EPIGENETIC LANDSCAPE OF HUMAN DISEASES

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Abstract: *The last years have brought profound insights into molecular mechanisms and application of epigenetics to medicine. Alteration of epigenetic profile is considered to be influential in both the normal and disease state of an organism. Various diseases, such as cancers, neuropsychiatric disease and other non-neoplastic disease are often associated with epigenetic alteration. In the light of increasing knowledge on the involvement of epigenetic factors in disease, it is now becoming apparent that epigenetic factors could be ideal therapeutic targets. In the context of the new insights of epigenetics, this review summarized the epigenetic mechanism of gene expression and the most important epigenetic pathologies.*

INTRODUCTION

The twenty-first century is highlighted by the important discoveries in the life sciences field. Genome projects, new technologies and databases led to a new emerging domain: epigenetics.

When the human genome sequencing was completed (first draft in 2000 and the final sequence was published in April 2003) the academic community thought that the problem of genetic diseases was solved. Unfortunately, the Human Genome Project did not aim to study the regulation of gene expression. The expected number of genes was much higher than the real number of genes discovered through this project (around thirty thousand).

Monozygotic twins are genetically identical, but in many instances, only one twin develops a disease as autism, cancer or some neurodegenerative disorders. Starting from this observation, correlated with molecular analysis has emerged the conclusion that the genetic information can be read in different ways, meaning that some parts of genetic material can be blocked (silenced) and others can be promoted (expressed). These differences in molecular organization and function of genetic material could be explained by the "Epigenetics".

The term "epigenetics" was used for the first time by Conrad Waddington to described events that could not be explained by genetic principles. He defined epigenetics as "the branch of biology which studies the causal interactions between genes and their products, which bring the phenotype into being".(1)

Epigenetics literally means "outside conventional genetics". It is now used to describe stable modification in gene expression pattern during development and cell differentiation. Epigenetic regulation of gene expression is a mechanism that is used by the organism to integrate in its genome, intrinsic and environmental signals.(2) Epigenetics was now concerned with the transmission of phenotype through cell division (mitosis and meiosis) by mechanisms that did not involve modifications in the DNA sequence.(3) In eukaryotes, genetic material represented by chromatin is a complex of macromolecules consisting in DNA, RNA, histone and non-histone proteins.(4)

The epigenetic modifications represent a base for transgenerational cell memory. Environmental factors can play an important role as inducers of different epigenetic mechanisms such as: DNA methylation, histone modifications, histone variants, noncoding small RNAs, resulting in changes of chromatin conformation.(5-7)

Distinct epigenetic marks decide the sets of expressed genes and the sets of silenced genes. Once established, epigenetic patterns are stable and are transferred to the next generation of somatic cells.

The molecular key players of epigenetic mechanisms are biochemical modifications of histone proteins and DNA. Posttranslational modifications occur primarily on N-terminus tail, and include phosphorylation, methylation, acetylation, ubiquitination and sumoylation. Because of their chemical properties, these modifications modulate the accessibility of DNA to the transcriptional factors.

Epigenetic modifications can have significant impact on human health, disease susceptibility, stem cell research and developmental biology. In recent years significant progress has occurred in this rapidly advancing field and many studies have been published. Even in the field of neuroscience, for both developmental processes and cognition, their relevance has been acknowledged.(8)

DNA methylation is one of the best characterized chemical modification of chromatin. In humans, nearly all DNA methylation occurs on cytosine residues of CpG dinucleotides (named CpG islands). Both core promoter and transcription start site are included within the CpG island and gene expression is completely repressed when this region becomes hypermethylated. This process can be reversibly regulating genome function through affecting gene transcription and chromatin remodelling.(9) During cell differentiation DNA methylation may specifically change to activate or inactivate specific genes.

Genome-wide methylation patterns are fully reprogrammed in human germ cells and in pre-implantation embryos.(10) In genomic imprinting and X-chromosome inactivation, which are major epigenetic phenomena in

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mammals, DNA methylation is the most important chemical modification. Over the last 30 years, there have been many studies that have shown alterations in patterns of distribution of 5-methylcytosine between neoplastic and normal cells.(11-13)

There are three major ways by which CpG methylation can contribute to oncogenesis: hypomethylation of proto-oncogenes (cell division controlling genes) and whole genome hypomethylation, focal hypermethylation of the promoter region of tumor suppressor genes and direct mutagenesis.(14)

The first recognized change in DNA methylation patterns in cancer cells and the most important is a global decrease of this modification.(15-18) Hypomethylation of DNA affects chromosomal stability and increases the risk of aneuploidy. Genomic instability caused by altered DNA-proteins interactions is a hallmark of cancer.(19) Hypomethylation of DNA it seems to be occurs in ageing and as result, the increased incidence of various types of cancer in elderly is age-related pathologies.

