Epigenetic Modifications in Human Disease

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Abstract

Epigenetics is one of the most rapidly expanding fields in science. Growing interest in epigenetics is due to recent advances in understanding the underlying mechanisms in epigenetic phenomena and the prevalence of epigenetic contributions to human disease. This review focuses on the epigenetic mechanisms that control gene expression in a potentially heritable way and their role in health and disease. Among the epigenetic modifications of interest are DNA methylation, histone modifications, and related transcription inactivation associated with chromatin architecture. Granted epigenetic changes are required for normal development and health, disruption to any one of these systems can cause abnormal activation or silencing of genes. Such disruptions have been associated with cancers, intellectual disability, immune, neuropsychiatric and pediatric disorders. As a result, epigenetic therapy has become an interesting phenomenon to counteract the epigenetic modifications that lead to various human disorders.

Keywords: epigenetics, epigenetic modifications, DNA methylation, histone modifications, small non-coding RNA, chromatin architecture, epigenetic disorders, epigenetic therapy

Introduction

Epigenetics is the study of heritable chemical modifications of specific genes or gene-associated proteins, their activity and expression that do not involve a change in the underlying DNA sequence – a change in the phenotype without a change in the

genotype. These modifications include histone modifications, like methylation and acetylation as well as DNA methylation. Epigenetic changes occur naturally and are affected by several factors such as age, disease state or environmental stimuli (e.g. nutrition, lifestyle, toxin exposure).

The field of epigenetics evolved in the early 1940s as a result of the work of a group of scientists including the British embryologist Conrad H. Waddington and Swiss developmental biologist Ernst Hadorn. The term epigenetics, which was coined by Waddington in 1942, was derived from the Greek word "epigenesis" which originally described the influence of the genetic processes on development (Waddington, 1942).

The experimental findings of Conrad Waddington using Drosophila fruit flies led to the discovery of "genetic assimilation" (a process by which a phenotype originally produced in response to an environmental condition, later becomes genetically encoded) as a new evolutionary process (Piqliucci and Murren, 2003). His studies were based on crossveinless trait (a trait that occurs at high frequency in heat-treated flies) of Drosophila. After a few generations, the trait was found in the population, without the application of heat, based on hidden genetic variation that has been assimilated in the organism's genome (Slack and Waddington, 2002). Since then, research efforts have been focused on unraveling the epigenetic mechanisms involved in these types of changes.

Today, epigenetics has become one of the fastest-growing areas of genetics and a central issue in studies of development and disease. In recent years, there have been rapid advances in the understanding of the epigenetic mechanisms. These mechanisms, in addition to other regulatory events involved in transcriptional, ultimately regulate gene activity and expression during development and differentiation of cells.

Histone Modifications

Histones are the primary protein component of chromatin around which DNA winds. They undergo post-translational modifications that influence the chromatin arrangement (Figure 1a, Figure 1b), which in turn determine whether the associated chromosomal DNA will be transcribed or not. If chromatin is in a lightly packed form, it is active (euchromatin), and will be transcribed. The relaxed state of nucleosome arrangement in euchromatin makes the DNA accessible in these regions. Conversely, if chromatin is condensed, then it is inactive (heterochromatin), because of the inaccessibility to the transcription factors or chromatin-assisted proteins and will not be transcribed (Rando and Chang, 2009).

Function of chromatin is currently extended beyond the simple packaging of DNA and regulation of genetic information. It is also a dynamically adjusted entity that reflects the regulatory cues necessary to program appropriate cellular pathways. One possible way this programming take place is via histone post-translational modifications (Margueron and Reinberg, 2010). Core histones, in the form of an octamer consisting of two copies of H2A, H2B, H3 and H4, are wrapped by 147 bp DNA to form the nucleosome. Each core histone has an amino terminal tail that protrudes from the nucleosome. These amino terminals of the core histones are subjected to several types of multivalent modifications, including acetylation, methylation, phosphorylation, ubiquitination, SUMOylation andADP-ribosylation (Rando and Chang, 2009). Such epigenetic modifications to histone proteins can alter the structure of chromatin resulting in transcriptional activation or repression (Margueron and Reinberg, 2010).

