15

Epigenetic Modifications: Genetic Basis of Environmental Stress Response

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1. Introduction

Genomic DNA is faithfully replicated and divided between two daughter cells in the course of each cell cycle. In order to maintain the inheritance of gene expression patterns, the cell must not only replicate the DNA, but also duplicate its chromatin structure (McNairn & Gilbert, 2003). Following replication, DNA is methylated and packaged into nucleosomes by the binding of histone octamers to form chromatin. DNA methyltransferases (DNMTs), the enzymes that transfer methyl (CH_3) residue to CpG dinulcleotides, are coordinated with DNA replication to maintain the DNA methylation pattern (Fig. 1). DNMTs recognize methylated CpG dinucleotides on the parent strand and methylate correlating CpG dinucleotides on the daughter strand (Bestor et al., 1996). This heritability of the DNA methylation pattern, as well as histone modification patterns, is mediated by epigenetic machinery.

Epigenetics was first used by Conrad Waddington in 1939 to describe "the causal interactions between genes and their products, which bring the phenotype into being" (Waddington, 1942). The current definition is "the study of heritable changes in gene expression that occur independent of changes in the primary DNA sequence" (Sharma et al., 2010). Waddington's definition initially referred to the role of the epigenetics in embryonic development, in which cells develop distinct identities despite having the same genetic information; however, the definition of epigenetics has evolved over time as it is implicated in a wide variety of biological processes, including maintenance of the normal gene expression, carcinogenesis and genomic response to environmental stresses.

In this chapter, we take a look at the courent understanding of epigenetic status in human cells, describe human diseases associated with congentital epigenetic errors, and also discuss how human diseases may be caused by acquired epigenetic errors as a result of environmental factors. We also discuss epigenetic therapies that take advantage of the fact that epigenetic changes are resversible.

2. Epigenetic status in human cells

The DNA methylation pattern is established during tissue development (Sakashita et al., 2001). Once the pattern is established in a cell, it is stably maintained through DNA replications at each cycle of cell division. Therefore, cells keep distinct identities while containing the same genetic information.

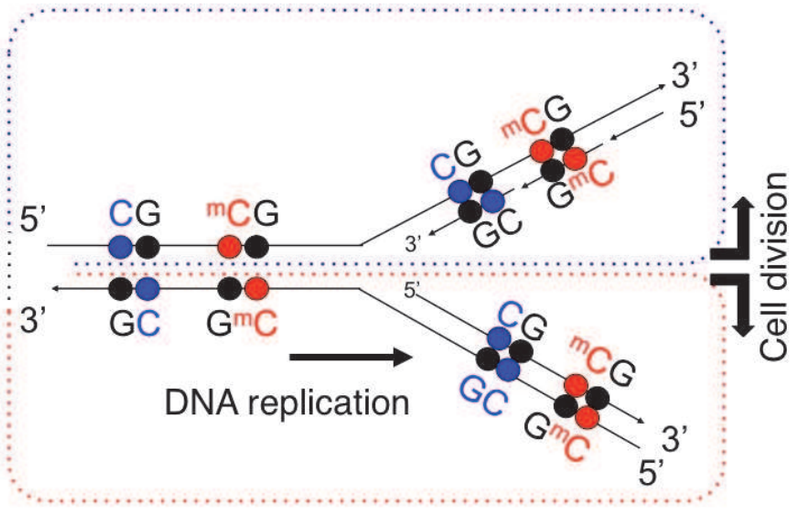

Fig. 1. Maintenance of the DNA methylation pattern during DNA replication and cell division

2.1 DNA methylation

During evolution, the CpG dinucleotide, the principal site of DNA methylation, has been selectively depleted through conversion of methylated cytosines to thymidines via a deamination process. Therefore, the human genome has only 10% of the expected frequency of CpGs, and 70 to 80% of these are heavily methylated. Small regions of DNA (1 to 2%), termed CpG islands, are not CpG-depleted. CpG islands are strongly protected from methylation and are associated with the transcription start sites in almost half of human genes. The genome organization facilitated by an epigenetic pattern is only present in higher order eukaryotes including mammals and humans. It is absent in *Drosophila, Caenorhabditis elegans,* and yeast (Baylin, 1997).

