Minireview: Epigenetic Programming of Diabetes and Obesity: Animal Models

Yoshinori Seki,* Lyda Williams,* Patricia M. Vuguin, and Maureen J. Charron

Departments of Biochemistry (Y.S., L.W., P.M.V., M.J.C.) and Pediatrics (P.M.V.), Division of Endocrinology, Children Hospital at Montefiore (P.M.V.), and Departments of Medicine, Division of Endocrinology (M.J.C.), and Obstetrics and Gynecology and Women’s Health, Albert Einstein College of Medicine (M.J.C.), Bronx, New York 10461

A growing body of evidence suggests that the intrauterine (IU) environment has a significant and lasting effect on the long-term health of the growing fetus and the development of metabolic disease in later life as put forth in the fetal origins of disease hypothesis. Metabolic diseases have been associated with alterations in the epigenome that occur without changes in the DNA sequence, such as cytosine methylation of DNA, histone posttranslational modifications, and microRNA. Animal models of epigenetic modifications secondary to an altered IU milieu are an invaluable tool to study the mechanisms that determine the development of metabolic diseases, such as diabetes and obesity. Rodent and nonlitter bearing animals are good models for the study of disease, because they have similar embryology, anatomy, and physiology to humans. Thus, it is feasible to monitor and modify the IU environment of animal models in order to gain insight into the molecular basis of human metabolic disease pathogenesis. In this review, the database of PubMed was searched for articles published between 1999 and 2011. Key words included epigenetic modifications, IU growth retardation, small for gestational age, animal models, metabolic disease, and obesity. The inclusion criteria used to select studies included animal models of epigenetic modifications during fetal and neonatal development associated with adult metabolic syndrome. Experimental manipulations included: changes in the nutritional status of the pregnant female (calorie-restricted, high-fat, or low-protein diets during pregnancy), as well as the father; interference with placenta function, or uterine blood flow, environmental toxin exposure during pregnancy, as well as dietary modifications during the neonatal (lactation) as well as pubertal period. This review article is focused solely on studies in animal models that demonstrate epigenetic changes that are correlated with manifestation of metabolic disease, including diabetes and/or obesity. (Endocrinology 153: 1031–1038, 2012)

The incidence of metabolic disease here and worldwide has reached epidemic proportions. A recent study, in which data for trends in glycemia and diabetes prevalence were obtained for adults, 25 yr of age and older, in 199 countries and territories, found that the number of people with diabetes had increased from approximately 153 million in 1980 to 347 million in 2008 (1). Of growing concern is the fact that the age of onset of these diseases has accelerated such that children and young adults are the fastest growing population with these conditions, which presents a significant human health problem. Genome-wide association studies, family linkages, and candidate gene analyses have all failed to account thus far for this rapid increase in incidence, early onset, and severity of these diseases. Epidemiological studies have suggested that modifications of the epigenome due to alterations in...
the intrauterine (IU) environment could play a significant role in the manifestation as well as the increased susceptibility to metabolic disease in later life. This concept, also known as the fetal origins of adult disease, has been extensively reviewed elsewhere (2, 3). There is evidence as well to suggest that postnatal alteration of the epigenome can also be associated with diabetes and obesity (4).

Molecular insight into some of the alterations in the epigenome has been gained from human population studies and animal models designed to mimic the human condition. These epigenomic modifications include posttranslational modifications (PTM) of specific amino acids on the tails of the histone subunits and the differentially methylated regions (DMR) of DNA (5, 6). These modifications alter chromatin packing, resulting in either “open” or “closed” states and thus affect gene expression. Some histone PTM, such as acetylation, are labile and associated with gene activation, others, such as methylation, are stable and are associated with gene inactivation (7). A number of studies has identified specific epigenetic changes associated with perturbations of the IU environment; thus, providing insight on some of the alterations of the epigenome in key organs of metabolism involved in glucose homeostasis, insulin sensitivity, and energy balance. They demonstrate how the IU environment may impact disease pathogenesis and suggest that these changes can be transmitted across multiple generations. Most of what we know about the epigenetic changes associated with metabolic disease has been gathered from animal models; thus, illustrating their utility. We will describe the benefits and limitations of each animal model as it relates to improving strategies to prevent diabetes and obesity in the future. A brief summary of all the known epigenetic changes that have been identified from animal models of diabetes and obesity are summarized in Table 1.

Maternal Nutrition

Nutrient manipulation during pregnancy [high fat (HF), low protein (LP), or global caloric restriction] has been an established model of fetal growth restriction in humans (8) and animal models (9). These dietary alterations result in poor fetal growth followed by an early life catch up growth that increases the exposed offspring’s susceptibility to insulin resistance, diabetes, and obesity later in life (9, 10). Studies using isolated mouse embryos have shown that culture conditions and the availability of nutrients can alter the expression of imprinted genes, such as the maternally expressed imprinted gene H19 (11) and the DMR upstream of H19. The latter was associated with a decreased expression of H19 and the IGF-II genes (12).

