-subunit gene NR3B and the promoter of the AMPA-receptor subunit gene GRIAZ) in dead human brains of schizophrenics were seen to have raised levels of glutamate. Because glutamate is the most common, fast excitatory neurotransmitter, its increasing levels may be responsible to the psychotic episodes related to schizophrenia.³³ Epigenetic alterations affecting a greater number of genes have been found in men having schizophrenia when compared with women with the ailment.³⁴ Studies have proved a strong affiliation linking schizophrenia in children born to older fathers.^{35,36} Children born to fathers over the age of 35 years have been seen to have up to three times the potential to have schizophrenia.³⁶ Epigenetic dysfunction in human male sperm cells affecting plenty genes have been shown to rise with age. This gives a possible explanation for increased rates of the ailment in men.^{34,36}

Further Examples of Effects of Epigenetics

Epigenetic alterations have been noticed to occur as a response to environmental exposure. For instance, mice that were given some dietary supplements had epigenetic changes that affected the expression of agouti gene which affected their fur colour, weight and potential to develop cancer.³⁷ One study showed that traumatic experience results in fearful memories that are passed on to future generations via epigenetics. A research work carried on mice revealed that mice could produce offsprings which had aversion to some items that had been a source of negative experiences for their ancestors.³⁸ Some mice were trained using foot shocks to fear an odour similar to cherry blossoms. Afterwards, they tested the extent to which the offsprings were extremely shocked when exposed to the same smell. The young generation though had not been conceived as at the time their fathers underwent the training, and had never smelt the odour prior to the experiment. The offspring of the trained mice could detect and respond to far less amounts of odour implying that they are more sensitive to it. They did not react the same way to other odours, and compared with the offspring of non trained mice were about 200 per cent stonger.³⁸

In a study in humans published in 2008 by Mehler M L, epigenetic differences were connected with differences in taking risk and how monozygotic twins react to stress. The study showed twins having different life paths. Whereas one of the twins displayed risk taking behaviors, the other twin showed risk averse behavior. Epigenetic differences in DNA methylation of CPG islands proximal to the DLX1 gene correlated with the differing behaviors.⁵

Epigenetics and Cancer

Reasearch work on tumour biology has provided facts on how genetic alteration plays a role in the initiation and progression of cancer. Abnormal DNA methylation is linked to unscheduled gene silencing and the gene with high levels of 5- methylcytosine in their promoter region are transcriptionally silent.^{39,40,41} DNA methylation is necessary at embryonic development period and in somatic cells. Patterns of DNA methylation are transmitted to daughter cells with a high degree of accuracy.^{42,43} Abnormal DNA methylation pattern has been linked with a huge number of human cancers. These are found in two hypermethylation different forms: and hypomethylation. When compared with normal tissue, hypermethylation is one of the main epigenetic modifications that suppress transcription via promoter genes. 39,44,45,46 suppressor region of tumour Hypermethylation mostly occurs at the CpG islands in the promoter region and is associated with gene inactivation. Global hypomethylation has been linked with the development and progression of cancer through different mechanism.³⁹

Epigenetics and Cancer Treatment

Recent research has revealed that epigenetic pharmaceuticals could be a replacement or aid therapy for presently accepted treatment methods such as radiation and chemotherapy or may augment these current treatments.⁴⁷ Mapping and characterizing epigenomic alteration transform the understanding of cancer pathology and improve the capability to diagnose and treat cancer. Epigenetic changes are easier to reverse than mutations affecting the genetic code.⁴⁷ The development of these drugs has focused mainly on histone deacetylase (HDAC). For instance, the drug vorinostat an inhibitor of histone deacetylase has been approved for the treatment of cutaneous Tcell lymphoma.⁴⁸ Some epigenetic drugs that target histone modifying enzymes or DNA methylation are already in clinical trials. Proper understanding of chromatin dysregulation will be translated into new and more efficient ways of treating cancer.⁴⁸

Conclusion

Research studies into epigenetics have revealed lots of knowledge pertaining to heritable changes in gene activities which do not result from changes in the DNA sequence. With advances and more researches in this aspect of science of genetics, lots more knowledge in this important discipline will be unfold in no distance future.

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