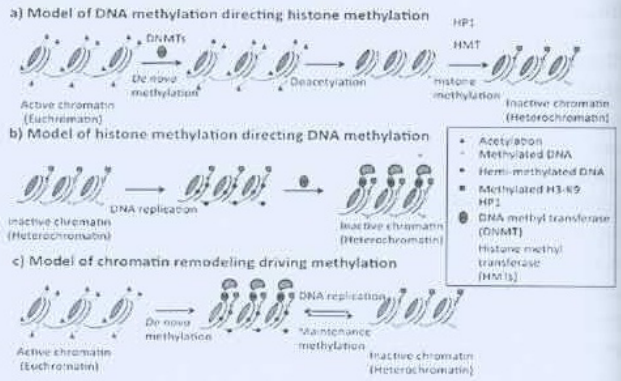

Figure 1 Schematic representation of epigenetic modifications by methylation a) histonemethylation b) DNA methylation and c) chromatin remodeling.

Acetylation of Histones

The acetylation/deacetylation of histones was the first epigenetic modification connected to biological activity (Feinberg and Vogelstein, 1983). It involves the enzymatic addition/removal of an acetyl group ($COCH_3$) from acetyl coenzyme A, to/from the amino acid residues (mainly lysine) at the N-terminus of histone tails. Two types of enzymes, histone acetyltransferase enzymes (HATs), and histone deacetylases (HDACs) take part in acetylation and deactylation reactions respectively (Bhaumik *et. al.*, 2007).

Positively charged lysine residues can bind tightly to the negatively charged DNA and condense nucleosomes, forming a closed chromatin structure, which is inaccessible to transcription factors (Feinberg and Vogelstein, 1983). Acetylation removes positive charges and reduces the affinity between histones and DNA, thereby opening the

condensed chromatin structure to allow easier access to promoter regions by the transcriptional machines (Bhaumik *et. al.*, 2007).

In most species, histone H3 is primarily acetylated at Lys 9, 14, 18, 23, and 56, methylated at Arg 2 and Lys 4, 9, 27, 36, and 79, and phosphorylated at Ser 10 and 28, Thr 3 and Thr 11. Histone H4 is primarily acetylated at Lys 5, 8, 12 and 16, methylated at Arg 3 and Lys 20, and phosphorylated at Ser 1 (Bhaumik *et. al.*, 2007). An imbalance in these modifications has been shown to associate with tumorigenesis and cancer progression (Bhaumik *et. al.*, 2007). Thus, quantitative detection of various histone modifications would provide useful information for a better understanding of epigenetic regulation in cellular processes and support the development of HAT-targeted drugs as well HDAC inhibitors as anticancer agents.

Methylation of Histones

Histone methylation involves the transfer of one, two, or three methyl groups from S-adenosyl-L-methionine to lysine or arginine residues of histone proteins by histone methyltransferases (HMTs) (Figure 1a). It is associated with transcriptional activation, repression or silencing of specific genomic regions (Jenuwein and Allis, 2001). Generally, an enrichment of histone methylation is observed at H3K4, H3K36, or H3K79, and these epigenetic markers are associated with transcriptional activation. In contrast, the enrichment of histone methylation at H3K9, H3K20, or H4K27 is implicated in gene inactivation or silencing (Kouzarides, 2007).

The effect of histone methylation on gene function and chromatin state is dependent not only on the specific lysine residue modified, but also on the degree of methylation. Recent studies have shown trimethylation of H3K9, H3K27, and K4K20 are associated with

transcriptional inactivation or heterochromatin formation while mono-methylation at these residues are distributed mostly in euchromatic regions and are linked with gene activation (Barski *et. al.*, 2007). For example, a group of HMTs called protein arginine methyltransferases (PRMTs) is involved in mediating mono or dimethylation of arginine residues and have been found strongly implicated in diseases like cancer. PRMT5 has been shown to play a role in the repression of certain tumor suppressor genes such as retinoblastoma protein (RB) tumor suppressors while PRMT7 overexpression has been observed in breast cancer (Chen *et. al.*, 1999). Thus, detection of activity and inhibition of type II PRMTs as well as other HMTs would be important in elucidating mechanisms of epigenetic regulation of gene activation and silencing, as well as cancer diagnostics and therapeutics.

