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Review Article

EPIGENETICS: EFFECT OF ENVIRONMENTAL FACTORS ON HUMAN GENOME

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ABSTRACT

The physical and social behavior of an organism is influenced by its epigenetic modification, which involved histone modification, DNA methylation, non-coding RNA expression and chromatin remodeling. In contrast to genetic sequence, the epigenetic patterns differ from cell to cell and are dynamically being modified throughout the life span. Though prenatal period is the time for epigenetic modification and cell programming, there are growing evidence showing the influences of nutritional and environmental factors on gene expression. As epigenome is responsible for gene expression and phenotypic plasticity, its alterations have the same consequences as DNA mutations. Studies are going on to reveal out that the DNA is not the only destiny of life, instead by having a good environment and healthy lifestyle we are able to get and express better genes and can transfer them to our next generations. In this review the basic mechanism of epigenetic and the effects of environmental factors including dietary factors and early maternal care on human behavior and health status are discussed and in this regard we will examine the possibility of epigenetic mechanisms involved in chronic disease, and also, we will be hopeful to develop new medicines acting specifically on epigenome with better results.

Keywords: Epigenetic, Histone modification, DNA methylation, Cell programming, Epigenome

INTRODUCTION

Different cell types of an organism have same DNA with the same sequence of base pairs, but cells of each organ have different morphological and physiological characteristic because they have different programming of gene expression which is highly responsive to developmental, physiological, pathological and environmental cue. This programming of gene expression that is responsible for the different characteristic of the different cell is called epigenetic [1].

In defining of cell function and other characteristics, the epigenetic markers are as important as the nucleotide sequence [2] and also epigenetic patterns can be transferred heritably from cell to cell in the somatic cell division and also generation to generation in germ line cells [3]. As epigenetic modification can be reversible, so the research is ongoing to find out the causes of silencing and stimulating of different gene expression thus the lifestyle will be suggested to prevent or treat different disorders, furthermore scientists are trying to develop medicine which act on epigenetic sites and it is considered that these medicines will be more effective for treatment of chronic disease [4].

Mechanism

Different types of epigenetic inheritance systems are known and are accepted as cell memory.

DNA methylation

DNA methylation is the process of methylation of cytosine residue at 5' position, which is then called 5th base of the genome [4]. Methylation of DNA mostly takes place at CpG region of the genome. The repeated CpG dinucleotide are called CpG Island that is present in the promoter region of the gene, methylation in the promoter region causes suppression of that particular gene [5, 6]. Analyses of uracil-containing DNA of bacteriophage showed that the uracil-containing DNA melts (denatures) at a lower temperature than normal DNA, thus it is revealed out that the process of cytosine methylation is not apathetic and useless instead it stabilize the double helix of DNA[7]. It is believed that the methylation of genome erases during fertilization of ovum and sperm and a series of de novo methylation takes place and thus each gene will gain a specific pattern of methylation [8]. The process of inactivation of X-linked genes in female embryo also occurs in this stage, leaving only one copy of an active gene for expression [9].