The best-understood mechanism by which DNA methylation causes cancer is the hypermethylation of the regulatory regions (promoters) of tumour suppressor genes (table no. 1).

Table no. 1. Genetic disorders affecting chromatin structure in *cis* (12)

No Crt	Classes of hypermethylated genes in cancer	Examples
1	Classic tumour suppressor genes known to be hypermethylated in families with hereditary cancer syndromes	VHL, E-cadherin, p16Inc4a, APC, Stk4, RB
2	Candidate tumor suppresor genes	RASSF1A, O6-MGMT, Gst-Pi, GATA4, GATA5, DAP-kinase
3	Genes discovered through random screens for hypermethylated genes	HIC1, BMP3, SLC5A8, SSI1

5-methyl-cytosine could be spontaneously converted to thyamine in the deamination process, generating gene mutations and in some instances leading to cancer.(11)

Methylation of cytosine residues has also been shown to favour the formation of carcinogenic adducts between DNA and carcinogens such as benzo(a)pyrene in cigarette smoke.(12)

DNA methylation can also alters the incidence of mutations in the p53 (suppressor gene) in sunlight-exposed skin.(20) In this case, the methyl group changes the absorption specrum for cytosine into the range of incident sunlight, thereby increasing the formation of pyrimidine dimers in the DNA.

Methylated DNA sequences are recognized by the methyl-CpG binding proteins (MBD family – methylated DNA binding domain) which mediate interaction s between DNA methylation, histone deacetylation and chromatin component. Various disfunctions in such genes lead to serious disorders. The MeCP2 gene locates on the X-chromosome is affected in the Rett syndrome patient. This syndrome affects most frequently females and is characterized by loos of speech, autism, ataxia, mental retardation.(21) The MBD4 gene is also altered in tumours with microsatellite instabilities.(11)

Histones are basic proteins, making an octameric structure that packages DNA in eukaryotes forming a structure knows as chromatin. The term chromatin was introduced by Flemming in 1879 for the stainable structures in the cell nucleus visible during cell division, which were later named chromosomes. Many epigenetic phenomena today relate to chemical or structural modifications of chromatin, i.e. complexes of DNA and proteins into which the genomes are packaged. Chromatin is not a uniform structure, however, and in recent years, an explosion in our knowledge of the variations in chromatin structure has occurred. Aminoacids that form histone tails are sites of chemical modifications such as: acetylation, methylation, phosphorylation, ubiquitylation, sumoylation. All these chemical modifications affect the structure of chromatin by preventing contacts that facilitate certain chromatin conformations or higher-order structure or by disrupting the bindings of proteins that associate with chromatin or histones. Alternatively, histone posttranslational modifications may provide altered binding sites that attract certain effector proteins. These various mechanisms established different functional outcomes. Some are transient, others are stable and epigenetically heritable.

Strahl and Allis (22) postulated the hypothesis of a "histone code" that links the histone specific modifications with individual processes. Schreiber and Bernstein (23) proposed a more general hypothesis were histone posttranslational modifications serve as a nuclear DNA-associated signal transduction pathway. The addition or removal of an array of covalent modifications in histones is catalyzed by the histone modifying enzymes. Some genes affected by mutation in various type of cancer recruit histone modifying enzymes and alter gene expression. For example, the PML-RAR gene translocation in acute promyelocytic leukemia recruit histone deacetylases (HDAC) that remodels the chromatin structure from active to silenced and lead to leukemic transformation.(24)

The most recent class of molecules contributing to the epigenetic signal is that of non-coding RNAs (snoRNA, miRNA, siRNA) Some of these small RNA molecules regulate chromatin modifications, DNA methylation, imprinting and transcriptional silencing.(6,25)

All these modifications regulate gene expression as well as other genomic functions and have been involved in establishing and maintaining a heritable epigenetic code that contributes to defining cell identity, fate and differentiation.(26).

EPIGENETICS AND HUMAN DISORDERS

The first evidence of a role for epigenetics in human disease came after the understanding of genomic imprinting and the finding that several genes are subject to regulation by this mechanism.(27) Genomic imprinting is a form of epigenetic regulation in which the expression of a gene depends the parental origin (inherited form the mother or the father). Mutations in genes encoding proteins involved in DNA methylation, binding to methylated DNA, histone modifications and small non-coding RNA, all contribute to the growing class of human disorders affecting the epigenome.