Additionally, short non-coding RNAs have been shown to induce heterochromatin formation via an RNA-induced transcriptional silencing (RITS) complex, which when bound to short non-coding RNA promotes H3K9 methylation and chromatin condensation together with other epigenetic modifications (Carthew and Sontheimer, 2009). In fact, the three major classes of short non-coding RNAs; microRNAs (miRNAs), short interfering RNAs (siRNAs), and piwi-interacting RNAs (piRNAs) have been shown to participate in histone modifications, DNA methylation mediated heterochromatin formation and gene silencing (Phillips, 2008). The long non-coding RNAs (lncRNA), a major group of non-coding RNA, also participate in targeted gene silencing through chromatin remodeling, nuclear reorganization, formation of silencing domains and controlling the entry of genes into silent compartments in modulating epigenetic regulation (Mercer and Mattick, 2013).

DNA methylation

DNA methylation was the first recognized and most well-characterized epigenetic modification that is linked to transcriptional silencing, and is important for gene regulation in, development, and tumorigenesis. DNA methylation occurs by the covalent addition of a methyl group (CH_3) at the 5'- carbon of the cytosine ring, resulting in 5-methylcytosine (5-mC) (Figure 1b). In human DNA, 5-mC is found in approximately 1.5% of genomic DNA (Lister, 2009). In somatic cells, 5-mC occurs almost exclusively in the context of paired symmetrical methylation, a CpG site, in which a cytosine nucleotide is located next to a guanidine nucleotide.

Methylation of DNA is controlled by DNA methyltransferases (DNMTs), including DNMT1, DNMT3a, and DNMT3b. DNMT1 is responsible for the maintenance of established patterns of DNA methylation, by copying DNA methylation patterns from parental to daughter strands. DNMT3a and DNMT3b on the other hand mediate establishment of *de novo* DNA methylation patterns in early embryonic stem cells or cancer cells (Esteller, 2008).

As DNA methylation is predominantly found in regions of CpG clustersof the mammalian genome, these sites tend to cluster in regions of large repetitive sequences such as centromeric repeats or at the 5' ends of many genes, called CpG Islands (CpGIs). In humans, 50-70% of all CpGs are methylated, mostly in heterochromatic regions. In contrast, euchromatic CpGIs remain largely unmethylated (Esteller, 2008). Thus, distribution patterns of CpG methylation are believed to control the gene silencing and protect chromosomal integrity by preventing reactivation of sequences that causes chromosomal instability, translocations and gene disruption.

Aberrant patterns of DNA methylation influence disease processes, especially those of human tumors. In cancers, global hypomethylation at repetitive sequences promotes chromosomal instability, translocations, gene disruption and reactivation of endoparasitic sequences leading to alterations in chromatin architecture, whereas local hypermethylation of CpGIs at the promoter region of tumor suppressor genes (TSGs) prevents activation of these genes. This epigenetic alteration can contribute to tumorigenesis.

Therefore, while epigenetic changes are required for normal development and health, they can also be responsible for some disease states. Disrupting any of the epigenetic regulatory systems can cause abnormal activation or silencing of genes. Such disruptions have been associated with various diseases.

Epigenetics and diseases

Cancer

The first human disease to be linked to epigenetics was cancer (Simmons, 2008). Researchers found that diseased tissue from patients with colorectal cancer had less DNA methylation than normal tissue from the same patients (Feinberg and Vogelstein, 1983). Since methylated genes are typically turned off, loss of DNA methylation can cause abnormally high gene activation by altering the arrangement of chromatin. On the other hand, too much methylation can undo the work of protective tumor suppressor genes.

Majority of the cytosines on CpG sites are methylated in mammals. However, there are stretches of DNA near promoter regions that have higher concentrations of CpG sites (CpGIs) that are free of methylation in normal cells (Simmons, 2008). These CpGIs become

excessively methylated (hypermethylated) in cancer cells, thereby causing genes that should not be silenced to turn off (Simmons, 2008). This abnormality is the trademark epigenetic change that occurs in tumors and happens early in the development of cancer (Egger, 2002). Hypermethylation of CpGIs cancause tumors by shutting off tumor-suppressor genes (Egger, 2002; Jones and Baylin 2002; Franklin and Mansuy, 2011). In fact, these types of changes may be more common in human cancers than in DNA sequence mutations (Simmons, 2008).

Furthermore, although epigenetic changes do not alter the sequence of DNA, they can cause mutations. About half of the genes that cause familial or inherited forms of cancer are turned off by methylation. Most of these genes, including O^6-methylguanine-DNA methyltransferase (*MGMT*), MLH1,cyclin-dependent kinase inhibitor 2B (*CDKN2B*), and *RASSF1A*, which are tumor suppressor genes regulated by epigenetic modifications, normally suppress tumor formation and help repair DNA.

