

Review

## The Role of Epigenetics in Developmental Programming and the Developmental Origins of Health and Disease

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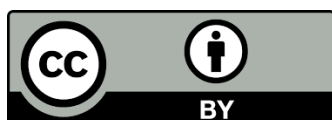
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### Abstract

A number of epidemiological studies have suggested that environmental stresses, such as malnutrition during the fetal period, can induce development of metabolic disorders, such as obesity, type 2 diabetes, and hypertension, and even psychiatric disorders in later life. This theory model is known as the Developmental Origins of Health and Disease (DOHaD) theory, in which postulates that “epigenetic memories”, involving DNA methylation, histone modifications and microRNA expression, are induced by environmental stresses during development. For example, the binding of transcription factors to cis-elements within the promoters and enhancer regions of genes induces demethylation leading to and subsequent histone acetylation and transcriptional activation. Several lines of evidence suggest that binding of bromodomain-containing protein 4 and positive transcription elongation factor B to acetylated histones within “gene body” regions initiates transcriptional elongation, and while histone H3K36 methylation and DNA methylation within “gene body” these regions



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terminates this transcriptional elongation. This new epigenetic model of the gene body regulation can be applied to the regulation of metabolic genes, which respond to carbohydrate signals and are associated with energy balance. Recent studies indicate that these new gene body epigenetic mechanisms, as well as the classical promoter/enhancer mechanism, are responsible for regulation of epigenetic changes found in offspring that have been exposed to malnutrition during the fetal period. In this context, further understanding of epigenetic gene regulation during the fetal period based on the “gene body epigenetic model” during the fetal period should provide new preventive and therapeutic strategies for adult diseases encompassed by DOHaD theory.

### **Keywords**

Epigenetics; histone acetylation; BRD4; gene body; DOHaD

## **Introduction**

Lifestyle choices, including dietary habits, can lead to the development of metabolic diseases, including obesity and type 2 diabetes, hypertension, lipid abnormalities, metabolic syndrome, and associated complications. These lifestyle factors are also relevant in the development of psychiatric disorders. Recent studies have demonstrated that these metabolic diseases develop via accumulation of the consequences of lifestyle choices throughout life; not only during adulthood, but also during development, including the fetal period and childhood. Newborns with low birth weight (under 2,500 g) have a higher risk of death resulting from cardiovascular diseases [1], type 2 diabetes [2], and metabolic syndrome [3]. In addition, a cohort study conducted in the Netherlands revealed a higher incidence of obesity among subjects born to women who had been malnourished during a period of famine in the Second World War than among their siblings who were not born during a time of severe food shortage [4]. A cohort study conducted in China also showed a higher incidence of integration disorder syndrome among subjects born to women who had experienced malnutrition during famine than among the generations born before and after this period [5]. In addition, in Japan, the number of newborns with low birth weight has increased rapidly in recent decades, while the average birth weight has decreased [6]. Therefore, it can be speculated that the children born during recent decades in Japan have a higher risk of developing metabolic diseases later in life. One cause of this may be the adherence to extreme diets before and during pregnancy by Japanese women in recent years.

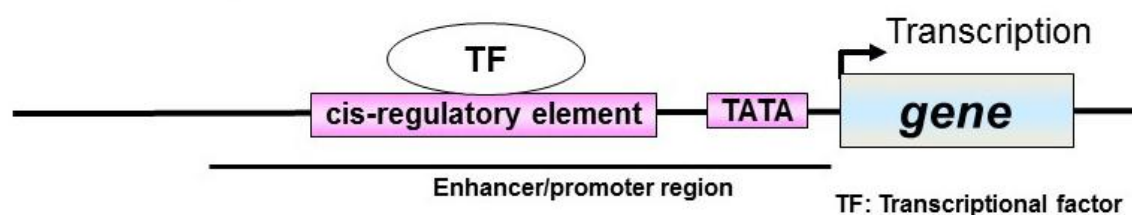
The Developmental Origins of Health and Disease (DOHaD) theory [7] postulates that a predisposition to metabolic diseases occurs through developmental programming that is regulated by exposure to environmental factors. Development of these metabolic diseases is considered to be caused by the long-term exposure of cells and tissues to environmental stimuli, such as hyper- or hyponutrition, during development as well as in adulthood. A candidate mechanism for the development of metabolic diseases is epigenetic memory of chromatin. The DOHaD theory is underpinned by epigenetics, rather than by changes in DNA sequence (genetics), because according to the DOHaD theory, diseases develop from stored memories of environmental

stimulation during development. Here, we review the relationship between epigenetics and the developmental programming/DOHaD theory.

