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Review article

Epigenetic modulation of DNA methylation by nutrition and its mechanisms in animals

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ABSTRACT

It is well known that phenotype of animals may be modified by the nutritional modulations through epigenetic mechanisms. As a key and central component of epigenetic network, DNA methylation is labile in response to nutritional influences. Alterations in DNA methylation profiles can lead to changes in gene expression, resulting in diverse phenotypes with the potential for decreased growth and health. Here, I reviewed the biological process of DNA methylation that results in the addition of methyl groups to DNA; the possible ways including methyl donors, DNA methyltransferase (DNMT) activity and other cofactors, the critical periods including prenatal, postnatal and dietary transition periods, and tissue specific of epigenetic modulation of DNA methylation by nutrition and its mechanisms in animals.

1. Introduction

It is well known that many organisms may respond to different environmental/nutritional factors by exhibiting phenotypic plasticity. One epitome is that honeybees grow to be either queens or workers depending on whether they are fed royal jelly or beebread (Kucharski et al., 2008). Another paradigmatic example is that of the Agouti mouse model where the maternal methyl dietary content affects the coat color of the rodent offspring (Wolff et al., 1998; Waterland and Jirtle, 2003; Dolinoy et al., 2006). These observations demonstrate that phenotype of animals may be modified by the nutritional modulations through epigenetic mechanisms, meaning dietary exposures can have long-term consequences for growth and health (McKay and Mathers, 2011). Mathers (2008) developed a model of Four Rs to explain the mechanism of nutritional epigenomics (Fig. 1).

Over recent years, there is increasing evidence that environmental (nutritional) stimuli can modify DNA methylation and therefore, affect phenotypic expression of genes (Lillycrop et al., 2005; van Straten et al., 2010; Farias et al., 2015; Farkas et al., 2015; Day et al., 2015). These work either empirical – possible changes in epigenetic marks were investigated in response to diet factor, or theoretical – hypothesized mechanisms were researched through which the nutrients could affect epigenetic markings. DNA methylation is a key component of an epigenetic network (Kucharski et al., 2008) and has long been considered as central to the field of epigenetics. DNA methylation process contributed the most significance of the "epi" prefix to "epigenetics". Hence, the mechanisms, critical periods, and the tissue specific of nutritional modulation of DNA methylation were reviewed here.

2. DNA methylation

Epigenetic marks on the genome can be copied from one cell generation to the next, which may change gene expression, but not primary DNA sequence (Reik, 2001). DNA methylation is a biological process that results in the addition of methyl groups to DNA. It contributes to the epigenetic network that controls the gene expression. DNA methylation occurs in many key physiological processes that including X chromosome inactivation, imprinting and the silencing of germline-specific genes and repetitive elements. Methylation marks on DNA are focused on the 5' position of cytosine residues of a Cytidine-Guanine dinucleotide (CpG, where p stands for a phosphate group between the two nucleotides). The majority of cytosine residues within CpG dinucleotides are methylated, but some of them are normally

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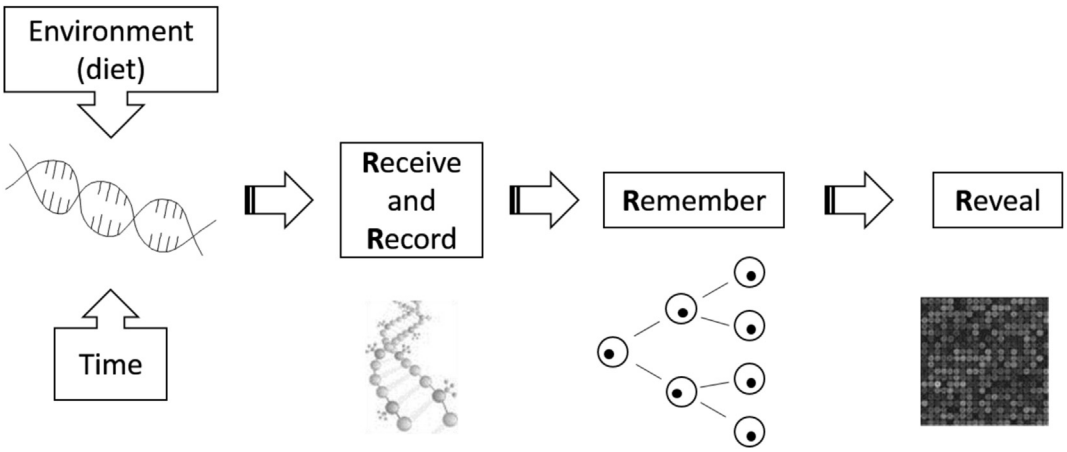