Hypermethylation can also lead to instability of microsatellites, which are repeated sequences of DNA. Microsatellites are common in normal individuals, and they usually consist of repeats of the dinucleotide CA. Too much methylation of the promoter of the DNA repair gene *MLH1* can make a microsatellite unstable and lengthen or shorten it. Microsatellite instability has been linked to many cancers, including colorectal, endometrial, ovarian, and gastric cancers (Franklin and Mansuy, 2011).

Intellectual disability

Intellectual disability (ID) is characterized by impairment of intellectual abilities and by deficits in the capacity to adapt to the environment and the social milieu (Gropman and Batshaw, 2010).

Distribution of these diseases in the world is 2.5 % (Gropman and Batshaw, 2010). Mental retardation is a symptom of several neuro-developmental disorders such as Rett, Prader-Williand, Fragile X syndrome.

Rett Syndrome

Rett syndrome (RTT) is an X-linked neurodegenerative disorder. This disease is caused by a mutation in the methyl CpG binding protein 2 (MeCP2) gene that encodes a nuclear protein which attaches to methylated DNA and act as a transcriptional repressor (Figure 2). Studies on MeCP2 have yielded surprising results in terms of the diversity of its functions with enormous potential for epigenetic regulation of target gene expression. MeCP2 was initially identified as a methyl-binding protein (Meehan, Lewis and Bird, 1992). Further investigations on MeCP2 function led to the discovery of its role as a transcriptional repressor and association with corepressor complexes such as mSin3A and HDACs (Nan, Ng and Johnson, 1998; Jones, Veenstra and Wade, 1998). Although this *de novo* mutation is possible in genes from both parents, it is more prominent in paternal gametes (Simmons, 2008). With this kind of situation, half of the females with classic RTT have mutation in MeCP 2 gene while the males normally do not survive. Neonatal demise in males can be caused by a severe neonatal encephalopathy due to germline MeCP2 mutation. Milder X-linked intellectual disability syndrome in females is also caused due to the same reason.

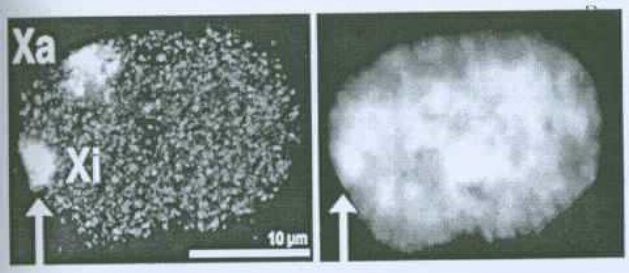

Figure 2 Nucleus of female cell in Rett Syndrome. **A**: Both X-chromosomes are detected, by FISH. **B**: The same nucleus stained with a DNA stain (DAPI). The Barr body is indicated by the arrow, it identifies the inactive X (Xi) (Simmon, 2008).

Prader-Willi Syndrome

Prader-Willi Syndrome (PWS) is the first human imprinting disorder that has been discovered. Many of the imprinted genes are preferentially expressed mono-allelically in the brain (Gropman and Batshaw, 2010).

PWS is characterized by severe hypotonia and feeding difficulties in early childhood. Insatiable appetite and obesity can be observed at later childhood. Severe behavioral problems and significant growth and language delays are also prominent symptoms of this disease (Simmons, 2008). PWS is caused by a paternal deletion in chromosome 15, maternal uniparental disomy (UPD) or imprinting mutation as illustrated in figure 3. During UPD both chromosome 15s come from the mother (Simmons, 2008). Hypomethylation of paternally inherited allele is also involved in small proportion of patients.

The preferred method of diagnosis is a "methylation analysis," which detects >99% of cases, including all of the major genetic subtypes of PWS (deletion, uniparental disomy, or imprinting mutation). A "FISH" (fluorescent in-situ hybridization) test will identify those patients with PWS due to a deletion, but it will not identify those who have Prader-Willi syndrome by "UPD" (uniparental disomy) or an imprinting error.