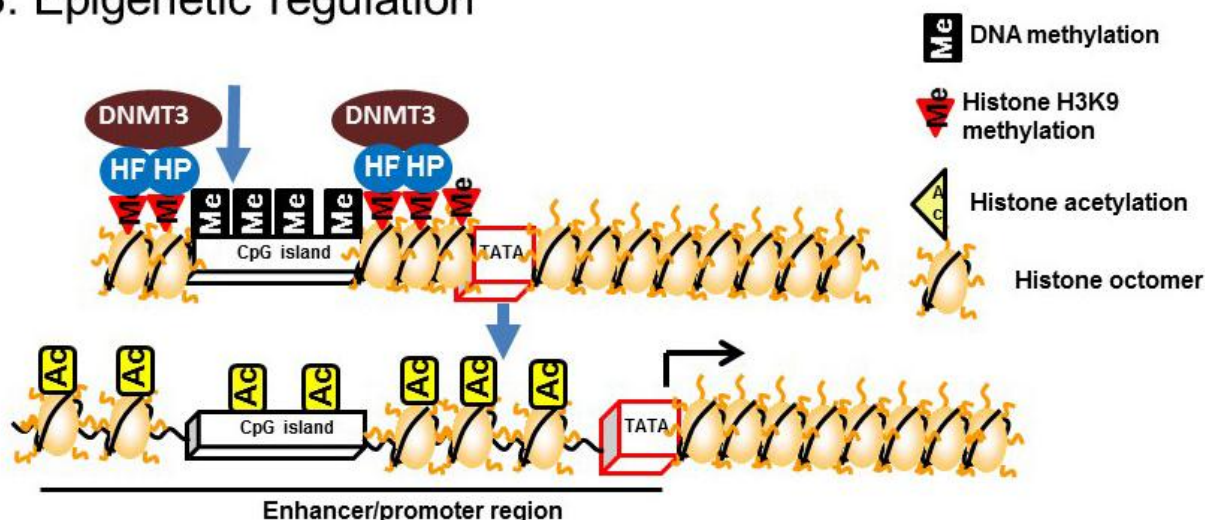
## General Epigenetic Regulation

In general, transcriptional regulation is mediated via transcription factors bound to DNA sequences located upstream of the transcription initiation site, particularly at promoter and enhancer regions. Transcription is initiated by the binding of transcription factors to specific sites, known as cis-regulatory elements, located in promoter and enhancer regions. This binding recruits transcription initiation complexes containing the RNA polymerase II–TATA box binding protein to the TATA box, which subsequently activates the transcription initiation reaction (Figure 1A).

### A. Genetic regulation



### B. Epigenetic regulation



**Figure 1** Genetic and epigenetic regulation. A) Genetic regulation. B) Epigenetic regulation.

Recent studies have demonstrated epigenetic regulation of transcription by DNA methylation of CpG dinucleotide-rich regions (CpG islands) in the promoter regions of genes. DNA methylation involves the addition of a methyl group to cytosine residues, particularly those within CpG islands. CpG islands hypermethylation leads to chromatin condensation by associating with heterochromatin binding proteins and DNA methyltransferases (DNMTs); this induces direct repression of transcription. Demethylation of CpG islands leads to the induction of transcription by altering histone modifications, such as acetylation, in enhancer/promoter regions (Figure 1B).

