

Epigenetics-The Rising Era.

Sourya Acharya*, Samrth Shukla**, S.N. Mahajan*

Department of Medicine* & Pathology**, Datta Meghe Institute of Medical Sciences, Acharya vinoba Bhawe Rural hospital, Swangi (Meghe), Wardha-442004 Maharashtra, India

Abstract: The term epigenetics refers to heritable changes in phenotype (appearance) or expression of genes caused by mechanisms not involving changes in the underlying DNA sequence. The term "epi" in Greek refers to "in addition to" or "on top of". So epigenetics is something in addition to the traditional molecular basis of inheritance (genetics). Epigenetic changes remain through cellular divisions for the remainder of the cell's life and may also last for multiple generations, without changes in the underlying DNA sequence of the organism¹, instead, non-genetic factors cause the organism's genes to behave differently². It can do so because the epigenetic state varies among tissues and during a lifetime, whereas the DNA sequence remains essentially the same. This concept of cellular adaptation to a changing Epigenetics, has incorporated the study of non-DNA sequence-related heredity, at the epicenter of modern medicine because it can help to explain the relationship between an individual's genetic and background, the environment, aging and disease. The common disease genetic and epigenetics (CDGE) model provides an epidemiologic framework that can incorporate epigenetic with genetic variation in the context of age-related susceptibility to disease. Under CDGE, the epigenetics program can modify the effects of deleterious genes or may be influenced by an adverse environment. Thus, including epigenetics into epidemiologic studies of human disease may help explain the relationship between the genome and the environment and may provide new clues to modifying these effects in disease prevention and therapy.

INTRODUCTION

Epigenetics has many definitions, which have changed over time. In simple terms it is a specific molecular phenomena occurring in organisms³. The term was coined by CH Waddington in 1942. When Waddington coined the physical nature of genes and their role in heredity was not known; he used it as a conceptual model of how genes might interact with their surroundings to produce a phenotype. Robin Holliday defined epigenetics as the study of the mechanisms of temporal and spatial control of gene activity during the development of complex organisms⁴. Thus epigenetic can be used to describe any aspect other than DNA sequence that influences the development of an organism. The modern definition of epigenetic is modifications of the DNA or associated proteins, other than DNA sequence variation, that carry information content during cell division⁵. The epigenome is a parallel to the world to genome and refers to the overall epigenome state of a cell. The phrase genetic code has also been adapted to the epigenetic code which describes the set of epigenetic features that create different phenotypes in different cells. The epigenetic code represents the total state of cell, with the position of each molecule accounted for; more typically, the term is used in reference to systematic measurement of specific, relevant forms of epigenetic information such as the histone or DNA methylamine.

MOLECULAR BASIS OF EPIGENETICS

The molecular basis of epigenetics is complex. It involves modification of the activation of certain genes, without altering the basic structure of DNA. In addition the chromatin of DNA may be activated or silenced. This means that each cell in the body has the same instruction manual, but different cell types use them differently. Epigenetic changes are preserved when cells divide. Most epigenetic change only occurs within the course of one individual organism's lifetime, but some epigenetic changes are inherited from generation to the next⁶. Specific epigenetic processes include: (1) Paramutation (2) Imprinting; (3) Reprogramming; (4) Transvection; (5) X-chromosome inactivation; (6) Positional effect; (7) Gene silencing; (8) Carcinogenesis; (9) Teratogenesis; (10) cloning

Epigenetic research uses a wide range of molecular techniques like: (1) chromatin immunoprecipitation, (2) fluorescent in situ hybridization, (3) methylation-sensitive restriction enzymes, (4) DNA adenine methyltransferase (DamID) and bisulfite sequencing, (5) bioinformatics (computational epigenetic)

THE MECHANISMS OF EPIGENETICS

The basic mechanisms on which the whole epigenetic science revolves are (a) DNA methylation and chromatin modification; (b) RNA transcripts with encoded proteins; (c) Prions; (d) Structural inheritance system.

A. DNA methylation

Basically, DNA methylation is a covalent addition of a methyl (CH₃) group to the nucleotide cytosine. DNA methylation during cell division in mammals only at dinucleotide C-G (CpG) by virtue of the enzyme DNA methyltransferase 1. This occurs because during semiconservative DNA replication, a methylated CpG on the parent is partnered with a newly synthesized unmethylated CpG on the daughter strand. DNA methyltransferase I searches out this hemimethylated DNA and places a new methyl group on the daughter CpG⁵. An important environmental connection to epigenetics is that the source of methyl groups in this reaction is methionine an essential amino acid, that is converted to a biologically active methyl donor state through a pathway that involves folic acid.

A second well-studied example of epigenetic mechanism is chromatin modification. Chromatin modification refers to covalent modification of the histone protein that makes up the nucleosomes around which the DNA double helix is coiled approximately 2 turns of 200 base pairs, including the linker DNA between each nucleosome. These chemical modifications also include methylation but in this case involve the amino acids arginine or lysine as well as phosphorylation of serine, acetylation of lysine, and ubiquitinylation of lysine⁷. Unlike DNA methylation, the mechanism of maintaining chromatin modification during cell division is not well understood because no enzyme has yet been identified that recognizes chromatin modification from the parent cell and reproduces them in the daughter cell⁵.