Fig. 1. The conceptual model of the Four Rs of nutritional epigenomics. The changed epigenomics markings resulted from environmental (nutritional) exposures are Received, Recorded, Remembered and Revealed (Mathers, 2008).

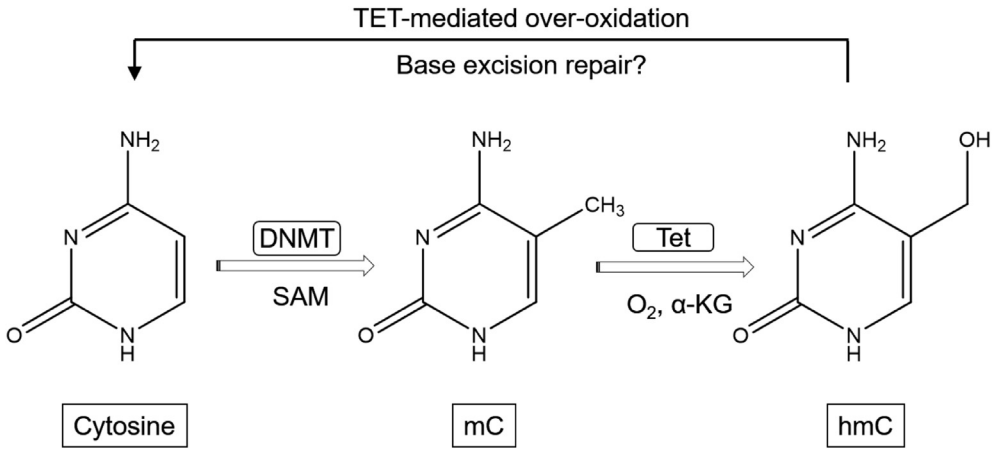

Fig. 2. Cytosine is methylated *in vivo* by DNA methyltransferase (DNMT), which uses S-Adenosylmethionine (SAM) as an electrophilic methyl source, to produce 5-methylcytosine (mC) at cytosine-phosphate-guanine (CpG) sites in double-stranded DNA. Maintenance DNMT may then methylate the complimentary cytosine to produce double-stranded CpG methylation. An otherwise stable epigenetic mark, mC can be oxidized by the α-ketoglutarate (α-KG) -dependent ten-eleven translocation (Tet) family of dioxygenases to yield 5-hydroxymethylcytosine (hmC), which is the first step in removing the methyl as an epigenetic mark (Day et al., 2015).

unmethylated, e.g., those in CpG islands within the promoter regions of housekeeping genes. Both CpG-rich and CpG-poor regions exist but occur infrequently than expected in DNA (Jones and Liang, 2009). DNA methylation is mediated by *de novo* DNA methyltransferases (DNMT) to yield 5-methylcytosine (mC), primarily at cytosine-phosphate-guanine (CpG) dinucleoside sites (Fig. 2) (Day and Sweatt, 2010, 2011; Day et al., 2015). There are three DNMT with different functions. DNMT3A and DNMT3B are responsible for addition of methyl group *de novo*, e.g., during embryogenesis, whereas DNMT1 is responsible for maintenance of DNA methylation patterns during cell replication. In addition, DNMT1 copying the methylation marks on the parental strand to the daughter strand after replication, DNMT3A and DNMT3B complete the methylation process and correct errors left by DNMT1 (Jones and Liang, 2009).