DNA methylation patterns closely correlate with patterns of gene expression (Fig. 2). Heavily methylated genomic regions are generally associated with chromatin organization that is inhibitory to transcription. In humans, such methylated genomic regions often contain highly repeated sequences; methylation may help guard against transcriptional

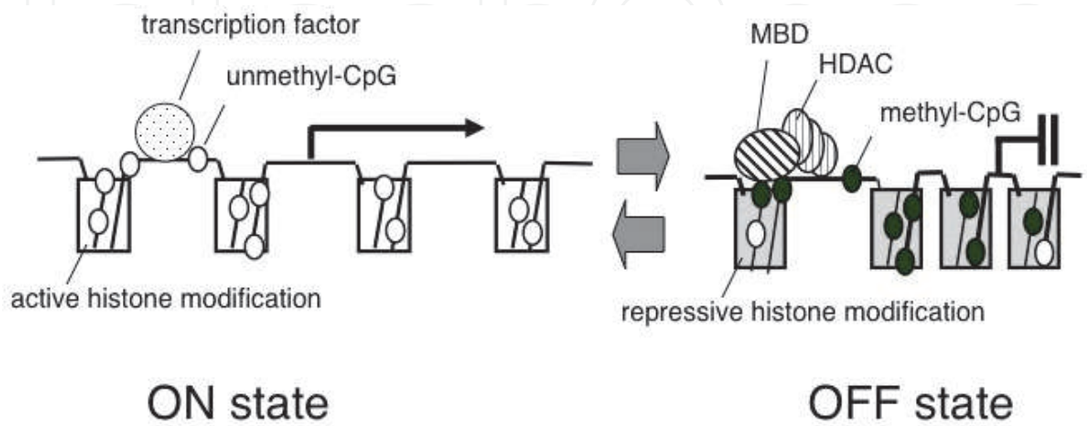

Fig. 2. Epigenetic gene regulation via DNA methylation and histone modifications

expression of parasitic sequences, which were introduced into the genome over evolution by transposable elements and DNA viruses (Bester et al., 1996). In contrast, the unmethylated CpG islands of genes are associated with chromatin containing highly transcribed DNA.

2.2 Histone modification

Histone proteins, which comprise the nucleosomes core, contain a globular C-terminal domain and an unstructured N-terminal tail (Lugar et al., 1997). The N-terminal tails of histones can undergo a variety of posttranslational covalent modifications including acetylation, methylation, phosphorylation, ubiquitylation, and sumoylation (Kouzarides, 2007). The complement of modifications is proposed to store the epigenetic memory inside a cell in the form of a "histone code" that determines the structure and activity of different chromatin regions (Jeniwein et al., 2001) (Fig. 2).

Unlike DNA methylation, histone modifications can lead to either activation or repression depending upon which residues are modified and the type of modifications present. For example, lysine acetylation correlates with transcriptional activation (Kouzarides, 2007; Hebbes et al., 1988), whereas lysine methylation leads to transcriptional activation or repression depending upon which residue is modified and the degree of methylation. For examples, trimethylation of lysine 4 on histone H3 (H3K4me3) is enriched at transcriptionally active gene promoters (Liang et al., 2004), and trimethylation of lysine 9 on histone H3 (H3K9me3) and trimethylation of lysine 27 on histone H3 (H3K27me3) is present at gene promoters that are transcriptionally repressed (Kouzarides, 2007). A vast array of active and repressive histone modifications have been identified, which constitute a complex gene regulatory network essential for the physiological activities of cells (Sharma et al., 2009).

2.3 Interplay of these epigenetic modifications

DNA methylation and histone modifications, not only perform individually, but also interact with each other at multiple levels to determine expression status, chromatin organization and cellular identity (Cedar et al., 2009). The two histone modifications (H3K9me3 and H3K27me3) that constitute the silencing mechanism in mammalian cells work in concert with DNA methylation. Furthermore, a histone methyltransferase (HMT) can direct DNA methylation to specific genomic targets by recruiting DNMTs to stably silence genes (Tachibana et al., 2008), and a histone demethylase (HDM) stabilizes DNMT1 protein to maintain DNA methylation (Wang et al., 2009).