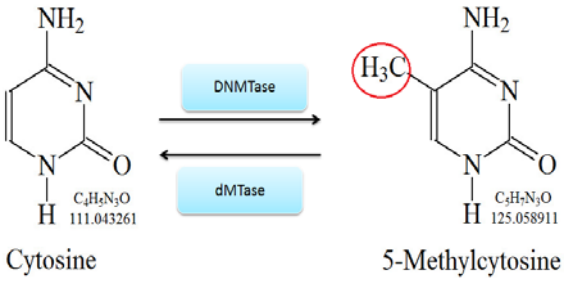

Fig. 1: The reversible DNA methylation reaction catalyzed by DNMT

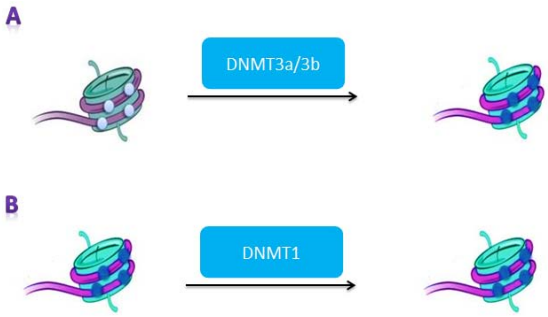

Fig. 2: [A] De novo methylation reactions of DNA. [B]Maintenance of methylation

Methylation of DNA is catalyzed by enzymatic family of the DNA cytosine methyltransferase, there are two groups of methyl-transferases, DMT1 which is responsible for methylation of daughter DNA at same points as paternal DNA, the process is known as methylation maintenance, DMT3A and DMT3B are responsible for de novo methylation of DNA during embryogenesis [10]. DNA methylation occurs during the development and remains stable throughout the life span of an individual thus DNA methylation have a key role in gene regulation and stabilization, alteration in methylation level of DNA can lead to cancer. Studies have shown

that there is hyper methylation of the promoter region of tumor suppressor gene in different types of cancers [11, 12]. Recently it is recognized that DNA methylation also has a central role in etiology of human neurodevelopment disease like Fragile X, ICF and Rett syndrome [13]. The epigenetic research focused on two main areas. First is how DNA methylation is incorporated and maintains in the genome and the second is the exploring the causes of where methyl groups are added throughout the genome [4]. Research has shown that one mechanism of controlling the methylation of DNA is the genetic code itself. The local base composition of promoter determines the methylation. However, it is not the single mechanism of controlling the gene methylation; other factors like the binding site of a factor along with the genome and mutation of a factor also have an impact on methylation of DNA [14]. Further researches are required to determine the role of environmental factors on DNA methylation.

DNA hydroxymethylation

One another important factor of mammalian DNA epigenetic modification is hydroxylation of 5' methylcytosine into 5' hydroxymethylcytosine. 5 hydroxymethyl cytosine is known as 6th base of DNA [15] which greatly expands the plasticity of the genome [16]. 5hmc is an intermediate in active demethylation of 5 methyl cytosine through the base excision repair pathway. The process is highly important for reprogramming of cell [16, 17]. This type of demethylation process is an analogue to the reactions takes place in the salvage pathway of thymidine[18] and direct repair of DNA alkylation by AlkB-oxygenases [19, 20] the reaction is catalyzed by TET 1 a 5mc hydroxylase[21]. 5 hmc is present in all tissues but is found in greater amount in embryonic stem cells [21] and Purkinje neurons [22]. Unlike 5mc which is found in the entire genome, 5hmc is enriched around genes especially at transcription start sites [23].

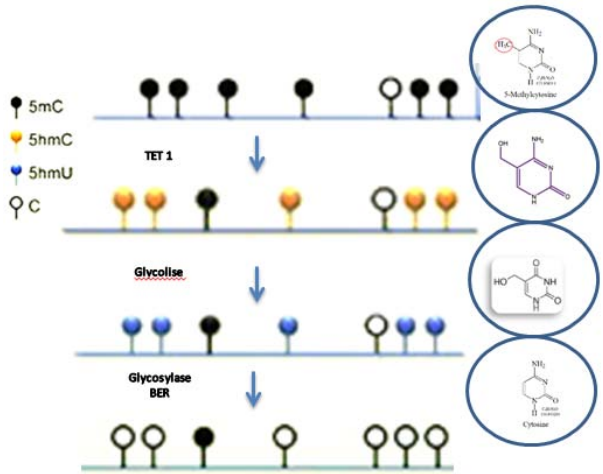

Fig. 3: Conversion of 5mc into 5hmc by TET1 and then conversion of 5hmc to cytosines

Covalent histone modifications

Histone proteins are found in the nucleus and act for DNA compaction, 2 copies of H2A, H2B, H3 and H4 histone proteins making an octamer, are tightly revealed by approximately 147 bps of DNA making nucleosomes[4]. Histone proteins are composed of the C-terminal globular domain and NH2 terminal tails [24], the core portion of histone proteins are densely packed, and their amine terminal tails are able to modify covalently by histone modification enzymes, resulting in acetylation, methylation, phosphorylation and ubiquitin [25]. These types of modifications either enhance or repress gene transcription depends on modified residue and type of modification [26], for example, lysine acetylation activates gene transcription and the effect of lysine methylation differs according to the position of lysine. The promoter region of active genes are rich in tri methylated lysine 4 on histone 3 [H3K4me3] [27], but tri-methylation of lysine 9 of H3 [H3K9me3] and H3K27 [H3K27me3] in promoter region suppress the underlying gene (fig. 4) [28]. There are a set of enzymes responsible for covalent modification of histone proteins. Histone acetyltransferase and histone methyltransferase add acetyl and methyl groups respectively while HDACs and histone demethylase remove acetyl and methyl groups [29].

