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Review Article

An introduction to the science of epigenetics

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ABSTRACT

Epigenetics has emerged as an important new discipline. This review provides deeper insights into understanding basic defects in methylation, histone modification, and RNA induced silencing of tumours. These mechanisms have important diagnostic and therapeutic implications for many tumours and diseases. New anti-epigenetic based drug therapies have been developed and drug trials are underway. The future will see further developments in this field.

INTRODUCTION

Popular past convention held that DNA was the master of all intracellular activities and regulator of all basic physiological functions in humans. Recent study of many tumours and many so called "genetic" diseases however suggests an even higher level cellular control by way of epigenetic mechanisms exists that regulate genes. Epigenetics literally means control over the genetics (i.e. the DNA of the body). Epigenetics refers to all the changes that occur in phenotypic expression of genes initiated by acquired environmental factors which are non-DNA induced.[1] These cellular changes can however remain throughout multiple cell divisions in the body and also be transmitted for future generations (fig.1).

The DNA of the cell is not in any way altered during epigenetic changes.

Historically epigenetics was coined by Waddington in 1939 to describe phenotypic expression by genes.[2] An interesting finding was observed by a Swedish worker, Pembrey in a famine in the 19th century. Preadolescent boys who were exposed to the famine were found to be less likely to suffer from cardiovascular disease during later life. Conversely, the paternal grand-daughters of women who were exposed to the famine lived shorter lives as their ova were formed during the famine. And finally it was found that when foodstuff returned to normal, diabetes mortality increased in the grandchildren suggesting changes in the epigenetic protective effect of the restricted famine induced calorie consumption.

Classical genetics so far limited itself to explain cellular function by the rather simplistic DNA, mRNA, tRNA, and ribosomal protein synthesis mechanism.

However classical genetics cannot explain all the diversity of all the population of the same species many of which are protective phenotypic adaptation measures to the changes in the environment. Even identical monozygotic or cloned twins who are born with identical genes at birth eventually in later life show much phenotypic diversity induced by external environmental factors.

The human cell nucleus shows a mass ratio of 1:50-100 between genetic and epigenetic material, suggesting a greater role of epigenetic over genetic control of cell differentiation and function (fig.2). So the future could even reveal more vital epigenetic roles in health and disease. Epigenetic factors in disease in humans were first detected

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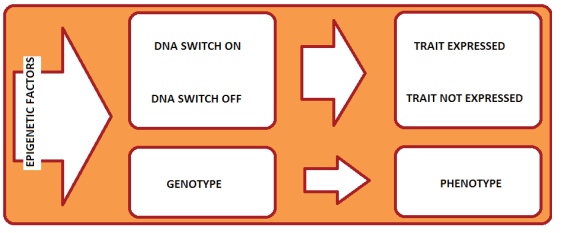

Figure 1: *Relationship between the epigenome, genotype and phenotype.*

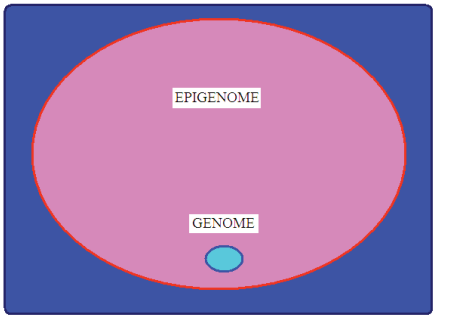

Figure 2: *The sizes of the genome and epigenome (1:50-100).*

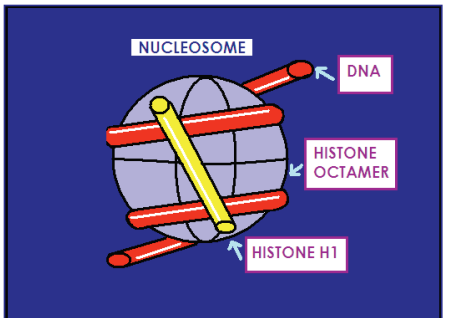

Figure 3: *DNA and Histone.*

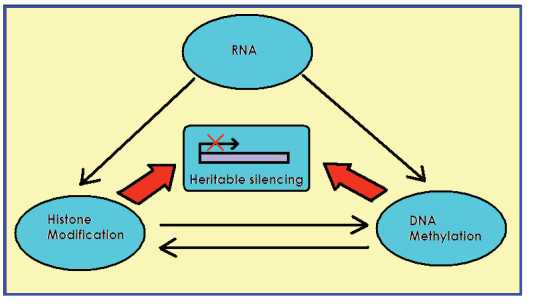

Figure 4: *Gene silencing.*

in 1983 by Feinberg and Vogelstein.[3] The majority of diseases in which epigenetic defects have been shown to be involved in disease pathogenesis are cancers. There is evidence suggesting that the primary (idiopathic) disorders like schizophrenia and bipolar disorder are due to epigenetic defects rather than genetic defects.