Prader-Willi syndrome (PWS) and **Angelman syndrome** (AS) are caused in a majority of cases by the same deletion (15q11-q13), but their clinical characteristics are different. PWS is caused by paternal inherited deletions whereas AS is determined by the maternal origin deletion (28). PWS (1:10000 births in general population) is characterized by developmental delay, infantile hypotonia, severe obesity, short stature, genital hypoplasia, some cognitive impairment, small hand and feet, almond-shape eyes, moderate mental retardation and anxiety.(25) In contrast, patients with AS (1:12000-20000 births in general population) have a "relaxed and happy disposition". They have severe developmental delay, ataxia, microcephaly and some dysmorphic features.

Imprinting defects represent another class of mutations leading to PWS and AS syndromes. Imprinting center having a bipartite structure is located within 15q11-q13. Defects in this center cause a chromosome of one parental origin to have an altered epigenotype, typically that of the chromosome of an opposite parental origin.

Silver Russel syndrome (SRS) is a developmental

disorder characterized by slow growth before and after birth, mental retardation, some dysmorphic facial and cranial features. The exact incidence of RSR is unknown. There is a range from 1:30000 to 1:100000 births in general population. SRS is genetically heterogenous and complex. Research has focused on genes located in particular regions of chromosome 7 and chromosome 11. About 10% of the cases result from maternal uniparental disomy for chromosome 7.(29) Researchers suspect that 30 to 50 percents of all cases of SRS result from changes in DNA methylation pattern on a region within chromosome 11 (11p15). At this region are located near one to another the H19 and IGF2 genes that are thought to be involved in directing normal growth. A loss of methylation pattern disrupts the regulation of these genes conducting to slow growth and other features of this syndrome. Actually, biallelic expression of H19 and decreased expression of IGF2 is the most prominent epigenetic defect.(30) In about 40% of people with SRS, the cause of the condition is unknown.

Beckwith-Wiedemann syndrome (BWS) is characterized by somatic overgrowth, congenital abnormalities and predisposition to childhood embryonal malignancies.(31) Patients with BWS manifest gigantism, macroglossia, variable degrees of ear and other organ anomalies. Many patients suffer from increased size of internal organs and in some instances from embryonic tumours such as hepatoblastoma, Wilm's tumour, rhabdomyosarcoma. The incidence of SRS is estimated at 1 to 13700 newborns worldwide. The majority of BWS cases are sporadic, but a small number of families with an autosomal dominant inheritance pattern (modified by genomic imprinting) suggested genetic etiology and linked the syndrome to 11p15 region. Abnormal methylation of imprinting center that controls the activity of several genes including *CDKN1C, H19, IGF2* and *KCNQ1OT1* disrupts the regulation of these genes leading to overgrowth and other characteristic features of BWS. About 20% of cases of BWS are caused by paternal uniparental disomy (people have two active copies of paternally inherited genes. In some instances, mutations in CDKN1C (cyclin-dependent kinase inhibitor) may cause BWS. About 1% of people with BWS have chromosomal abnormality (translocation, duplication or deletion).

Pseudohypoparathyroidism (PHP) is a genetic disorder in which the body is unable to respond to parathyroid hormone. There are several clinical variants with a variety of developmental and somatic defects. The clinically heterogenous phenotypes result from mutations in the GNAS1 gene encoding the α-stimulating activity polypeptide 1. GNAS1 is located within chromosome 20q13.2. This gene has three alternative exons (1A, XL and NESP55) that are spliced to exon 2-13 to produce different transcript.(25) There are differentially methylated regions near to exons, causing NESP55 to be expressed exclusively from maternal alleles. XL and exon 1A are paternally expressed.

Rubinstein-Taybi syndrome (RSTS) is a disorder characterized by intellectual disability, facial abnormalies, dental problems, congenital heart defects and risk of tumorigenesis. Leukemia also occur more frecvently in people with RSTS. The incidence is 1:100,000 – 1: 125,000 newborns. Cytogenetic abnormalities involving chromosome 16 (16p13.3) were identified in several RSTS people.(32) The *CREBBP* gene provides instructions for making a protein that helps control the activity of many other genes. This protein, CREB binding protein is involved in regulation of cell growth and division. If one copy of this gene is affected, a reduction in the amount of CREB binding protein occur. A small percentage of cases of RSTS is caused by mutations in *EP300* gene. This gene encoding a histone acetyl transferase (HAT) and transcriptional coactivator.(25) For 50% of people with RSTS, the cause is unknown. They do not have a mutation identified in CREBBP or EP300 genes.(33)