DNMTs can in turn recruit methyl-binding domain proteins (MBDs) and histone deacetylases (HDACs) to achieve gene silencing and chromatin condensation (Jones et al., 1998; Nan et al., 1998) (Fig. 2). DNA methylation can also induce histone H3K9 methylation through an MBD (MeCP2), thereby establishing a repressive chromatin state (Fuks et al., 2003).

The interplay of these modifications creates an epigenetic landscape that regulates the way the mammalian genome manifests itself in different cell types, developmental stages and disease states. The distinct patterns of these modifications present in different cellular states serve as a guardian of cellular identity (Sharma et al., 2009).

2.4 Aberrant epigenetic modifications

A normal epigenetic landscape is known to be disturbed in specific disease conditions. For example, the cancer epigenome (the whole genomic epigenetic state) is marked by genome-

wide hypomethylation and site-specific CpG island promoter hypermethylation (Jones & Baylin, 2002). Global DNA hypomethylation plays a significant role in tumorigenesis and occurs at various genomic sequences including repetitive elements, retrotransposons, CpG poor promoters, introns and gene deserts (Rodriguez et al., 2006). Activation of the retrotransposons due to hypomethylation lead to increased genomic instability by promoting chromosomal rearrangements (Jones et al., 2002; Eden et al., 2003; Howard et al., 2008). Furthermore, methylation is known to stabilize various repetitive sequences. Thus, hypomethylation CAG trinucleotide repeats in a DMNT1-deficient mouse display increased repeat instability (Dion et al., 2008).

In contrast to hypomethylation, which increases genomic instability and activates proto-oncogenes, region-specific hypermethylation contributes to tumorigenesis by silencing tumor suppressor genes, such as *Rb, p16 and BRCA1* (Sharma et al., 2009). These genes are involved in cellular processes integral to cancer development and progression, including DNA repair, cell cycle regulation, cell adhesion, apoptosis and angiogenesis. Silencing of DNA repair genes enables cells to accumulate further genetic lesions leading to the rapid progression of cancer. Hypermethylation at the binding site for CCCTC-binding factor (CTCF), a chromatin barrier by preventing the spread of heterochromatin structures, inhibits CTCF binding, and leads to instablity of repetitive sequiences, which is a causing-mechanism for varios neurodegenerative diseaases (López Caste et al., 2010). However, how genes are targeted for this aberrant DNA methylation is still unclear.

Both aberrant histone acetylation and histone methylation are found in cancer cells. These changes associated with overexpression of HDACs and dysregulation of HMTs (Halkidou et al., 2004; Song et al., 2005). Alterations in H3K9 and H3K27 methylation patterns are associated with aberrant gene silencing in cancers. It has recently demonstrated that aberrant nucleosome positioning is created by a co-repressor Nerd (nucleosome remodelling and deacetylase) complex that recruits PML-Para (an oncogenenic transcription factor), polycomb repressor complex 2, DNMT3A, and MBD2, resulting in abnormal gene silencing in leukemia (Feng et al 2001; Morey et al., 2008).

Re-establishing normal histone acetylation patterns through treatment with HDAC inhibitors have been shown to have anti-tumorigenic effects, via reactivation of silenced tumor suppressor genes (Carew et al., 2008). Suberoylanilide hydroxamic acid (SAHA), which is an HDAC inhibitor, has now been approved for use in the clinic for treatment of lymphoma (Sharma et al., 2009).

2.5 Understanding of the global epigenetic landscape

The global epigenetic landscape that is correlated with important biological processes and disease state has not been comprehensively investigated for most cell types. However, recent advances in genomic technology, in particular high-throughput sequencing, have enabled genome-wide analysis of histone modifications and DNA methylation at nucleotide resolution (Beck, 2010). Large-scale epigenomic mapping studies have the potential to enhance three major areas of science: basic gene regulatory processes, cellular differentiation and reprogramming and the role of epigenetic regulation in disease (Satterlee, 2010). Understanding how the epigenomic state of human embryonic stem (ES) cells changes during the differentiation process is crucial for understanding normal development and establishing epigenomic maps of induced pluriopotent stem (iPS) cells will be essential to enable regenerative medicine to reach its full potential for treating diseases (Deng et al., 2009; Ball et al., 2009; Doi et al., 2009). Genome-wide association studies have been