In contrast to the chemical modifications of DNA, those associated with chromosome histone proteins are rich in variety and include acetylation, methylation, phosphorylation, and

ubiquitination (Figure 2). Histones form nucleosomes, which consist of a segment of DNA wound around a histone octamer containing two molecules each of H2A, H2B, H3, and H4. Methylation of histone H3 at lysine 4 (K4) generally confers transcriptional activation, while methylation of histone H3K9/K27/K36 and H4K20 is associated with transcriptional repression. Each histone methylation site can be mono-, di-, or trimethylated although, in general, transcriptional activation or repression is strongly associated with changes from mono- to trimethylation. Histone acetylation relaxes the chromatin structure by changing the histone charge. In addition, histone acetylation activates transcription by recruiting epigenetic “reader” or “writer” proteins. Reader proteins bind to sites of epigenetic modification and recruit a variety of complexes to chromatin, while writer proteins, such as histone acetyl-transferases (HATs), histone methyl-transferases, and DNMTs, induce epigenetic modifications of chromatin. Histone methylation does not alter the charge of histones, but induces changes in transcriptional activation/repression by recruiting methylated histone binding proteins (containing a chromodomain, tudor domain, plant homeodomain finger, or WD40 repeat domain) to the chromatin [8].

### A. Histone H2A



### B. Histone H2B



### C. Histone H3



### D. Histone H4

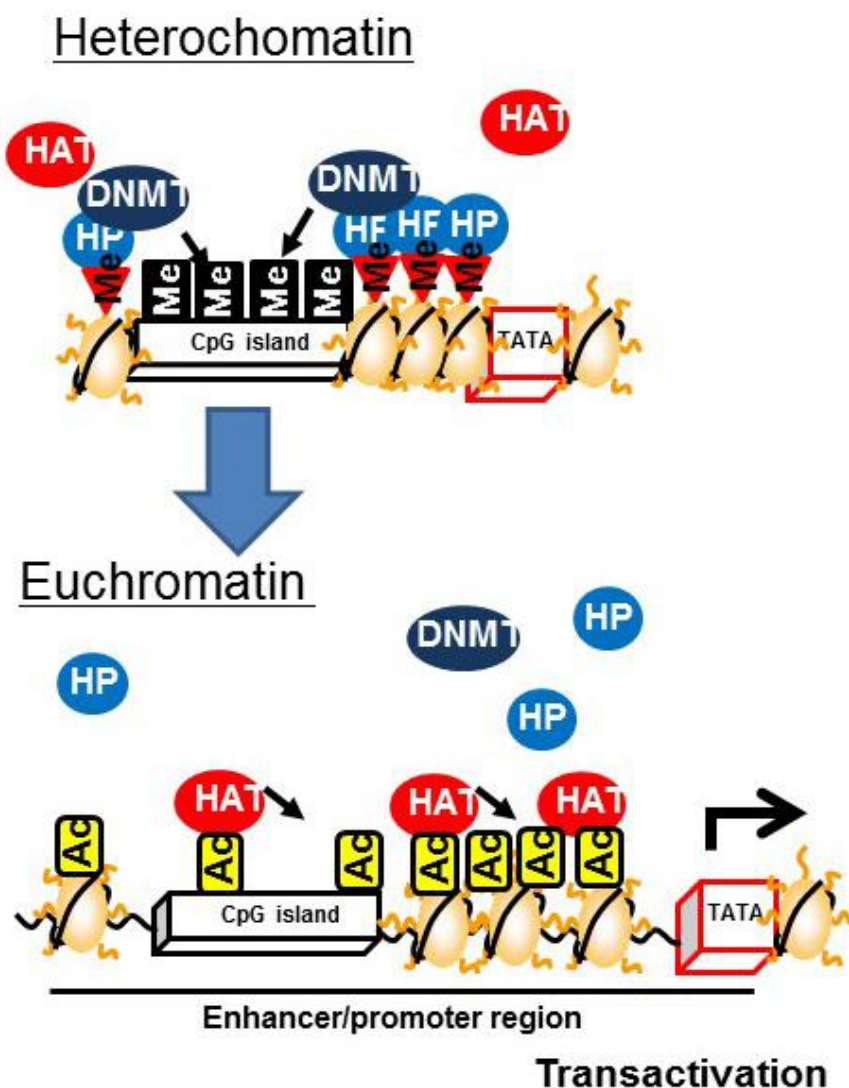


Acetylation methylation Phosphorylation Ubiquitination

**Figure 2** Histone modifications. A) Histone H2A. B) Histone H2B. C) Histone H3. D) Histone H4.

Heterochromatin is formed by enhancing the methylation of CpG islands mediated by DNMT bound to heterochromatin binding proteins on the methylated histones of CpG islands. In contrast, euchromatin is formed by the demethylation of CpG islands and subsequent histone acetylation mediated by HAT [9] (Figure 3). The induction of histone H3K4 monomethylation around the nuclear factor- $\kappa$ B gene by exposing primary human aortic endothelial cells to high glucose for a relatively short time (16 h) was reported to be maintained for 6 days when the cells were incubated under normal glucose conditions [10]. Therefore, it is postulated that environmental

factors prevailing during development can lead to a predisposition to diseases later in life that is controlled by epigenetics (Figure 4).