Nevertheless, mC can be oxidized by the α-KG-dependent Tet family of dioxygenases to yield 5-hydroxymethylcytosine (hmC) (Fig. 2) (Tahiliani et al., 2009; Day et al., 2015). The hydroxymethyl mark itself is stable and exists in relatively elevated levels in the brain. However, it is also the first step in active demethylation, and either over-oxidation by the Tet family of proteins to aldehyde or carboxylate products or deamination mechanisms followed by base excision repair then erases cytosine alkylation (Ito et al., 2011; Song et al., 2013).

3. Mechanisms of nutritional modulation of DNA methylation

There are now mounting evidences supporting that nutrients may modify the pattern of DNA methylation, either at the global scale or at locus-specific sites (Vucetic et al., 2010; Bogdarina et al., 2010; Jousse et al., 2011; Dudley et al., 2011; Altmann et al., 2012). There are three possible ways that nutrition influences patterns of DNA methylation (Fig. 3): first, provision of substrates being necessary for proper DNA methylation; second, provision of cofactors modulating the enzymatic activity of DNMT; third, changing activity of the enzymes regulating the one-carbon cycle. Importantly, all three mechanisms are mutually compatible and may operate together in time.

3.1. Methyl donors from diet

As the universal methyl-donor for DNA and protein methyltransferases (Loenen, 2006), S-Adenosylmethionine (SAM) is synthesized in the methionine cycle from several precursors present

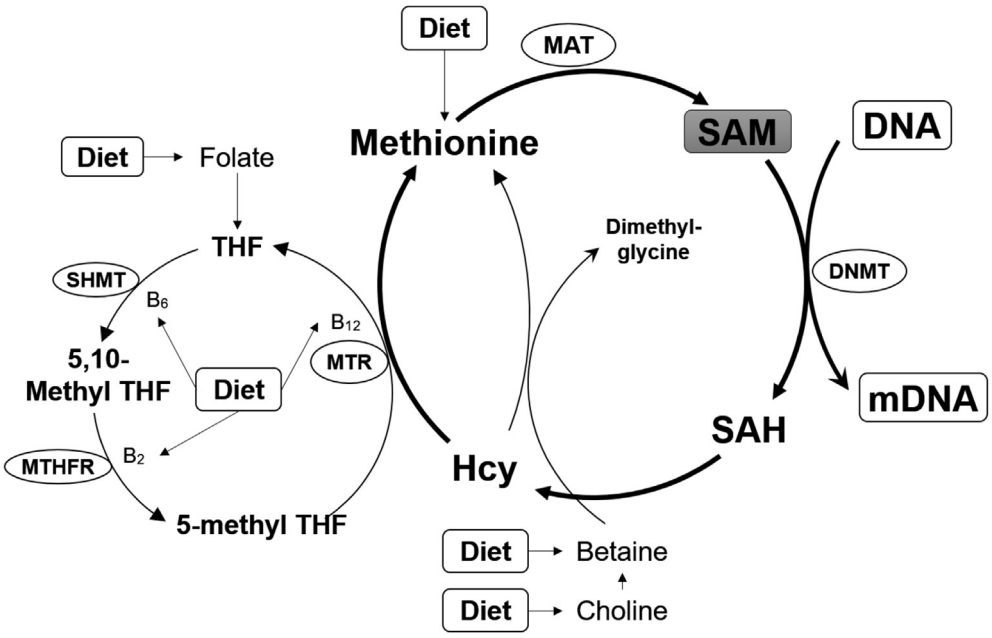

Fig. 3. Possible ways that nutrition influences patterns of DNA methylation (Revised from McKay and Mathers, 2011). MAT = methionine adenosyltransferase; SAM = S-adenosyl methionine; SHMT = serine hydroxymethyltransferase; THF = tetrahydrofolate; DNMT = DNA methyltransferase; MTR = 5-methyltetragydrofolate-homocysteine methyltransferase; MTHFR = methylentetrahydrofolate reductase; Hcy = homocysteine; SAH = S-adenosylhomocysteine; mDNA = methylated DNA.