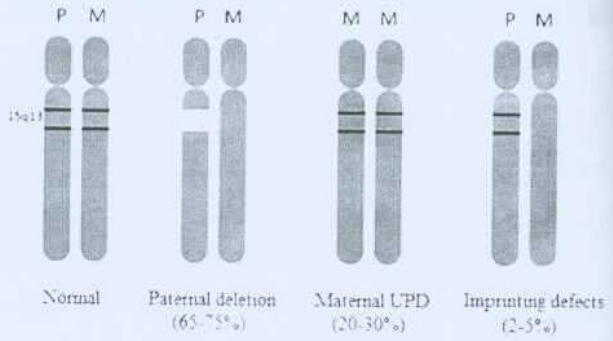

Figure 3 Schematic diagram showing the deletion of 15q13 gene from paternal and maternal chromosomes in Prader-Willi Syndrome.

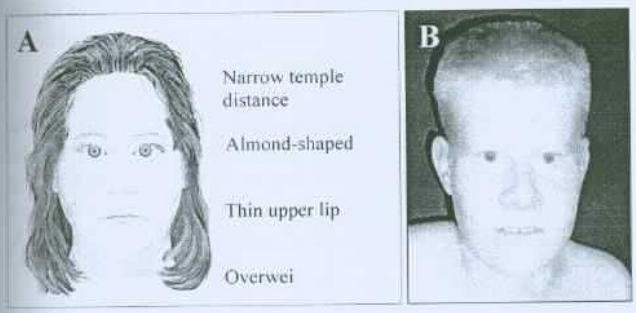

Figure 4 Illustration showing the symptoms related to the Prader-Willi Syndrome (**A**) and patient with the disease (**B**) (Prader-Willi Syndrome Association, USA, 2011).

Fragile X Syndrome

Fragile X syndrome is the most frequently inherited mental disability, particularly in males. Both sexes can be affected by this condition, but because males only have one X chromosome, one fragile X will impact them more severely. Indeed, fragile X syndrome occurs in approximately 1 in 4,000 males and 1 in 8,000 females (Plazas-Mayorca and Vrana, 2011).

Fragile X arises from increasing the number of CGG triplet repeats within the initial 5' untranslated region of fragile X mental retardation protein (FMR1) gene. Numbers of CGG repeats are 6 – 40 approximately. This value can be increased to 50-200, at premutation state and to >200 for full mutation state (Simmons, 2008). The reason for expansion of these repeats is hypermethylation of the promoter region of FMR1 gene that results in repression of FMR1 expression

and subsequent loss of FMR1 protein. Normally methylation of CpGIs in the promoter region of gene prevents the gene expression by preventing transcription and translation (Simmons, 2008).

A specific genetic test (polymerase chain reaction [PCR]) can be performed to diagnose fragile X syndrome. This test looks for the expanded mutation (the triplet repeat) in the FMR1 gene. DNA testing detects more than 99 percent of individuals (both males and females) with Fragile X, as well as Fragile X carriers. (National Fragile X Foundation, 2012)

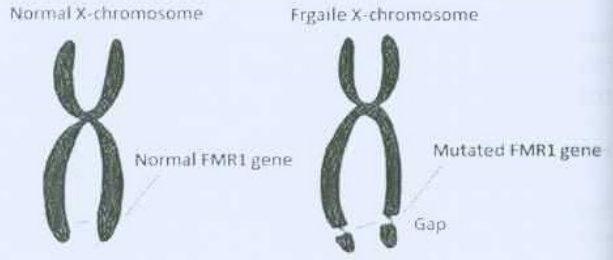

Figure 5 Schematic diagram showing the normal and mutated FMR1 gene related to Fragile X syndrome.

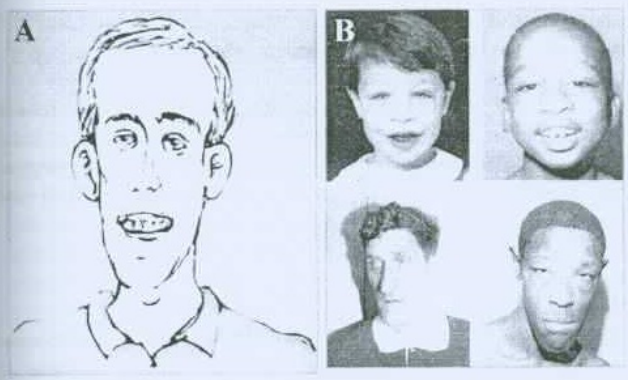

Figure 6 Illustration showing the symptoms related to the Fragile X Syndrome (**A**) and patients with the disease (**B**) (Fragile X syndrome, 2014).