successful in identifying genetic variants associated with many different diseases. In the case of diseases that have a strong environmental component, epigenome-wide association studies based on the epigenomic maps of specific cell types that statistically correlate epigenetic variation with phenotypes, could be of great value (Kong et al., 2009).
To generate epigenomic maps for cell types, large-scale epigenomics effort have already been initiated. The NIH Roadmap Epigenomics Program (http://www.roadmapepigenomics.or) will permanently archive data in the GEO database (Http://www.ncbi.nlm.nih.gov/epigenomics) at the US National Center for Biotechnology Information (NCBI), and the International Human Epigenome Consortium (IHEC) (http://ihec-epigenomes.org) aims to expand the number of cell types and generate additional 1,000 reference epigenomes (Beck, 2010) that are not being characterized in the NIH Roadmap Program.

3. Human diseases associated with congentital epigenetic errors

Epigenetic gene control is an intrinsic mechanism for normal tissue development and abnormalities in the molecules associated with this mechanism are known to cause various congenital diseases.

3.1 Genomic imprinting diseases

Genomic imprinting is the epigenetic phenomenon initially discovered in human diseases. In an imprinted gene, out of the two parental alleles, one allele is active and the other allele is inactive due to epigenetic mechanism such as DNA methylation (Fig. 3C). Therefore, defect in the active allele of the imprinted gene results in the loss of expression. This has been found in neurodevelopmental diseases, Prader-Willi syndrome and Angelman syndrome (Kubota et al., 1997).

3.2 X-chromosome inactivation disorders

The X chromosome has a large number of genes, whereas the Y chromosome has relatively few genes. Thus, females (XX) have more genes than males (XY). To minimize this sex imbalance, one of the two X chromosomes in females is inactivated by epigenetic mechanism (Kubota et al., 1998). Improper X inactivation is though to be an embryonic lethal condition. This hypothesis is supported by the recent findings in cloned animals produced by somatic nuclear transfer in which failure of X-chromosome inactivation was observed in the clones with embryonic abortion (Xue et al., 2002; Nolen et al., 2005).Even if one of the X chromosomes is extremely small due to a large terminal deletion, so that over dosage effect of X-linked genes is minimized, the affected female show a severe congenital neurodevelopmental delay(Kubota et al., 2002), indicating that proper gene suppression by epigenetic mechanism is essential for normal development (Fig. 3D).

3.3 DNA methylation-associated protein diseases

DNA methylation is a fundamental step in epigenetic gene control, and it is achieved by an addition of the methyl group (CH_3) to CpG dinucleotides mediated by DMNTs. Defect in a DNMT (e.g., DNMT3B) can causes an ICF syndrome that is characterized by Immunodeficiency, centromere instability, facial abnormalities, and mild mental retardation (Fig. 3A) (Okano et al, 1999; Shirohzu et al., 2002; Kubota et al., 2004).

MBDs are also important molecules in the control of gene expression. Mutations in a MBD (e.g., MeCP2) can cause Rett syndrome, which is characterized by seizures, ataxic gait, language dysfunction and autistic behavior (Amir et al, 1999; Chunshu et al., 2006). Therefore, it has been thought that MeCP2 dysfunction leads to aberrant gene expression in the brain associated with neurological features of the disease. Recent studies have shown that MeCP2 controls a subset of neuronal genes (Chen et al., 2003; Martinowich et al., 2003; Horike et al., 2005; Itoh et al., 2007), suggesting that epigenetic dysregulation of the neuronal genes may cause neurological features of the disease (Fig. 3B).