in the diet (McKay and Mathers, 2011; Feil and Fraga, 2012). All these precursors, including methionine, folate, choline, betaine and vitamins B_2, B_6 and B_{12}, enter at different sites in the methionine pathway and contribute to the net synthesis of SAM. Hence, reduced availability of methyl donors should result in low SAM synthesis and global DNA hypomethylation, and vice versa.

In fact, numerous information about the effects of methyl donors on DNA methylation is available from studies with animal models (Pogribny et al., 2008; Cordero et al., 2013, 2014; Amarasekera et al., 2014; Llanos et al., 2015; Farkas et al., 2015). Accordingly, diets deficient in methyl donors result in global DNA hypomethylation in rodents (Pogribny et al., 2008, 2009; Mehedint et al., 2010; Craciunescu et al., 2010). Conversely, maternal diet supplemented with methyl donors increases DNA methylation in specific loci (Waterland, 2006; Waterland et al., 2008; de Vogel et al., 2011; Li et al., 2015; Farias et al., 2015).

Although methyl donors can alter DNA methylation patterns, little is known about the necessary doses and the exact durations of dietary exposure or depletion contributing changes in epigenetic marks. There are too many uncertainties about the effects of different doses and duration of dietary exposure on DNA methylation (Cravo et al., 1994, 1998). Therefore, it merits more systematic studies to provide more unequivocal findings.

Besides, other studies showed a more complex scenario. Low protein or 50% global malnutrition during gestation in mice led to both hyper- and hypo-methylation at specific loci in the offspring (van Straten et al., 2010). Likewise, undernutrition in utero in humans resulted in both hypo- and hyper-methylation of different specific loci (Heijmans et al., 2008; Tobi et al., 2009; Waterland et al., 2010). It is not reported whether the amount of methyl-donors is reduced in these specific studies, but it is commonly accepted that undernutrition correlates with reduced methyl-donor availability. Therefore, there is not a simple correlation between methyl donor concentration and DNA methylation. Other mechanisms might contribute to set patterns of DNA methylation in cells.

3.2. DNA methyltransferase activity

It is well known that DNMT require SAM as a cofactor for their full activation. Methyl donors from the diet may contribute to modulate DNMT activity by changing the intracellular concentration of SAM. Besides an indirect regulation of DNA methylation patterns through modulation of SAM pools, several compounds can also directly influence the expression or activity of DNMT (Mukherjee et al., 2015). Evidence of a competitive inhibition of DNMT activity has been demonstrated for the (−)-epigallocatechin-3-gallate (EGCG), polyphenol in green tea, or the genistein present in soybean (Fang et al., 2007; Vanhees et al., 2011; Xie et al., 2014; Zampieri et al., 2015). Myricetin can also decrease DNA methylation by inhibiting SssI DNMT (Lee et al., 2005).