Immunity & related disorders

Autoimmune diseases are a complex group of diseases that do not have the same epidemiology, pathology, or symptoms but do have a common origin. All autoimmune diseases share immunogenetic mechanisms mediated in part by several pleiotropic genes which produce apparently unrelated phenotypic effects (Anaya, 2010). Many studies over the years have shown that alterations in many loci and genes in the human genome cause these diseases. Therefore, it is important to underline the fact that autoimmune diseases may be generated by several alterations in the same epigenetic mechanism. Also, it is essential to understand that epigenetics is not the only mechanism that may cause autoimmunity. In fact, there are intrinsic

and extrinsic components (mutations, polymorphisms, and environmental factors) that predispose to autoimmunity.

As mentioned before, DNA methylation is the most widely studied mechanism in autoimmune diseases. Several studies have found global hypomethylation on the promoter regions in the cells targeted by diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA).

Systemic Lupus Erythematosus

Systemic Lupus Erythematosus (SLE) is a systemic multi-organ autoimmune disease characterized by autoantibody response to nuclear and/or cytoplasmic antigens. Several studies have shown that there is a global hypomethylation on the promoter regions such as ITGAL, CD40LG, PRF1, CD70, IFGNR2, MMP14, LCN2, and in the ribosomal RNA gene promoter (18S and 28S) that are overexpressed in the disease (Lei *et. al.*, 2009). The DNA hypomethylation may also affect the chromatin structure of T-cells thus enhancing the overexpression of those genes (Lei *et. al.*, 2009). This gene overexpression will cause cell hyperactivity, perpetuation of the immune response and consequently, the perpetuation of inflammatory response (Lei *et. al.*, 2009).

Rheumatoid Arthritis

Rheumatoid Arthritis (RA) is a disease characterized by the progressive destruction of joints by invasive synovial fibroblasts. The RA synovial fibroblasts (RASFs) play a major role in the initiation and perpetuation of the disease, which is the reason why several epigenetic studies of RA are focused on these synovial cells. Researchers have found a global hypomethylation of these cells,

which could be responsible for the overexpression of inflammatory cytokines in synovial fluid. Some examples of hypomethylation in RA are in CpGIs upstream of an L1 open-reading frame and the Interleukin-6 (IL-6) promoter gene in monocytes (Neidhart *et. al.*, 2000). L1 is one of the major classes of repetitive elements that are spread throughout the genome. They are used as markers because they are methylated in normal synovial tissue. In synovial tissue from patients with RA, L1 is hypomethylated as a consequence of reduced expression of DNMTs (Bull *et. al.*, 2008). This reduction of methylation in inflammatory response promoter genes causes an overexpression of growth factors and receptors, adhesion molecules, and cytokines. In the end, these will cause irreversible phenotypic changes in synovial fibroblasts (Neidhart *et. al.*, 2000). The other example is the hypomethylation in CpG islands within the IL-6 promoter gene in monocytes. IL-6 is a proinflammatory cytokine that participates in B cell response. When this promoter is hypomethylated, there is an overexpression of IL-6 that will cause an overexpression of pro-inflammatory cytokines at the same time. This will be associated with a local hyperactivation of the inflammation circuit. There is also evidence that we can also find a hypermethylation mechanism in monocytes such as in the case of the CpG islands within the promoter of death receptor 3 (DR-3). DR-3 is a protein that causes apoptosis and activation of transcription factor NF-kappa-B (NF-κB). Down regulation of this protein due to hypermethylation of its promoter, results in resistance of RA synovial cells to apoptosis (Bull *et. al.*, 2008).

Multiple Sclerosis

Multiple Sclerosis (MS) is a chronic inflammatory disease characterized by myelin destruction and is followed by a progressive degree of neurodegeneration. Recent studies have shown that the

promoter region of peptidylarginine deiminase type II (PAD2) is hypomethylated (Musse *et. al.*, 2006). PAD2 plays a key role in the citrullination process of myelin basic protein (MBP). Citrullination promotes protein autocleavage, which increases the probability of creating new epitopes and also modulates the immune response. In MS, PAD2 promoter region was found to be hypomethylation due to increased demethylase activity (Portela and Esteller, 2010). Hypomethylation of the PAD2 promoter, results in overexpression of PAD2 and an increase in the MBP citrullination process with a subsequent increase in the production of immunodominant peptides (Portela and Esteller, 2010).