**Figure 3** Changes associated with the formation of euchromatin from heterochromatin

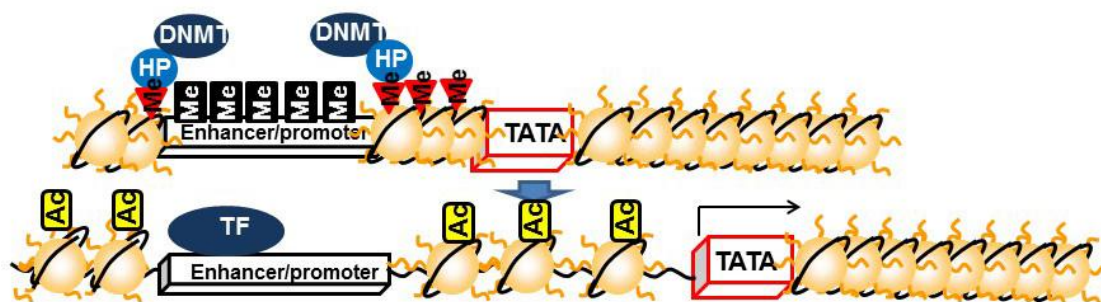
### Epigenetic Responses to Environmental Factors

It is not fully understood how environmental factors, including nutrient availability during development, affect metabolic gene expression and subsequent development of metabolic diseases. The classic model involves binding of transcription factors to cis-elements located in promoter/enhancer regions. Transcription factor-associated HAT acetylates histones in promoter and enhancer regions, and subsequently, bromodomain proteins bind to the acetylated histones to induce the formation of transcriptional initiation complexes around the TATA box of the promoter region. Nutrients, such as vitamins A and D, as well as unsaturated fatty acids and their metabolites, are ligands for nuclear receptors [retinoic acid receptor, vitamin D receptor, and peroxisome proliferator-activated receptor (PPAR), respectively] [11] (Figure 5A).