The EGCG can re-express many transcriptionally silenced genes through inhibition of DNMT1 enzymatic activity (Berletch et al., 2008; Kato et al., 2008), and was shown to decrease growth and induce apoptosis in renal cell carcinoma by re-expressing tissue factor pathway inhibitor-2 (TFPI-2) and decreasing its promoter hypermethylation (Gu et al., 2009). The EGCG also decreases the promoter methylation of other genes such as hTERT and CDX2, thereby helping in tumor suppression (Qi and Ohh, 2003; Hirata et al., 2009). Genistein was also found to decrease DNMT activity resulting in transcriptional activation of genes such as p16INK4a, RAR beta, MGMT, PTEN, and CYLD in prostate cancer and RAR beta 2 in cervical cancer (Fang et al., 2005; Kikuno et al., 2008). Genistein-mediated modulation of methylation of protumorigenic miRNA-1260b and its targets sFRP1 and Smad4 inhibits prostate cancer cell proliferation, invasion, and TCF reporter activity (Hirata et al., 2014). Other dietary phenolic compounds, including hesperetin, naringin, apigenin, and luteolin, can also modulate DNA methylation by indirectly regulate DNMT activity through regulating the ratio of SAM and SAH (Lee et al., 2005; Fang et al., 2007; Mukherjee et al., 2015), although these compounds are not as efficient as EGCG in directly inhibiting DNMT activity. Curcumin was found to bring about global hypomethylation in the MV4–11 leukemia cell line by inhibiting DNMT (Liu et al., 2009). It was also

found to regulate DNMT1 negatively in ovarian cancer and melanoma (Abusnina et al., 2011; Parashar et al., 2012).

3.3. Activity of enzymes from methionine cycle

Vitamins B_2, B_6 and B_{12} are cofactors involved in the regulation of the catalytic activity of enzymes from the folate cycle, thus determining SAM bioavailability. Specifically, vitamin B_6 is a cofactor to serine hydroxymethyltransferase (SHMT) in the conversion of tetrahydrofolate (THF) into 5,10-methylene THF. Vitamin B_2 is a precursor to FAD, which is a cofactor to methylenetetrahyrofolate reductase (MTHFR) in the conversion of 5,10-methylene THF to 5-methyl THF. Vitamin B_{12} is a cofactor of the 5-methyltetrahydrofolate-homocysteine methyltransferase (MTR) that catalyzes the conversion of homocysteine (Hcy) into methionine, the direct precursor of SAM. Therefore, bioavailability of these cofactors may influence DNA methylation by modifying the activity of the one-carbon cycle and the production of SAM (Feil and Fraga, 2012).

Thus, it is conceivable that supplementing diets with these vitamins will contribute to the maintenance or establishment of DNA methyl marks. Farias et al. (2015) showed for the first time that HCT116, LS174T, and SW480 cells grown without adequate folate significantly impaired colonosphere forming ability. These differences were accompanied by concomitant changes to DNA methyltransferase (DNMT) enzyme expression and DNA methylation levels. Li et al. (2015) reported that folic acid can down-regulate tau protein phosphorylation by inhibiting the demethylation reactions of PP2A. High folic acid concentrations (20 and 40 μmol/L) increased ratio of SAM to SAH and cell viability.

4. Critical periods of nutritional modulation of DNA methylation

4.1. Prenatal period

Early embryogenesis in mammals is the most critical period for the establishment of the epigenome. Failure to complete these programs in time might be irreversible and lead to permanent dysregulation of gene expression (Lumey et al., 1993; Gallou-Kabani and Junien, 2005). Importantly, this is a period especially vulnerable to environmental cues, such as nutrition, that can disrupt the correct establishment of epigenetic marks that, once established, remain highly stable (Burdge and Lillycrop, 2010). This is the reason why nutritional challenges during early development stage might have such long-term effects.

There is greater evidence about the impact of maternal nutrition on epigenetic marks in the progeny (Dominguez-Salas et al., 2014; Cannon et al., 2014; Mozhui et al., 2015). Protein restriction is frequently used model for maternal malnutrition. For example, Feeding a low protein diet to pregnant rats resulted in global or locus specific changes in DNA methylation (Rees et al., 2000; Altmann et al., 2013). Reported genes (or loci) affected by protein malnutrition include the glucocorticoid receptor (GR), peroxisome proliferator-activated receptor alpha (PPARa) and liver X receptor-alpha (Lxra) in liver (Lillycrop et al., 2007, 2008; van Straten et al., 2010, 2012; Altmann et al., 2013); the hepatocyte nuclear factor-4-alpha (Hnf4a) in islet cells (Sandovici et al., 2011); the AT(1b) angiotensin receptor in adrenal gland (Bogdarina et al., 2007, 2010); the orexigenic/anorexigenic genes neuropeptide Y (Npy) and proopiomelanocortin C (Pomc) in hypothalamus (Coupé et al., 2010); and the leptin gene (Lep) in adipose tissue (Jousse et al., 2011).