Neuropsychiatric disorders

Psychiatric symptoms caused by neurobiological brain disorders are called neuropsychiatric disorders. Majority of these neuropsychiatric disorders have unknown, underlying causes. Recent discoveries provide evidences for the epigenetic regulation of diseases marked by neuropsychiatric symptoms such as depression, schizophrenia, and drug addiction. Epigenetics involved in here are linked to genetics, environmental factors and behavior (Portela and Esteller, 2010). Gene transcription of neurons in the brain is also regulated by the epigenetic modifications.

Depression

Depression is a common, chronic and debilitating disease, which affects someone's strength or ability to carry on regular activities. Long lasting nature and delayed response to the anti-depressant treatment of depression is evidence for its involvement with epigenetic regulation. In accordance with the studies done with animal

models (rat, hippocampus), depression involves the methylation of *Bdnf* promoter (Schroeder *et. al.*, 2010).

Schizophrenia

Epigenetic regulators of gene expression including DNA cytosine methylation and post-translational histone modifications could play a role for some of the molecular alterations associated with schizophrenia. For example, in prefrontal cortex of subjects with schizophrenia, abnormal DNA or histone methylation at sites of specific genes and promoters is associated with changes in RNA expression (Akbarian, 2010).

Drug addiction

Cocaine and nicotine are two drugs that humans get addicted. This is a psychiatric disorder that affects the mesolimbic dopamine system. Many studies have been carried out in relation to drug addiction. However, several problems like (the reason for the persistence of addictive behaviors long after drug abstinence) remain unresolved (Anaya, 2010).

Pediatric Syndromes

In addition to epigenetic alterations, certain mutations that affect components in the epigenetic pathway that are responsible for several syndromes have been identified: DNMT3b in ICF (immunodeficiency, centromeric instability and facial anomalies) syndrome, MeCP2 in Rett syndrome, ATRX in ATR-X syndrome (α-thalassemia/mental retardation syndrome, X-linked), and DNA repeats in facioscapulohumeral muscular dystrophy (Portela and Esteller, 2010).

Rett syndrome

In Rett syndrome, mutations in MECP2 protein cause abnormal gene expression patterns within the first year of life. Girls with Rett syndrome display reduced brain growth, loss of developmental milestones and profound mental disabilities (Simmons, 2008; Portela and Esteller, 2010).

ATR-X syndrome

ATR-X syndrome also includes severe developmental deficiencies due to loss of ATRX, a protein involved in maintaining the condensed, inactive state of DNA. This pediatric syndrome is associated with alterations in genes and chromosomal regions necessary for proper neurological and physical development.

The diversified knowledge and technologies in epigenetics over the last ten years have given a better understanding of the interplay between epigenetic modifications, gene regulation and human diseases. This has provoked interest for development of new approaches for molecular diagnosis and disease treatments – epigenetic therapy (Simmons, 2008; Portela and Esteller, 2010).

Epigenetic terapy

As discussed above, there are many diseases involving epigenetic changes. Therefore, it seems reasonable to attempt to counteract these modifications as a therapeutic approach. Unlike DNA sequence mutations, epigenetic modifications are reversible by nature. Thus, these changes seem an ideal target for therapy. The most popular of these treatments aim to alter either DNA methylation or histone acetylation.

One approach in epigenetic therapy is the reactivation of genes that have been silenced due to epigenetic modifications. Several drugs aimed at inhibiting DNA methylation have been designed which include5-azacytidine, 5-aza-2'-deoxycytidine, etc (Egger, 2002). These drugs are mistaken for cytosine residues and thus get incorporated into DNA during replication. After incorporation into DNA, these drugs are able to block DNMT enzymes thus inhibiting DNA methylation.

Several drugs aimed at histone modifications have also been designed and are referred to as histone deacetylase (HDAC) inhibitors. The function of HDACs is to remove acetyl groups from DNA, which condenses chromatin and thereby stops transcription. Inhibition of this process using HDAC inhibitors will turn on transcription. The most commonly used HDAC inhibitors are phenylbutyric acid, SAHA, depsipeptide and valproic acid (Egger, 2002).

Epigenetic processes and changes are so widespread, which require careful handling and caution. Non-selective activation of gene transcription in normal cells could make them cancerous, where the treatments could cause the very disorders they are trying to counteract. Thus, successful epigenetic treatments require selectivity towards abnormal cells. Despite this possible drawback, epigenetic therapy is beginning to look increasingly promising. In fact, the researchers are finding ways to specifically target abnormal cells with minimal damage to normal cells.

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