Schimke immune-osseous dysplasia (SIOD) is an autosomal recessive multisystem disorder characterized by growth deficiency, dysplasia of the spine and ends of long bones, hypothyroidism, renal disfunction and defective T-cell-mediated immunity.(25) The prevalence in North America is estimated to be 1:1,000,000 -1:3,000,000.(34) SIOD is caused by mutations in SMRCAL1 gene. The protein of this gene influences the expression of other genes through chromatin remodeling. This protein is a SW1/SNF2 related polypeptide that binds to chromatin and regulate transcriptional activity.(35) Mutations in SMARCAL1 gene lead to disease by affecting protein activity, protein stability or protein's ability to bind to chromatin.

Fragile X syndrome is one of the most common causes of inherited mental retardation. Some affected patients display autistic behaviours. Prevalence is estimated to affect 1:25,000 newborn males. The gene responsible for this condition is FMR1, which encodes FMRP protein. The most common mutational mechanism is an expansion of an unstable non-coding CGG repeat.(25) A CpG island in the 5' regulatory region of FMR1 becomes aberrantly methylated upon repeat expansion. Decreased histone acetylation at the 5' end was found in cells from fragile X patients (36). The altered DNA methylation and histone acetylation profiles conduct to loss of FMR1 expression in patients with X fragile syndrome. These patients have a primary genetic mutation and a secondary epigenetic mutation.(25)

Facioscapulohumeral dystrophy (FSHD) is an autosomal dominant muscular dystrophy characterized by progressive weakness and atrophy of muscle. The signs and symptoms of FSHD usually appear in adolescence. This condition has an estimated prevalence of 1:20,000 people. The major locus for FSHD maps to the subtelomeric region of chromosome 4q35. Near to this region is located D4Z4, a low copy repeat that contains 11-150 repeated segments of 3.3 kb GC rich units.(37) The entire D4Z4 region is normally hypermethylated. In FSHD, D4Z4 is hypomethylated because of the abnormally shortened repeats (1 to 10 repeats) or because of mutations in SMCHD1 gene, which provides instructions for making a protein that normally methylates the D4Z4 region.

Methylene tetrahydrofolate reductase deficiency is a rare autosomal recesive disorder characterized by mental retardation.(38) Methylene tetrahydrofolate reductase (MTHFR) is important for chemical reaction involving forms of the folate (vitamin B9). This enzyme converts 5,10 – methylenetetrahydrofilate to 5-methyl tetrahydrofolate. A methyl group is acquired from 5MTHF during conversion of homocysteine to methionine and then, is converted to S-adenosyl methyionine (SAM), the major methyl donor for all methyl transferases. The polymorphism for MTHFR has been found as a risk factor of atherosclerosis, neural tube defects and cancer.(38)

ENVIRONMENTAL EPIGENETICS AND PATHOGENESIS

In the last years, many studies underlining the interaction between environment and genome via epigenetic regulation were performed. Multiple epidemiological and experimental studies indicate that asthma risk may be modified by an epigenetic pathway.(39)

Some prospective studies indicate a correlation between prenatal exposure to environmental tobacco smoking, with impaired respiratory function, asthma, respiratory infections in young children and teenagers.(7,40) The asthma

was considered to be determined only by interactions between genetic polymorphisms and environmental exposures, but nowadays epigenetic mechanisms including developmental reprogramming and imprinting are also considered as important factors in inducing and developing this pathology as it was suggested in 2007.(7)

In early life, the influence of dietary and environmental exposures can have a profound effect on the epigenetic pattern, potentially resulting in diseases later in the life.(7) New studies concluded that epigenetic processes are emerging as major factors in obesity, diabetes and heart disease. Early nutrition might play a critical role in disease susceptibility.

CONCLUSIONS

Our genetic information is differentially expressed both in space and time through not yet understood mechanisms. Epigenetic mechanisms constrain expression by adapting some genome regions to maintain either gene activity or gene silencing. This is archived through chemical modification of chromatin.

Epigenetic mechanisms play a crucial role in regulation of function in the entire tissues diversity. In the light of their complexity, the term of a "histone code" or "histone language" may now be extended to that of an "epigenetic code" that engage multiple and complex processes.

The high-throughput sequencing technologies and the sophisticated algorithms designed to analyse the large amount of data will provide a chance to discover the epigenetic marks associated with specific disease and will help to diagnose patients.

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