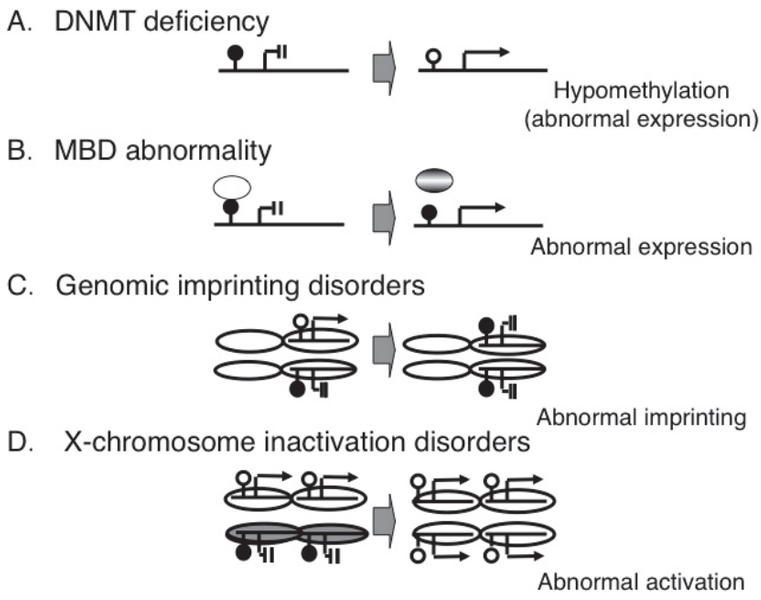

Fig. 3. Abnormal epigenetic patterns in human congenital diseases

4. Proposed human diseases associated with acquired epigenetic errors caused by environmental factors

Health or diseases is shaped for all individuals by interactions between their genes and the environment. How the environment changes gene expression and how this can lead to a disease are being explored in a fruitful new approach to environmental health research. If these causal relations become clear, they offer new avenues for risk assessment for diseases (Edwards & Myers, 2007).

4.1 Social background

The Ministry of Health, Welfare, and Labor in Japan has recently reported that the number of children with mild neurodevelopmental disorders, such as autism, is increasing by 10,000 cases per year (Basic report, 2005). Similar trends are found in other countries, including the US (Yeargin-Allsopp et al., 2003; Holoden, 2009; Fombonne, 2009), in which the increase is partly attributed to social factors, such as diagnostic substitution in which children formerly diagnosed with mental retardation or learning disabilities are now diagnosed with autism. However, the increase in cases cannot be fully attributed to such diagnostic substitutions,

and it is possible that biological changes in the brains of the children are also involved in this increase. Thanks to advances in genomic research, several genetic factors for autism have been identified. Mutations in genes encoding synaptic molecules have been identified in a subset of autistic children (Zoghbi, 2003; Persco & Bourgeron, 2006). However, the increase in autism cannot be solely attributed to genetic factors, because it is unlikely that mutation rates suddenly increased in recent years. Therefore, environmental factors are more likely to be involved in this increase. Epingenetic modifications repreent one mechanism by which enviromental factors can lead to health effects (Qiu, 2006).

4.2 Acquired neurodevelopmental diseases

It is known that either a mutation, deletion or a duplication of a specific-neuronal gene causes a neurological disease. In other word, loss-of function, deficiency, or over-dosage can result in the same disease phenotype. For examples, Pelizaeus-Merzbacher disease, a severe child onset disorder, is caused by either a mutation, deletion or a duplication of the *PLP1* gene (Inoue et al., 2001), lissencephaly syndrome, a child-onset migration disorder, is caused by either a mutation, deletion or a duplication of *LIS1* (Reiner et al., 1993; Bi et al., 2009), Charcot-Marie-Tooth disease, an adult-onset neuromuscular disorder, is caused by either a mutation, deletion or a duplication *PMP22* (Roa & Lupski, 1993), and Perkinson disease is caused by either a mutation, deletion or a duplication the *α-synuclein* gene (Obi et al., 2008). This suggests that the brain is sensitive to the dosage of gene products that requires a strict control system for gene expression. In fact, congenital diseases with defects in epigenetic gene regulation usually show neurological features and mental retardation.

It has recently been reported that short-term mental stress after birth can alter the epigenetic status in the brain, resulting in abnormal behaviour (Weaver et al., 2004). In rats, when the offspring is separated from the mother for a couple of weeks, DNA methylation at the *GR* (glucocorticoid receptor) gene is increased in the hippocampus in the brain, and this change suppresses gene expression. This study is now considered as an animal model for cuelty in childhoood in human, because hypermethylation of the neuron-specific glucocorticoid receptor promoter, in combination with decreased levels of its expression, have been found in human postmortem hippocampus obtained from suicide victims with a history of childhood abuse (MacGowan et al., 2009), suggesting that adverse effects of early-life stress last life-time long on the DNA methylation programs (Margatroyd et al., 2009). It raise the question of whether neurodevelopmental problem may be the result of epigenetic dysregulation caused by environmental factors in the early life.