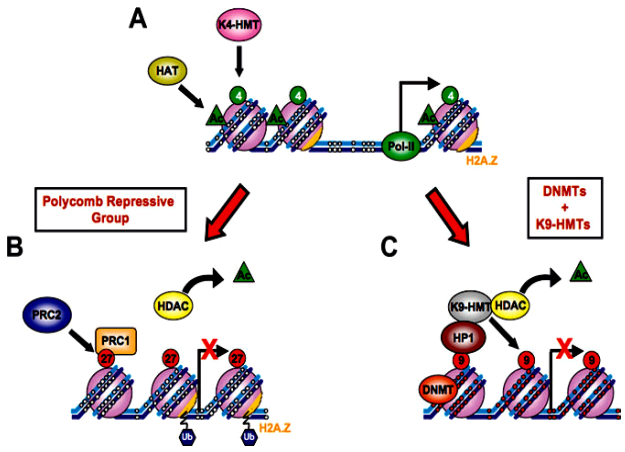

Fig. 4: [A] An active gene shows an open chromatin structure consisting of un methylated promoter region with no nucleosome upward on the transcription start site.[B]Gene repression by the action of PRC1 and PRC2 that mediate the repressive H3K27 methylation and by removal of the acetyl group by histone decarboxylase. [C] Long term silencing through DNA methylation performed by DNA methyltransferase [28]

Although the vast variety of histone modifications are identified, that regulate gene transcription and are essential for the physiological activities of cells [25, 30], but the exact mechanism of inheritance of the histone code is still not fully understood [28].

Chromatin remodeling

As we know that DNA is packed inside the cell as chromatin and the process of gene transcription just can take genes that are located on the surface of nucleosome [4], thus for transcription of genes that are inside the nucleosome cannot be take place until the chromatin is opened by specific proteins and produces the genes, this process of opening of genes is called chromatin remodeling. Various molecules are known as remodelers that provide the mechanism for chromatin remodeling and thus either enhance or repress gene transcription depending on opening or compaction of gene into nucleosome

There are two types of chromatin remodeling mechanisms [4] 1. ATP-dependent 2. Through combined covalent modification of histone tails.

ATP-dependent: Remodelers hydrolysis ATP and thus provide energy for nucleosome mobilization [31]. However, this is still unknown that how the energy provided by ATP hydrolysis is converted into mechanical energy to mobilize nucleosome and how different remodelers select that which nucleosome should be moving and restructure.

ATP-independent: Recent research explored the link between covalent histone modification and nucleosome remodeling [32], study done by Zhang *et al.* 1999 showed that DNA methylation binding proteins (MBD2) interacts with nucleosomal remodeling complex (NuRD) and directs this complex toward methylated region of DNA [33]. Also the catalytic component of the chromatin remodeling complex, Brahma (Brm) is associated with methylated DNA binding protein MeCP2 [34]. In addition covalent modification of histone also has a key role in ATP dependent chromatin

remodeling mechanisms[35] so all above 3 processes silence genes (for example cancer genes) permanently.

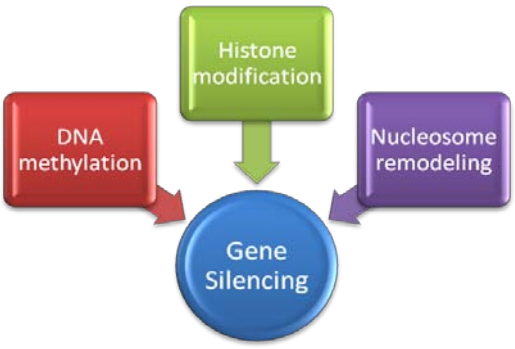

Fig. 5: Different mechanisms of gene silencing

Micro RNAs

Micro-RNAs are a group of non-coding RNAs containing 20–30 nucleotides that regulate gene transcription by negative gene translation mechanism [36]. Micros RNA regulate gene transcription by two distinct mechanisms [37].