Because DNA methylation and chromatin remodeling play a central

role in many types of epigenetic inheritance, the “epigenetic” is sometimes used as a synonym for these processes. However, this can be misleading. Chromatin remodeling is not always inherited and not all epigenetic inheritance involves chromatin remodeling⁸.

B. RN transcripts and their encoded proteins

Sometimes a gene when become active, transcribes a product that either directly or indirectly maintains the activity of that gene.

Example Hnf4 and Myo D enhance the transcription of many liver- and muscle-specific genes, respectively their own, through the transcription factor activity of the proteins they encode.

Other epigenetic changes are mediated by the production of different splice forms of RNA or formation of double-stranded RNA (RNAi). Descendants of the cell in which the gene was turned on will inherit this activity, even if the original stimulus for gene-activation is no longer present. A larger amount of RNA and protein is contributed to the zygote by the mother during oogenesis or via nurse cells, resulting in maternal effect phenotypes. A smaller quantity of sperm RNA is transmitted from the father, but there is recent evidence that this epigenetic information can lead to visible changes in several generations of offspring.

C. Prions

Prions are infectious proteinaceous particles. These are capable of forming an infection conformational state known as a prion are more loosely defined by their ability to catalytically convert other native state versions of the same protein to an infection conformational state. It is in this latter sense that they can be viewed as epigenetic agents capable of inducing a phenotypic change without a modification of the genome⁹.

D. Structural inheritance systems

In ciliates such as tetrahymena and paramecium, genetically identical cells show heritable differences in the patterns of ciliary rows on their cell surface. Experimentally altered patterns can be transmitted to daughter cells. It seems existing structures act as templates for new structures. The mechanisms of such inheritance are unclear, but reasons exist to assume that multicellular organisms also use existing cell structure to assemble new ones¹⁰.

EPIGENETICS AND HUMAN DISEASE

1. **Colorectal cancer** due to loss of DNA methylation, This hypomethylation leads to abnormal activation of cancerous genes, along with genetic instability and chromosomal rearrangements¹¹.
2. **Acute lymphocytic leukemia** due to abnormal histone modification and excess of chromatin factors such as trithorax group proteins (ALL1) that promote gene expression.
3. **Metastatic cancers** due to polycomb proteins (EZH2) that suppress gene expression⁵.
4. **Lung cancer** due to LOI in PEG/MEST gene.
5. **Glioma** due to LOI in PEG3
6. **Wilm's tumor** due to LOI in IGF2.
7. **Rett syndrome** which is a X-linked disorder to females. It is caused by mutations in methylcytosine binding protein-encoding gene2 (MECP2). This epigenetic mechanism involves chromatin modifying genes. In this disease initially girls are born normally, but they gradually develop inability to talk and walk, movement disorder, dementia and finally death¹².
8. **ICF Syndrome** Immunodeficiency, chromosomal instability and facial anomalies is caused by mutation in de novo DNA methyltransferase (DNMT3B)¹³.
9. **Beckwith - Wiedemann syndrome (BWS)**, which is characterized

by prenatal overgrowth, middle abdominal wall defects, ear creases or pits, neonatal hypoglycemia, and a high frequency of Wilms and other embryonal tumors, such as rhabdomyosarcoma and hepatoblastoma. BWS is a paradigm for understanding the epigenetic changes in several genes. Just as Li-Fraumeni is a paradigm for understanding the traditional genetic of cancer because it involves familial transmission of mutations in the P53 gene. The idea for both BWS and Li-Fraumeni is that what occurs constitutionally in these well-defined syndromes may also occur as somatic alterations in common tumors, a principle of conventional cancer epidemiology pioneered by Knudson^{14,15}. The basic epigenetic defect is LOI (loss of imprinting) of insulin like growth factor (IGF2).

10. **Angelman syndrome and Prader - Will syndrome** - both can be produced by the same genetic mutation chromosome 15 q partial deletion, and the particular syndrome that will develop depends on whether the mutation is inherited from the child's mother or from their father¹⁶. This is due to the presence of genomic imprinting in the region.

FUTURE PROMISES

If we peep into the future of epigenetic application, then first of all we have to answer some basic questions.

- (1) How is epigenetic memory established and maintained
- (2) What are the determinations in chromatin remodeling that maintain epigenetic state?

Landmark experiments suggest that subnuclear compartmentalization is the most important ingredient of chromatin state. Most studies till date have been targeting the nucleosome-the promoter, but it is suggested that full understanding of carcinogenesis may require elucidation of the role in specific topographic domains (nuclear periphery).

This hope of cancer epigenetics may lead to a breakthrough revolution in cancer prevention and management, because of the fact that epigenetic changes are more malleable than conventional genetic mutations.

CONCLUSION

Humans have just started to explore the unfathomable depths of Epigenetics, which delves deeper into the mysterious genetic onion, involving information stored in the proteins and chemicals that surround and stick to DNA. A five-year Human Epigenome Project to map all the DNA methyl 1 sites was launched in October 2003 in the UK. Finally, the fact that epigenetic anomalies can be reversed makes then inviting targets for a whole new generation of medicine.

This may be the first time we have heard of epigenetic. Clearly, it won't be the last.

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