4.3 Environmental factors in fetal period

Another social issue in Japan is that birth weight has decreased during the past 20 years. This trend is thought to be caused by the popularity of dieting among young women and obsteric physicians' recommendations to minimize pregnacy weight gain in order to reduce the risk of diabetes mellius (Gluckman et al., 2007). Based on current epidemiological studies for famines in the Netherland and China (St Clair et al., 2005; Painter et al., 2006), the generation with lower birth weight is expected to have increased risk for obesity and adult diseases in the future in Japan. This hypothesis is referred to as "Developmental Origin of Health and Diseases (DOHaD)"(Gillman et al., 2007; Silveira et al., 2007). Recent animal expreriments suggest that the developmental basis of adult diseases is due to a change of DNA methylation status of the *PPARα* gene, a thrifty gene, in the liver due to malnutrition

in the fetal period(Lillycrop et al., 2005; Lillycrop et al., 2008) (Fig. 4). Such DNA methylation alterations have been confirmed in individuals who suffered malnutrition during a period of faminine (Tobi et al., 2009).

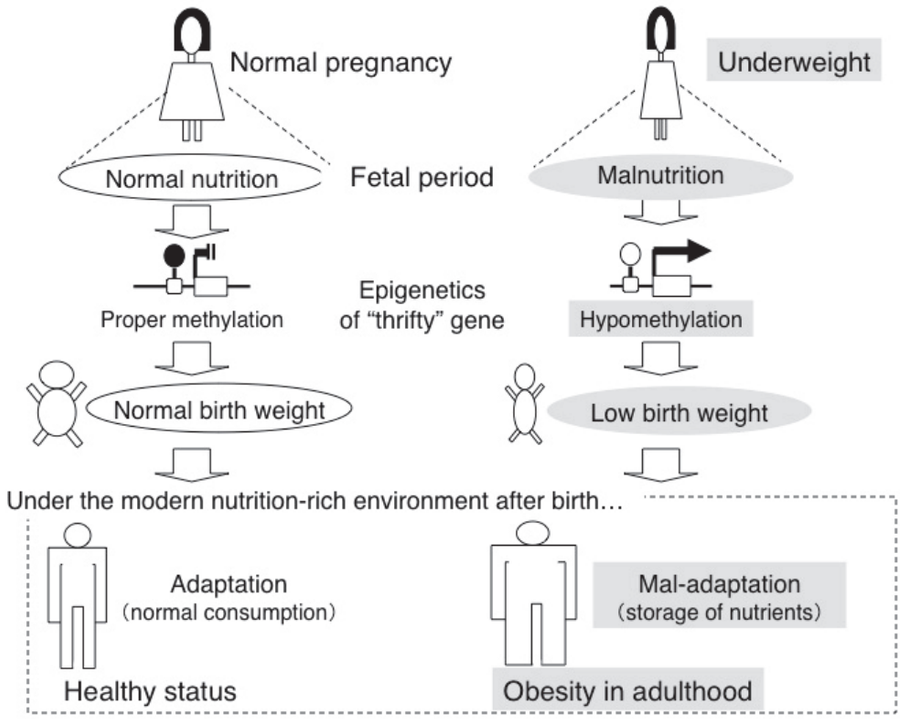

Fig. 4. Epigenetic mechanism proposed in the "Developmental Origin of Health and Diseases" hypothesis

4.4 Drugs and chemicals affecting epigenetic status

Drug addiction is an example of mental diseases acquired via epgenetic change. Cocaine and alcohol alter the epigenetic state (chromatin structure) on a subset of neuronal genes, inducing a drug addiction state(Kumar et al., 2005; Pacual et al., 2009). Chemical compounds related to plastics alsopotentially affect the epigenetic status of genes in the brain (Yaoi et al., 2007).

Imipramine, a major antidepressant, in turn has recently been found to retore a depressive state by altering the epigenetics (histone modification) of the *Bdnf* gene in the hippocampus (Tsankova et al., 2006). Valproic acid (VPA), a histone deacetylase (HDAC) inhibitor, is another drug that alters the epigenetic state. VPA normalizes histone acetylation of genes in the hippocampus, which leads to suppression of seizure-induced cognitive impairment by blocking seizure-induced aberrant neurogenesis (Jessbrger et al., 2007). These observations indicate that chemicals that alter epigenetic gene expression, such as HDAC inhibitors, may become candidates for the treatment of neurodevelopmental diseases (Renthal et al., 2008).