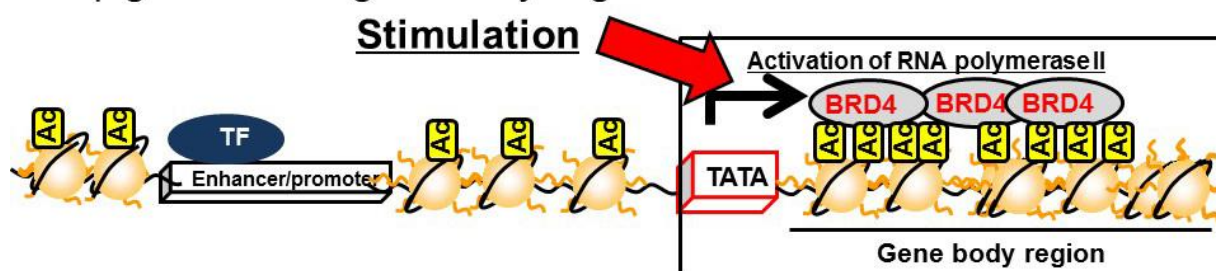




## A. Epigenetics via enhancer/promoter region

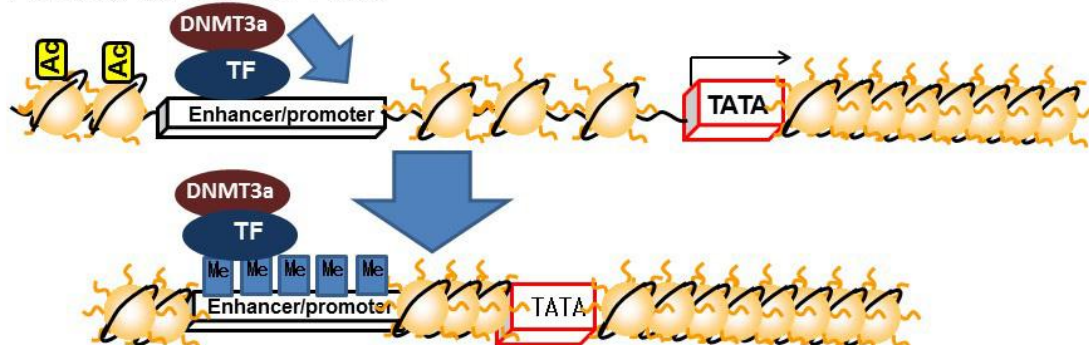


## B. Epigenetics via gene body region

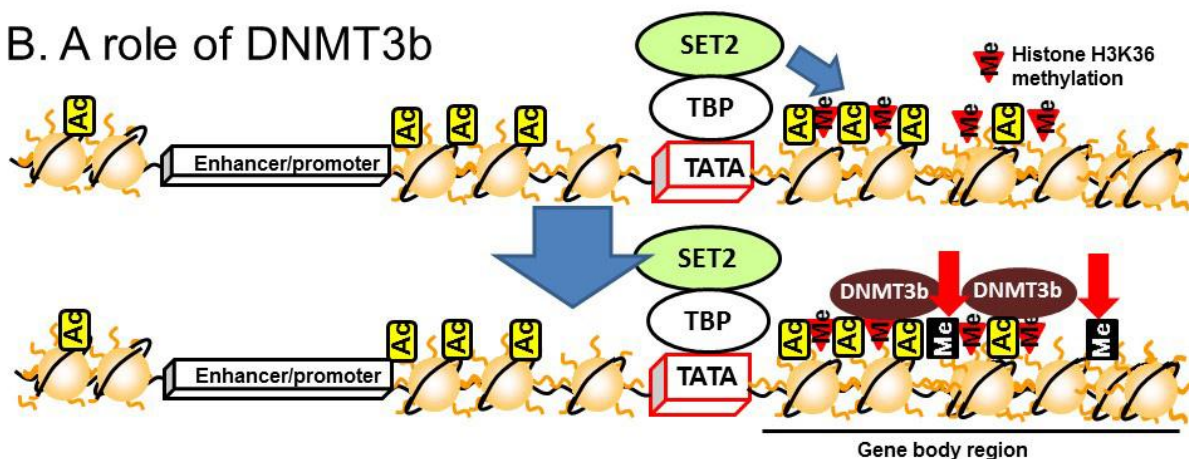


**Figure 5** Epigenetics of the enhancer/promoter region and the gene body. A) Epigenetics of the enhancer/promoter region. B) Epigenetics of the gene body.

## A. A role of DNMT3a



## B. A role of DNMT3b



**Figure 6** Roles of DNMT3 in the enhancer/promoter and gene body regions. A) DNMT3a. B) DNMT3b

The epigenetic model of gene regulation based on histone modifications and DNA methylation in the gene body region explains the efficacy of mRNA synthesis. Our recent studies in rats have demonstrated that carbohydrate intake increases histone acetylation in the gene body region, rather than in the promoter/enhancer region, of carbohydrate metabolism-related genes, such as sucrose-isomaltase, sodium glucose transporter 1, and glucose transporter 5 in the small intestine [12, 13], and fatty acid synthase in the liver during the suckling–weaning transition period [14]. In addition, we have demonstrated that fructose-inducible genes related to fat accumulation, such as *Cyp8b1*, *Dak*, and *Plin5*, are regulated by BRD4 in the liver [15]. Histone acetylation in the gene body region of adiponectin has also been reported to be accompanied by the induction of mRNA synthesis during the differentiation of 3T3-L1 adipocytes [16]. Disturbance of the expression of these genes leads to metabolic diseases and animals exposed to low energy and low protein conditions during the fetal period show abnormal expression of genes regulated by BRD4 and/or histone acetylation in the gene body region; therefore, BRD4-driven gene body acetylation is implicated as an epigenetic mechanism for the development of metabolic diseases induced by the fetal nutritional environment. Indeed, heterozygous *Brd4*-knockout mice showed growth abnormalities, such as reduced adiposity and abnormal bone metabolism, similar to those of mice exposed to fetal malnutrition [17]. Although there is little evidence supporting a role for the histone H3K36 in this process, our recent study demonstrated that a starvation signal induced H3K36 tri/dimethylation in genes expressed in the small intestine of *Xenopus laevis* [18].