1. Micro RNA contains a perfect signal to the targeted RNA, it binds on it and this complex is cleaved by ribonuclease present in RISC [38].

2. Target RNA containing signal imperfectly to the micro-RNA can be subject to translational control [39].

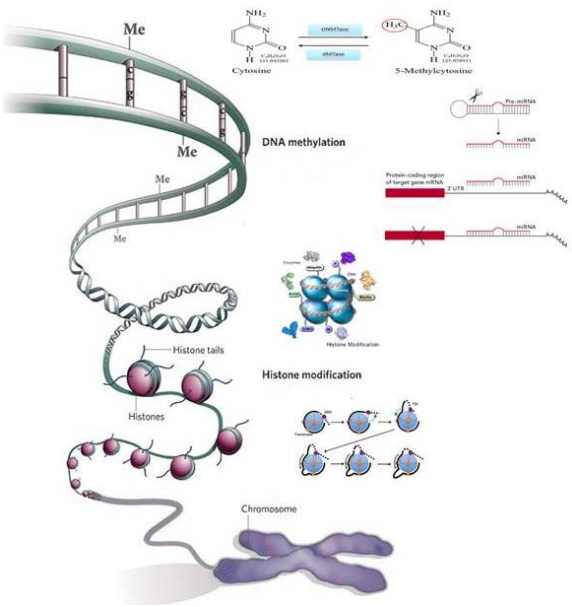

Fig. 6: Different mechanism of gene regulation

Effect of dietary factors on epigenetic modifications

Energy restriction and protein deficient diet

Studies have shown that energy restriction and protein deficient diet during pregnancy can modify DNA methylation or Histone modification thus, can alter gene expression of neonate which persist throughout life, and make the individual susceptible to different disease like cardiovascular, hypertension, diabetes mellitus, etc [38, 41].

Energy restricted diet during the periconceptional period is considered as a stressor by increasing the adrenal mass, increased cortisol response and also by epigenetic modification such as a decrease in methylation of IGF2/H19 gene in the adrenal gland. Energy restriction also can cause changes in covalent histone modification [33]. The chromatin immunoprecipitation assay of GLU4 promoter revealed that there was an increase in the acetylation level of histone in adipose tissue of well-fed mice which was not seen in mice with an energy restricted diet [42]. The link between energy restriction and DNA methylation in humans was observed for the first time by intense studying of people who were born during the Dutch Hunger Winter of 1944-1945 that showed persistent epigenetic differences associate with prenatal exposure to famine [43].

Maternal low protein diet persistently alters the offspring's methylation of specific cytosine in the hepatic PPARa promoter. The study was done by Lillycrop *et al.* (2008) and is considered as a milestone in metabolic programming studies. Thus, maternal low protein di*et al.* ters the gene expression of IgF2 and H19 by regulating their methylation [44] and also increases acetylation of histone 4 and 3 at C/EBPB and also the acetylation of Glu4 promoter. It also changes the methylation of histone in the liver and thus elevates the cholesterol level of offspring [45]. These studies are showing that maternal diet during pregnancy has a high impact on offspring's physical and mental health. That can be the cause of the alarmingly high incidence of different disease like obesity, Diabetes mellitus type 2, Hypertension, etc., in less developed countries.

High fat diet

High-fat diet changes the expression of neuropeptides in the medial hypothalamus which is responsible for the regulation of feeding and energy metabolism [40]. The study which was done on rodent by Milagr *et al.*(2009) showed that taking of high-fat diet for long term affects methylation of an obesity-related gene such as leptin, thus contributing in gene expression and appetite regulation.

Maternal overfeeding with a high-fat diet in rodents results in phenotypic obese offspring which was completely independent of its postnatal nutrition [46] and also the offspring showed non-alcoholic steatohepatitis because of hepatic mitochondrial metabolism and up-regulation of hepatic lipogenesis [47]. Maternal consumption of high fat diet can change epigenetic markers in the brain of offspring, alter the expression of genes related to mesocortico-limbic reward circuitry (dopamine and opioids) so increasing the preference for palatable foods, rich in sucrose and this characteristic was seem to be transferred at least two generation later too, and could contribute to the rising prevalence of obesity [48].