In a similar rat model, 50% caloric restriction decreased the abundance of H3K4Me2 at the IGF1 locus of liver from the newborn offspring. This epigenetic modification alters IGF1 expression and contributes to post-natal catch-up growth (Fu et al., 2009; Tosh et al., 2010). Moderate caloric restriction (30%) decreased methylation in fetal kidney during early stages of gestation, whereas it increased DNA methylation by the end of gestation (Unterberger et al., 2009). Maternal high fat diet may also alter DNA methylation and gene expression in the offspring. For example, maternal high fat feeding during gestation changed methylation and gene expression of opioid and dopamine related genes in the brain of offsprings (Vucetic et al., 2010). Likewise, offspring from mothers fed a high fat diet showed reduced methylation, and increased expression, of the cyclin-dependent kinase inhibitor 1A (Cdkn1a) during neonatal liver development (Dudley et al., 2011). In another study, global and gene-specific (dopamine reuptake transporter, m-opioid receptor and pre-proenkephalin) promoter DNA hypomethylation were observed in the brains of offspring from dams that were fed a high-fat diet (Marco et al., 2014). In oocytes of obese mice that were induced by a high-fat diet, the leptin promoter DNA was significantly hypermethylated, but the PPARa was hypomethylated (Ge et al., 2014). More recently, maternal high-fat diet during gestation and lactation induced global DNA hypermethylation, including fatty acid and cholesterol metabolism-related genes (Yu et al., 2015).

Importantly, changes in DNA methylation correlate with altered gene expression. Therefore, such nutritionally-induced changes in DNA methylation may explain, at least in part, metabolic dysfunction in the adult. there is now sufficient evidence to support that maternal malnutrition may induce permanent alterations in gene expression through epigenetic modifications.

4.2. Postnatal period

It is now becoming clear that nutritional effects on the epigenome are not limited to the intrauterine life, but extend to early postnatal period. The early postnatal nutrition is a vital determinant of adult animal's health. Rat pups receiving high-protein diets via gastrostomy display enhanced short-term weight gain, insulin resistance, and modified expression of adipocyte glucose transporter type 4 and liver glucose transporter type 2 (des Robert et al., 2009). The high-carbohydrate rats have increased expression of pancreatic duodenal homeobox factor-1, protein kinase 2, and phosphatidylinositol 3-kinase (Srinivasan et al., 2000; Petrik et al., 2001; Srinivasan et al., 2001). Postnatal nutritional modulation altered the gene expression, suggesting that epigenetics may contribute to programming of animals. As expected, Neonatal overfeeding in rats led to rapid early weight gain, resulting in a metabolic syndrome phenotype. Accompanying, increased methylation of the promoter of the hypothalamic anorexigenic factor proopiomelanocortin (Pomc) was observed (Plagemann et al., 2009). It is the first time demonstrates a nutritionally acquired alteration of the methylation pattern and, consequently, the regulatory 'set point' of a gene promoter that is critical for body weight regulation. Likewise, in a follow-up study, neonatal over nutrition increased mean methylation of the insulin receptor promoter in the hypothalamus (Plagemann et al., 2010). This alteration might additionally contribute to induce hypothalamic insulin resistance, thus contributing to the development of metabolic syndrome. Neonatal overfeeding in the mouse also provoked permanent modifications in DNA methylation in the liver from adult individuals, as assessed by CpG island microarrays (Pentinat et al., 2010). Furthermore, the obese phenotype from neonatal-overfeeding-mothers can be passed onto the subsequent generation, which is possibly associated with hypothalamic leptin resistance (Wang et al., 2015). Future epigenetic studies in animal models with postnatal dietary manipulation will be necessary to

facilitate identification of dietary approaches that can be applied in the postnatal period.