Recent studies have also demonstrated that gene body epigenetics regulate pre-mRNA splicing. For example, one report described that alternatively spliced exons (ASE) were highly methylated and widely bound to a methylated DNA binding protein MeCP2, and ablation of which resulted in the induction of ASE-skipping in mRNA splicing [19]. However, associations between pre-mRNA spliceosome and DNA methylation or MeCP2 have not yet been established. The relationships between pre-mRNA splicing and gene body epigenetics and between gene body epigenetics and DOHaD require further investigation.

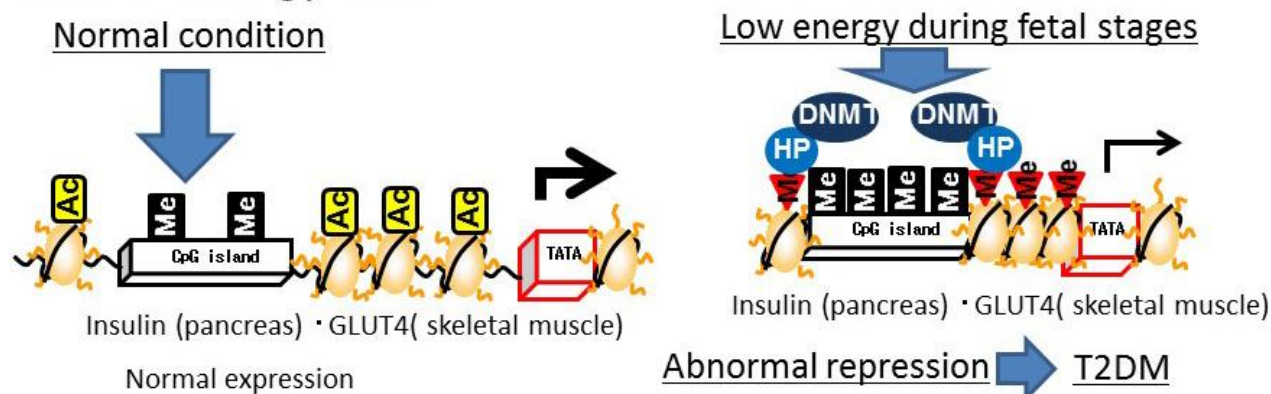
### **The Mechanism of Epigenetics in the DOHaD Theory**

Several animal studies have demonstrated that nutritional conditions during development disrupt epigenetic regulation later in life. For example, the expression of insulin and insulin promoter factor 1 (PDX1), which is a transcription factor for insulin expression in the pancreas, was lower in adult mice exposed to low energy in the fetal period compared with that in mice exposed to normal energy levels. Exposure to starvation conditions in the fetal period induced DNA methylation and histone H3K9 dimethylation, and reduced histone H3 acetylation in the promoter region of *Pdx1*. Malnutrition during the fetal stage repressed *Glut4* gene expression in skeletal muscle, while H3K9 dimethylation, DNMT3a binding, and histone deacetylase (HDAC)1 and 4 were induced and histone H3K14 acetylation in the *Glut4* promoter region was reduced [20]. These results suggest that malnutrition during the fetal period reduces insulin activity and induces impaired glucose tolerance in epigenetic disorders of the pancreas and skeletal muscle [20] (Figure 7A).