Epigenetic factors have also been shown to be involved in ageing, in rare monogenic disorders like fragile-X mental retardation and in lymphomas, conditions for which epigenetic therapy is being developed. Epigenetic processes in disease can include three processes. They are DNA methylation, histone modification and RNA associated silencing (fig.4). The best-known epigenetic marker is DNA methylation. The initial finding of global hypo-methylation of DNA in human tumors was soon followed by the identification of hypermethylated tumor-suppressor genes.[4] DNA methylation occurs in a complex chromatin network and is influenced by the modifications in histone structure that are commonly disrupted in cancer cells.

DNA methylation has critical roles in the control of gene activity and the architecture of the nucleus of the cell. In humans, DNA methylation occurs in cytosine that precedes guanine; these are called dinucleotide CpGs. DNA methylation results in formation of loose euchromatin which is loose and more open and exposed and hence more vulnerable to damage rather than the tightly bound healthy non-methylated heterochromatin. Hypermethylation of the CpG islands in the promoter regions of tumor-suppressor

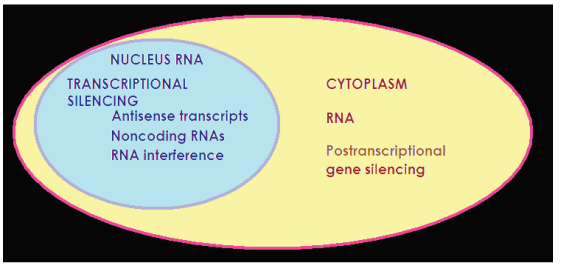

Figure 5: *RNA mediated silencing.*

genes is a major event in the origin of many cancers.[5,6] Hypermethylation of the CpG-island promoter can affect genes involved in the cell cycle, DNA repair, and metabolism of carcinogens, cell-to-cell interaction, apoptosis, and angiogenesis, all of which are involved in the development of cancer.[7]

Histones are not merely DNA packaging proteins, but molecular structures that participate in the regulation of gene expression.[8] They store epigenetic information through such post-translational modifications as: lysine acetylation, arginine and lysine methylation, serine phosphorylation. These modifications affect gene transcription and DNA repair.

Acetylation of histones which occurs at lysine residues and is catalyzed by

histone acetyltransferases (HATs) is associated with activation of gene transcription. Deacetylation of histones, catalyzed by histone deacetylases (HDACs), is associated with silencing of gene transcription.

RNA in various forms such as antisense transcripts, noncoding RNAs, or RNA interference (RNAi) can also induce transcriptional silencing of genes by facilitating histone modification and DNA methylation. The DNA-methylation and histone-modification patterns associated with the development and progression of cancer have potential clinical use. DNA hypermethylation markers are under study as complementary diagnostic tools, prognostic factors, and predictors of responses to treatment. Clinical examples include: Glutathione S-transferase gene (GSTP1) is hypermethylated in 80 - 90% of prostate cancer and not in BPH tissue,[9] methylation silencing of SFRP genes leads to early dysplastic colon mucosal lesions in mice, methylation of the cyclin-dependent kinase inhibitor p16Ink4 gene (a tumor suppressor) leads to immortalization of breast and lung epithelial cells, and hypermethylation of MGMT is an independent predictor of a favorable response of gliomas to carmustine (BCNU) or temozolomide.

Unlike mutations, DNA methylation and histone modifications are reversible. Dormant, hypermethylated tumor-suppressor genes can be awakened with drugs. It is possible to re-express DNA-methylated genes in cancer cell lines by using demethylating agents and to rescue their original functions.

Epigenetic drug therapy include:

DNMT inhibitors: DNA demethylating inhibitors drugs, HDAC inhibitors: Histone deacetylases inhibitors drugs, and

Antisense oligonucleotides: Antisense oligonucleotides are short, defined sequences of nucleotides that are complementary to mRNAs and hybridize with them and make them inactive, thereby blocking translation.[10, 11]

CONCLUSION

We can predict rapid developments in the science of epigenetics, many of which can be fruitfully utilized for the prevention, diagnosis and management of many diseases at present considered “genetic” in origin.

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