The findings above are mainly obtained from animal experiments, and there is little evidene from human studies. However, epigenetic differences increase with age in monozygotic twins (Fraga et al., 2005), suggesting that epigenetic status may be altering during aging by environmental factors in humans.

5. Epigenetic therapies

Because epigenetic modifications are a reversible mechanism unlike mutations (substitutions of nucleotides), correction of the epigenetic deffect is potentially easier than correction of the mutations (Fig. 5).

5.1 DNA methylation donor

Folic acid is the methyl-donor for transfer to cytosine. Therefore, in order to maintain DNA methylation, sufficient intake of folic acid is essential. Folic acid deficiency during pregnancy is now increasing in Japan. This increases the risk of having babies with neural tube defects (Watanabe et al., 2008). As mentioned above, inappropriate supply of nutrients from mother to the fetus also increases the susceptibility of fetus to develop diabetes mellitus due to epigenetic changes (Park et al., 2008). However, supplementation of folic acid during pregnancy protects the fetus by enriching DNA methylation of the promoter regions of *PPARα* and glucocorticoid receptor genes in the liver, leading to suppress gene expression (Buedge et al., 2009). These findings indicate that proper nutrient intakes may alter the phenotype of the offspring through epigenetic changes.

Since 1980s, folic acid has empirically been used for the treatment of autistic children and adults with mental diseases, and several studies have shown that folic acid is effective in a subset of patients (Rimland, 1998; James et al., 2004; Moretti et al., 2005). Although the precise mechanism is not known, it is also possible that folic acid administration may correct the DNA methylation status in genes.

5.2 Nutrition

A honey bee secretion known as royal jelly can cause phenotypic change in genetically identical female honeybees to induce the development of a fertile queen. This effect may be mediated by epigenetic changes. A recent study showed that royal jelly removes global DNA methylation, silencing the expression of Dnmt3 during larval development (Kucharski et al., 2008). The phenotypic change from a worker bee to a queen is reproduced by using siRNA that inhibit Dnmt3 (Kucharski et al., 2008). More recently, many kinds of nutrition have been shown to have epigenetic effects and epigenetic therapeutics have been approved by the US Food and drug Administration for treating specific cancers and seizure disorders (Mack, 2006; Sharma et al., 2010).

5.3 Gene-specific therapy

Folic acid is relatively safe, since it is a nutrient. However, its effect is global, and it is not specific to a certain gene. It may be better if epigenetic correction is made only to a specific gene that is associated with a disease state. This kind of therapy can be achieved using pyrrole-imidazole (PI) polyamides, small synthetic molecules that recognize and attach to the minor groove of DNA, thereby inhibiting gene transcription by blocking transcription factor binding in a DNA sequence specific manner (Matsuda et al., 2011). Furthermore, PI polyamide conjugated with SAHA, a HDAC inhibitor, can alter the histone modification in a gene-specific manner, resulting in up-regulation of the target gene (Ohtsuki et al., 2010).

5.4 Exercise and environmental enrichment

It has recently been discovered that DNA sequence is different in each neuron (Coufal et al., 2009), and that epigenetic change underlies the somatic change (Muotri et al., 2005). This

phenomenon is based on retrotransposition, in which a repetitive L1 sequence is inserted into various genomic regions when it is hypomethylated, potentially altering expression of adjacent genes. Retrotranposon insertion is activated by deficency of MeCP2 (Muotrri, etal., 2010). Interestingly, the retrotransposition is also activated by voluntary exercise (running) in mice (Muotri et al., 2009), suggesting that exercise may alter the DNA methylation status in neurons.

Studies using a Rett syndrome mouse model that lacks MeCP2 show that environmental enrichment (e.g., availability of stimulating toys) during early postnatal development produces effects on neural development and ameliorates the neurological phenotypes associated with Rett syndrome (Lonetti et al., 2010; Kerr et al., 2010). This suggests that DNA methylation status may be corrected by an apprpriate environment, conpensating for the insuffient MeCP2 function.