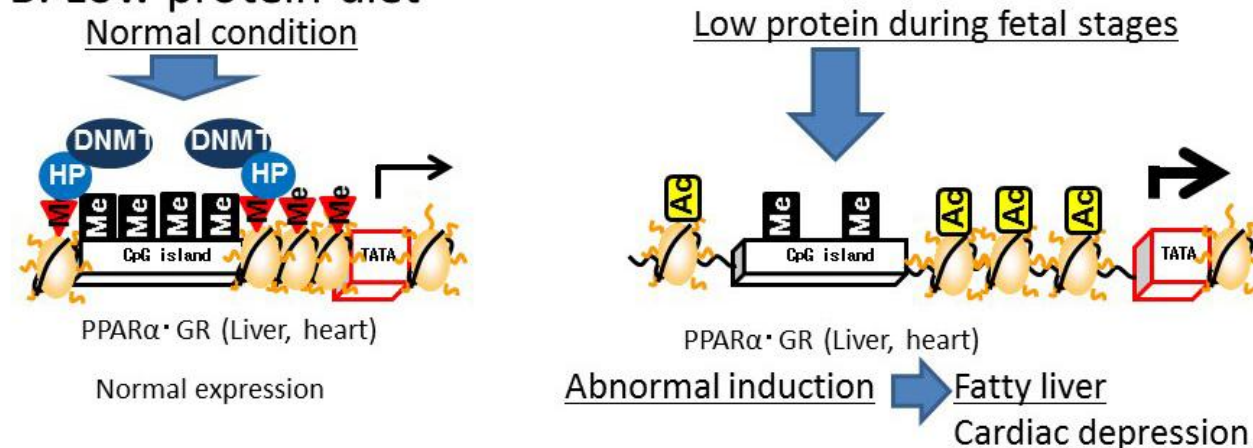
A low-protein diet fed to mice during pregnancy led to DNA demethylation in the promoter/enhancer regions of *Ppara*, which encodes a transcription factor for lipid metabolism, in the liver and heart [21], and in the glucocorticoid receptor (*Gr*) in the heart [22] of their newborn



## A. Low energy diet



## B. Low protein diet



**Figure 7** Effects of environmental conditions on Developmental Origins of Health and Disease (DOHaD) epigenetics. A) Low-energy diet. B) Low-protein diet

In addition, a restricted protein diet fed to pregnant rats enhanced the expression of *Dnmt1* in the liver of their newborn offspring [23]. A cause of the reduced DNA methylation in the promoter/enhancer regions of *Ppara* and *Gr* in the offspring of protein-restricted mothers was reduced *Dnmt1* expression. Folic acid supplementation in the pregnant mice led to improved DNA methylation in the upstream region of these genes in the offspring. However, *Dnmt3* expression in the newborns was not affected by exposure of the pregnant mice to a protein-restricted diet. DNMT1 maintains DNA methylation by attaching the methyl group to the complementary strand of previously hemi-methylated DNA during replication, while DNMT3 is responsible for *de novo* methylation. Thus, protein restriction may lead to disruption of the maintenance of DNA methylation during cell division in a pregnancy. In addition, deficiency of choline, which is a nutrient associated with one-carbon and methyl-group metabolism, was shown to induce DNA methylation throughout the genome and around the insulin-like growth factor 2 gene (*Igf2*), accompanied by the DNA methylation around *Dnmt1* [24]. These results indicate that protein-restriction and deficiency of folic acid and choline during the fetal period induce epigenetic disruption in adulthood. Subjecting pregnant rats to protein-restriction led to fatty livers in the offspring [25]. PPARA enhances the utilization of fat under conditions of reduced carbohydrate metabolism, such as insulin-resistance, while GR induces gluconeogenesis and fat accumulation. Excessive PPARA expression in the heart is associated with

cardiac muscle disorders [26]. Therefore, the induction of PPARA and GR expression in the heart and liver triggered by a reduction in DNA methylation around the genes encoding these proteins could lead to cardiac muscle disorders and fatty liver (Figure 7B). Regarding gene body epigenetics, DNA methylation in the gene body of liver X receptor A (*Lxra*) was reduced in the liver of F<sub>1</sub> and F<sub>2</sub> intrauterine growth-restricted mice [27]. However, since most animal model studies focused on the epigenetics of promoter/enhancer regions, further studies are required to establish the relationship between the epigenetics of gene body regions and developmental programming/DOHaD theory.

The relationship between genomic imprinting and DOHaD is still unclear. However, the fetal environment has been confirmed to induce alterations in the expression and promoter DNA methylation of the paternally-imprinted *IGF2* gene in humans and animals. Furthermore, expression of the paternally-inherited *IGF2* gene is enhanced by DNA methylation of the differentially methylated region (DMR) located upstream of the adjacent *H19* gene, which facilitates the access of proteins to an enhancer region. In contrast, in the case of the maternally-*IGF2* gene, the DMR is demethylated and binding of the CTCF protein to this region inhibits the access of proteins to an enhancer region and inactivates the *IGF2* gene [28]. It has been reported that the DNA methylation of the DMR upstream of paternally-inherited *H19* and *IGF2* gene expression are lower in patients with Silver–Russell syndrome [29, 30]. Therefore, the fetal environment could affect genomic imprinting, particularly that of the *IGF2* gene, and alterations in genomic imprinting may affect the development of metabolic disorders and psychiatric disorders in newborns. However, this issue remains to be clarified in further studies.