Methyl donors

Dietary methyl donors are derived from foods containing folate, methionine, betaine and choline that are able to transfer a methyl group to DNA and histone through S-adenosyl methionine and thus influence gene expression [49].

Methionine is formed from homocysteine in the liver using methyl group from tetrahydrofolate or from betaine derived from choline in the presence of zinc, selenium, vit B6 and vitB12, thus, if the individual is derived from choline they use more folate to compensate the requirement of the body and also vice versa [50].

The importance of maternal methyl donor deficiency was first observed in mice with abnormal agouti gene with fat, yellow color morphology and more susceptible to disease like diabetes. The agouti gene was transferring from generation to generation when agouti mother was fed with high folate diet, her offspring become normal brown in color and with normal body weight [51]. Also, the methyl donor deficient diet in adult mice changed their liver morphology similar to human HFD induced non-alcoholic fatty liver [52]. Interestingly it has been demonstrated that the folate epigenetic modification can be reversible in adulthood by methyl donor supplementation and this study opens new doors to cancer therapy by methylation and suppression of oncogenes but further studies are required for demonstrating the optimum dose and type of methyl donor to prevent and treat cancer and another disease such as diabetes.

Other nutrients

Few studies have evidenced the role of n-3 and n-6 PUFA, eicosapentaenoic acid, docosa hexanoic acid and arachidonic acid of DNA methylation [40].

In amino acids, Methionine has a significance role in DNA methylation [53]. However, the metabolism of other amino acids (serine, glycine, and histidine) has an important role in DNA methylation, and histone modification [54] but neither methionine nor other amino acids consider as predisposing factors for obesity. Different minerals have role in DNA methylation and thus in the regulation of gene expression. For example, Zn and selenium have a role to play in one carbon metabolism's pathway intervention in the regulation of DNMT and activate HDACs [55]. Mg also has an important role in epigenetic markers. Mg deficiency in pregnant rats leads to different metabolic disorder in offspring by altering methylation of specific cytosine in the hepatic hydroxysteroid dehydrogenase 2 promoters. Low Mg intake is associated with numerous pathological conditions characterized by chronic inflammatory stress such as hypertension, obesity, osteoporosis, and atherosclerosis. In animal models, the maternal magnesium level is important in long-term programming in body adiposity and insulin secretion in offspring, but in human there are diverse effects of Mg level. However, studies have shown that the Mg supplementation increase response of cells to insulin but in a diabetic patient it increases insulin resistance [56].

Calcium, chromium, vit C and vit E are considered to reduce body weight, but further studies are required toward the evidence of their epigenetic mechanism [57].

Effect of childhood environment

One of the interesting areas of epigenetic research is the effect of one's environment of early childhood and its effect on the central nervous system and response to stress. For example, the methylation level of promoter region of the nuclear receptor subfamily 3 (NR3C1) in hippocampi of suicide victims were so much higher than control, and after comparing the childhood environment of both suicide victim and control it is roll out that all of the suicide victim and none of the control had abused childhood environment [9]. The NR3C1 is the specific gene for encoding of neuron-specific glucocorticoid receptor. Thus, the hypothalamic-pituitary-adrenal stress response cannot be inhibited [58]. The same results were seen in pups of mouse, the pups that were subjected to the highly aggressive mother with less grooming and liking and poor maternal nursing care were more sensitive to stress [59] and more interestingly male and female mice whom father was exposed to mental stress were also more sensitive to stress along with more plasma corticosterone concentration [60] this study has shown the epigenetic transformation of characteristics. Molecular effects of social stress on mice brain were decreased in the expression of brain-derived neutrophil factor (BDNF) transcripts, as well as an increase in methylation of histone 3 lysine 27 corresponding to the promoter region of transcripts [61].