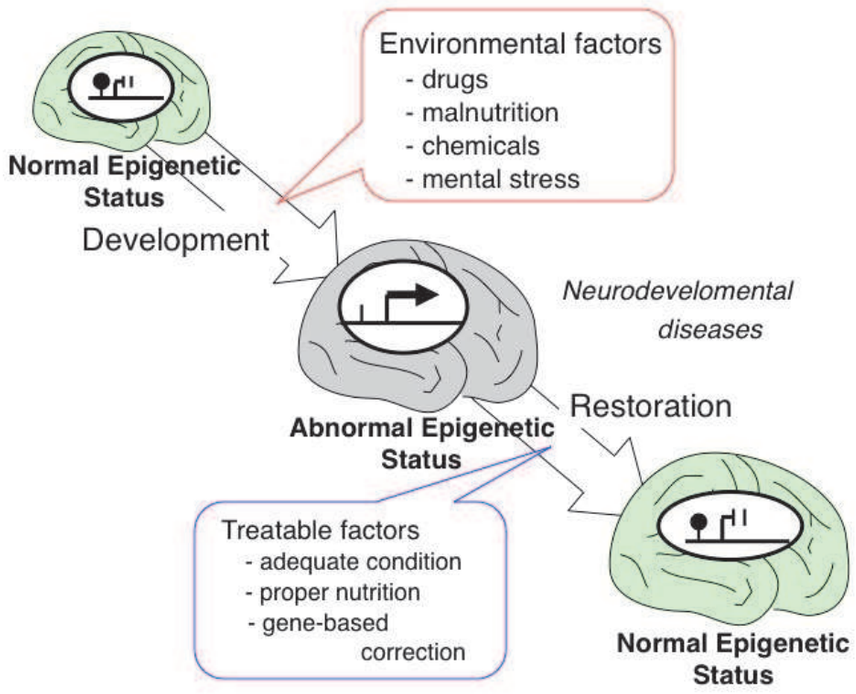

Fig. 5. Overview of epigenetic change and environmental factors in the brain

6. Conclusion

Epigenetics is a genetic code, not within the DNA but upon the DNA. Until recently, it has been believed that the epigenetic code is faithfully maintained at the step of DNA replication. However, various environmental factors potentially rewrite the epigenetic codes, which can lead to a disease condition. Moreover, a recent animal study has shown that mental stress not only rewrite the epigenetic code in the brain but also in the gerrmline. Hence, the altered epigenetic code can be transmitted to the next generation, escaping the erasure of epigenetic marks that typically occurs during gametogenesis (Franklin et al., 2010). However, epigenetics is a reversible mechanism, and thus, epigenetic changes are treatable. Therefore, if the transgenerational inheritance of the epigenetic code is true in

humans and we transmit our own altered epigenetic code to our children, the code can be restored with the offer of appropriate environment and treatment. Although the number and kinds of environmental factors that can alter the epigenetic code are increasing, the precise mechanism is stll largely unknown. Further understanding of how epigenetic modications are changed during DNA replication is warranted in order to elucidate the genetic basis of environmental stress response.

7. References

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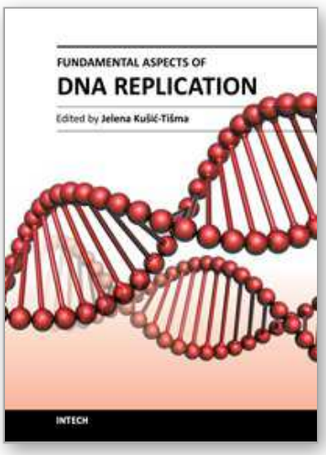

Fundamental Aspects of DNA Replication

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DNA replication, the process of copying one double stranded DNA molecule to produce two identical copies, is at the heart of cell proliferation. This book highlights new insights into the replication process in eukaryotes, from the assembly of pre-replication complex and features of DNA replication origins, through polymerization mechanisms, to propagation of epigenetic states. It also covers cell cycle control of replication initiation and includes the latest on mechanisms of replication in prokaryotes. The association between genome replication and transcription is also addressed. We hope that readers will find this book interesting, helpful and inspiring.

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