Regarding psychiatric disorders, symptoms of schizophrenia, including hyperkinetic disorder, have been reported in the offspring of rats subjected to immobilization stress during pregnancy. Specifically, following the induction of DNA methylation in the promoter regions of the reelin and glutamate decarboxylase 1 genes, reduction of their expression and the induction of *Dnmt1* gene expression in the frontal cortex were observed in the offspring of rats subjected to immobilization stress during pregnancy [31]. This indicates that the development of psychiatric disorders which are induced by the fetal environment are caused by epigenetic defects.

### **Epigenetic Mechanisms Associated with Metabolic Disease According to the DOHaD Theory**

In humans, it is not yet known whether the development of metabolic and psychiatric disorders induced by the fetal environment is regulated by epigenetic memory. A cohort study conducted in subjects born to mothers who had suffered malnutrition in the Netherlands during the Second World War showed that DNA methylation in the promoter region of *IGF2* was significantly lower in the blood of subjects exposed to these conditions during early gestation compared with that detected in their siblings who had not [4]. Methylation of the *IGF2* promoter region was also found to be lower in lymphocytes isolated from umbilical cord blood of infants born to subjects with gestational diabetes than in those born to healthy subjects [32]. In addition, DNA demethylation of the *IGF2* promoter region in these cells was positively associated paternal obesity [33]. However, the roles of *IGF2* in the development of metabolic diseases are still unclear. An animal study showed that a high-fat diet fed to the offspring of rats exposed to a low-protein diet during pregnancy not only induced obesity and insulin resistance, but also upregulated expression of the *Igf2* gene [34]. Therefore, it can be speculated that exposure to environmental

factors during human pregnancy induces metabolic and psychiatric disorders by altering the methylation of genes, including *IGF2*. It has been reported that carbohydrate restriction during pregnancy is positively associated with methylation in the promoter region of retinoid X receptor A (*RXRA*) in lymphocytes isolated from umbilical cord blood [35]. In addition, the body mass index (BMI) of pregnant women is positively associated with methylation of the PPAR $\gamma$  co-activator 1 $\alpha$  (*PGC1A*) promoter in their newborns [36]. Methylation of the aryl-hydrocarbon receptor DNA promoter in newborns was also reported to be positively associated with maternal obesity during pregnancy, infant gestational age, and birth weight for gestational age [37]. However, there is no evidence in humans that environmental factors during pregnancy alter the methylation of the *GLUT4*, *PPARA*, *GR*, and *LXR* genes that are affected in animal models. Despite the absence of reports of gene body epigenetic markers associated with metabolic disease development in relation to the developmental programming/DOHaD theory, several studies have been conducted focusing on promoter/enhancer regions. For example, methylation of the gene body region of the glucokinase (*GCK*) gene in peripheral blood samples was lower in subjects with coronary heart disease and higher in subjects with essential hypertension compared with that in healthy subjects [38, 39]. A minor polymorphism in *DNMT3B*, which regulates DNA methylation in gene body regions, was also associated with an increased risk of premature birth [40]. Thus, it is possible that disrupted gene body epigenetics is linked to developmental programming/DOHaD theory, although this hypothesis requires further examination. In addition, the relationship between histone modification and DNA methylation induced by the fetal environment has not been studied in humans. Further studies using peripheral and umbilical cord blood are required to clarify these relationships in humans.

## Conclusion

In this review, we discuss two models of epigenetics based on the promoter/enhancer region and the gene body region. Several studies have demonstrated the existence of epigenetic memory in promoter/enhancer regions and in gene body regions in animals and humans exposed to environmental stress conditions, including malnutrition, during the fetal period as well as in adulthood. However, these findings are preliminary and further studies are required to elucidate the epigenetic mechanisms underlying the development of metabolic diseases associated with exposure to environmental stress during development.

## Competing Interests

The authors have declared that no competing interests exist.

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