4.3. Dietary transition period

Epigenetic variations are not restricted to pre- or post-natal period but may occur throughout an individual life-course (Grayson et al., 2014). Epigenetic research involving monozygotic twins, who are born with identical genomes, yet exhibit different phenotypes later in life, are an excellent example of how impactful environmental factors can be in the developmental plasticity of organisms. Such epigenetic variations accumulate over a long period and may ultimately influence phenotypic outcomes (growth and health). However, the amount of data linking adult dietary interventions with epigenetic modifications is much more limited than that for dietary interventions during pre- and postnatal development. Nevertheless, nutrition can still have long lasting effects, especially during long-term "Dietary Transitions" (Jiménez-Chillarón et al., 2012), which can be defined as a period in which animals are exposed over a prolonged period of time (ranging from weeks–months in animals) to a diet characterized by malnutrition. This type of transitions may cause subtle long-lasting (or permanent) changes in gene expression. Epigenetically associated changes in these gene expressions, although potentially reversible, tend to be stable and contribute to the age-dependent decrease of growth and health (Li et al., 2011a; Chalkiadaki and Guarente, 2012; Jiménez-Chillarón et al., 2012).

For example, Chronic high fat feeding in mice (from weaning to $>$ 15 wk) altered patterns of DNA methylation within the promoter regions of the mu-opioid receptor in both the VTA and NAc in the brain (Vucetic et al., 2011; Pitman and Borgland, 2015). Likewise, post-weaning diet (high content of fat and carbohydrate) influence the hepatic intracisternal A particle (IAP) methylation patterns in mice (Warzak et al., 2015). Furthermore, Postweaning high-fat diet predisposes the mouse offspring for obesity, and hypomethylation of proopiomelanocortin (POMC) promoter in the hypothalamus occurred (Zheng et al., 2015). Likewise, male mice fed a low protein diet from weaning to age 9 to 12 wk induced numerous changes of DNA methylation, as assessed by microarray analysis, in livers from the offspring. Among positive loci, an enhancer of the lipid regulatory protein PPARa was identified (Carone et al., 2010). Again, a sustained dietary change on the epigenome of isogenic mice with methyl-supplemented diet over 6 generations increased DNA methylation variation in liver (Li et al., 2011b), suggesting that some of the induced changes are heritable. Moreover, caloric restriction influences expression of specific genes associated to age-related diseases and senescence through modulating the enrichment binding of HDAC1 to their promoter regions (Ferguson-Smith and Patti, 2011; Li et al., 2011b).

5. Tissue specific of nutritional modulation of DNA methylation

There is growing evidence that DNA methylation patterns are tissue specific (Ollikainen et al., 2010; Schneider et al., 2010; Herzog et al., 2013; Wan et al., 2015). Moreover, it is well documented that DNA methylation varies between tissue types (Illingworth et al., 2008; Christensen et al., 2009; Maegawa et al., 2010; Thompson et al., 2010). Recent technical advances have made it possible to monitor DNA methylation patterns on a genome-wide scale (Meissner et al., 2008). Unbiased analysis of genome wide methylation patterns reveals that DNA methylation is not always negatively correlated with gene expression, challenging the traditional view that DNA methylation represses gene expression. In addition, positive tissue-specific differentially methylated sites (T-DMRs) are likely to play a functional role in regulating tissue associated gene expression (Wan et al., 2015). It is evident that a clear tissue-specific dependence of methylation levels exists at the differentially-methylated-regions (DMR) in exon 9 of IGF2 (IGF2 *ex9* DMR) for peripheral blood leucocytes and whole cord blood (Schneid et al., 1993; Reik et al., 1994; Guo et al., 2008; Ollikainen et al., 2010; Buckberry et al., 2012; Nordin et al., 2014; Ideraabdullah et al., 2014). The IGF2 *ex9* DMR have highly variable tissue-specific methylation levels at imprinting associated DMR (Tierling et al., 2010). However, according to the current knowledge about the regulation of this locus and its postulated role in regulating fetal growth and development, factors contributing to tissue-specific DMR differences at birth are less clear (Guo et al., 2008; Dilworth et al., 2010). Schneider et al. (2010) studied the methylation patterns of seven neighboring CpG sites in the APC promoter region. They found the methylation patterns appeared to differ among tissues, indicating a true tissue-dependent differences in nucleosome positioning (Dodd et al., 2007) and/or binding of specific transcription factors (Pant et al., 2004).