Epigenetic and diabetes mellitus

Studies suggested the role of epigenetic factors in the pathology of type 2 diabetes mellitus, although different mechanisms are known I will mention here some of these epigenetic mechanisms. The active gene of insulin which is seen only in ß-cells shows hyperacetylation of H4 and hypermethylation of H3 at lysine 4, a specific characteristic of active genes [62]. Furthermore, in ß cells, HATp300 and the histone methyltransferase SET7/9 are recruited to the promoter region of the insulin gene for the activation of the gene [63].

The ß cell proliferation decline after birth but in the case of increasing demand for insulin imposed by insulin resistance the proliferation of ß cells has an important role. The increase expression of Ink-4a/Arf (ADKN2A locus) is associated with regeneration of reduced ß cell, for expression of Ink-4a/Arf there should be less level of trimethylation of H3, lys 27 at Ink-4a/Arf and histone methyltransferase,Ezh2 together with decreased Bmi binding and loss of H2A ubiquitination at Ink-4a/Arf. A common variant at CDKn2A locus is associated with type 2 DM [64].

Epigenetic and mental health problems

Data collected from the mechanism of the pathology of human mental health problems has shown that there is a number of mental diseases associated with changes in epigenetic markers. I will refer to some examples with their epigenetic mechanisms.

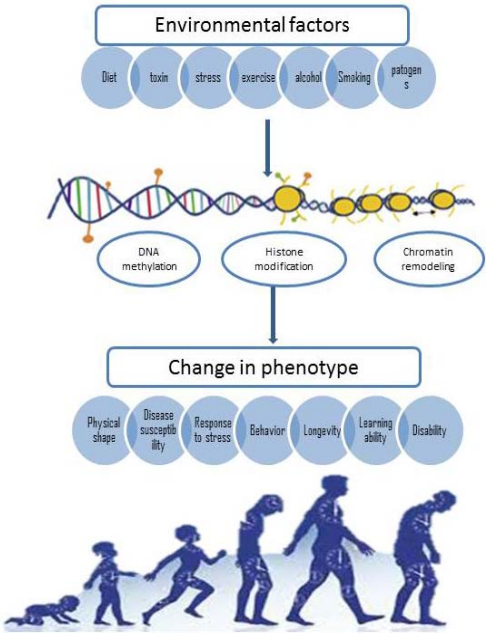

Fig. 7: Effect of environmental factors on DNA methylation

RETT syndrome, a progressive neurodevelopmental disorder which is one of the most common cause of mental retardation in the female, the mechanism behind this disorder is the mutation in methylated DNA binding protein MeCP2[65], mutation and less expression in MeCP2 have widespread neurological defects associated with autism [66].

ATRX an X-linked syndrome of mental retardation associated with a-thalassemia is caused by mutation of the gene responsible for SNF-2 subgroup of protein superfamily with similar helicase and ATPase domain involved in chromatin remodeling [67]. ATRX mutation is due to aberrant DNA methylation [67].

Aberrant DNA methylation is involved in psychopathology. The mechanism of which was discussed in the previous section (the effect of childhood environment) the example of suicide victims was given.

The data of pathology of distinct mental disease indicating aberrant DNA methylation but still it is unclear whether these changes in DNA methylation originate during embryogenesis or later in life.

Conclusion and future perspective

The field of epigenetic is the center of interest in genetic and biomedical research now a day. Every day the epigenetic mechanism of disease is elucidating and as research is going on the link between environment and gene expression is, being better understood. Now we know that our environment, the food that we eat and the stress that we compensate at the work or at home can modify our genes, the genes of our children and even lasting the following generation.

Different types of food that someone eats, childhood environment, maternal care that someone had and maternal diet during prenatal life, can alter gene expression that can modify the response of individual to stress, ability of learning, type of thinking and susceptibility of individual to different disease like Diabetes mellitus, hypertension, hyperlipidemia, different mental disorder like Alzheimer's disease, schizophrenia etc. Thus, by studying epigenetic mechanisms, we can know about harmful signals of environment toward our genome and by achieving healthy lifestyle we can prevent not only our own but also our next generations' genome.

Understanding epigenetic consequences of social exposures stand not only to revolutionize medicine but also to transform social science and humanities as well. Epigenetic could act as a bridge between the social science and biological sciences, allowing a truly integrated understanding of human health and behavior.

CONFLICT OF INTERESTS

Declared none

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