For the effects of nutritional modulation on DNA methylation, a hepatic global DNA hypomethylation and brain hypermethylation was occur together in methyl deficient rats (Pogribny et al., 2006, 2008), suggesting differential tissue responsiveness to the same methyl deficient insult. At first, a long-term administration of a diet deficient in methionine, choline, and folic acid resulted in the progressive hypomethylation of DNA in livers associated with substantial alterations in one-carbon metabolism (Pogribny et al., 2006). Surprisingly, a significant increase in DNA methylation and unaffected SAM and SAH levels was found in the brains of folate/methyl-deficient rats (Pogribny et al., 2008). Furthermore, a partial change in the DNA methylation patterns of the prostate occur after genistein exposure, but not in the liver in male mice feeding a genistein supplemented diet (300 mg/kg diet) for 4 wk (Day et al., 2002). The methylation in the promoter region of the skeletal α-actin (Acta1) gene increased at some CpG sites within pancreas but not the liver in mice feeding a diet containing both daidzein and genistein (Guerrero-Bosagna et al., 2008). Whereas tissue specific differences in methylation profiles were also observed for estrogen receptor-α (ERα), which show a well-defined methylation profile in liver, contrasting with an absence of methylation seen in pancreas (Guerrero-Bosagna et al., 2008). Further, an interaction between folate depletion and tissue methylation was observed at the Igf2 DMR2 locus in which methylation was increased in the liver but decreased in the blood with folate depletion, whereas methylation within the kidney remained unchanged (McKay et al., 2011). It will be especially essential to specify the methylation in specific tissue of genes because it is basal for nutrition regulation.

6. Prospective of nutritional modulation of DNA methylation

It is unequivocal that nutrition is influencing the epigenome. This dynamic relationship between nutrition and genes throughout an organism's lifetime has now been recognized as a subfield called Nutritional Epigenomics or 'Nutri-epigenomics' and provides promising insight for how to target growth and health from a nutritional standpoint (Reik, 2007). This process includes the modification of DNA by methylation at CpG sites (Jaenisch and Bird, 2003), one of the most widely studied form of epigenetic modification. This article has detailed the current knowledge regarding the biological mechanisms, the critical period, and the tissue specific of nutritional modulation of DNA methylation. The epigenetic mechanisms may explain the way by which dietary factors in several critical developmental steps modulate the growth and health of animals in adulthood. However, our

knowledge regarding nutritional epigenomics is still limited. Further studies in animal subjects using the latest technologies are needed to better understand the roles of nutrition for maintaining health through modifiable epigenetic mechanisms. Future work is needed to systematically analyze the influence of methyl donors on the DNA methylation patterns in order to predict their usefulness as epigenetic modulators. Further, more attention should be focused on dietary bioactive ingredients when DNMT are being tested. Additionally, the interactions among micronutrients required in one-carbon metabolism and those that may indirectly affect their supply to maintain cycle efficiency merits more study. Totally, continued animal nutri-epigenomic research will strengthen our understanding in the biological pathways associated with diet and health.

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