LP diets (8 vs. 20%) are associated with impaired fetal growth and the development of obesity, diabetes, and hypertension in the offspring (13, 14). Many epigenetic changes have been reported in diverse organs of offspring exposed to a maternal LP diet. In the liver of a LP Wistar rat model, decreased acetylation of histone H3 lysine K9 and K14 and increased histone H3K9me3 was shown to be associated with decreased fetal hepatic Jmjd2a (histone H3 K9 demethylase) expression, decreased cholesterol 7α-hydroxylase (Cyp7a1) expression and increased cholesterol levels (15). Also in Wistar rats, LP diet has been associated with hypomethylation of the promoter of the glucocorticoid receptor (GR) (16) in addition to a reduction in DNA methyltransferase (DNMT)1 expression and reduced expression and binding of methyl CpG binding protein 2 (MeCP2) in liver. This was correlated with altered histone modifications at the GR110 promoter (H3K9 and H4K9 hyperacetylation, increased H3K4 methylation and H3K9me3) that resulted in increased GR promoter activity (17). Another epigenetic change associated with a LP diet in this model is DNA hypomethylation of the peroxisomal proliferator-activated receptor α (PPARα) promoter that resulted in increased PPARα expression (16). In Sprague Dawley (SD) rats, LP diet resulted in DNA hypermethylation of H19/IGF-2 locus, in addition to an increased expression of DNMT1, DNMT3a, and methyl-CpG binding domain protein 2 in liver of male offspring associated with increased expression of IGF-II and H19 (18). Additionally, LP diet in C57BL/6J mice is associated with DNA hypermethylation of the liver X-receptor (LXR)α promoter and reduced mRNA levels of LXRα and its target genes Abcg5/Abcg8 in fetal liver (19). In skeletal muscle (SM), a LP diet in SD rats is associated with hyperacetylation of lysines on histones H3 and H4 in the promoter region of (CCAAT/enhancer binding protein β, C/EBPβ) along with increased levels of C/EBPβ mRNA and protein levels in liver of female offspring (20, 21). Similarly, increased gene expression was measured for the amino acid response pathway and phosphoenol pyruvate carboxykinase (PEPCK), and the latter was associated with increased histone H3K9me3 and acetylated H4 (20, 21). In the SM of Meishan pigs exposed to a maternal LP diet, increased H3 acetylation and H3K27me3 (3) and decreased H3K9me on the myostatin promoter were observed (22). Lastly, IU exposure to a LP diet in Balb/c mice is associated with DNA hypomethylation of the leptin promoter in adipose tissue, changes in body composition (lower weight/adiposity), and increased food consumption in male offspring (23).

Nutrient restriction during gestation is also associated with metabolic dysfunction, including hypertension, hyperinsulinemia, hyperleptinemia, and obesity (24). Ma-


<table>
<thead>
<tr>
<th>Animal model</th>
<th>Epigenetic change</th>
<th>Disease association</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal nutrition</td>
<td>Rat</td>
<td>Decreased acetylation of H3K9 and K14 and increased H3K9me3 postnatafly in liver and decreased Jmjd2a in fetal liver</td>
<td>Obesity</td>
</tr>
<tr>
<td>LP Rat</td>
<td>Hypomethylation of PPARα and GR promoter in liver</td>
<td>Obesity</td>
<td>16, 17, 52, 53</td>
</tr>
<tr>
<td>LP Rat</td>
<td>Hypermethylation of IGF2/H19 locus in liver</td>
<td>Obesity</td>
<td>18</td>
</tr>
<tr>
<td>LP Mouse</td>
<td>Hypermethylation of LXR promoter in fetus (19.5 d) in liver</td>
<td>Obesity</td>
<td>19</td>
</tr>
<tr>
<td>LP Rat</td>
<td>Hyperacetylation of histone H3 and H4 at the C/EBP promoter in SM</td>
<td>Obesity</td>
<td>20</td>
</tr>
<tr>
<td>LP Rat</td>
<td>Increased H3K9me3 and acetylated H4 in female liver</td>
<td>Obesity</td>
<td>21</td>
</tr>
<tr>
<td>LP Pig</td>
<td>Hyperacetylation of histone H3 and H3K27me3 in SM; hypoacetylation of histone H3K9me at the myostatin promoter in SM</td>
<td>Obesity</td>
<td>22</td>
</tr>
<tr>
<td>LP Mouse</td>
<td>Hypomethylation of leptin promoter in adipose tissue</td>
<td>Obesity</td>
<td>23</td>
</tr>
<tr>
<td>Calorie restriction Sheep</td>
<td>Hypomethylation of IGF/H19 DMR in adrenal gland</td>
<td>Obesity</td>
<td>25</td>
</tr>
<tr>
<td>Calorie restriction Rat</td>
<td>Hypoacetylation of histone H3K14 and increased H3K9me2 at the glucose transporter 4 promoter in SM</td>
<td>Diabetes</td>
<td>26</td>
</tr>
<tr>
<td>Periconceptional restriction B12, folate, methionine Sheep</td>
<td>Altered methylation at 4% of 1400 CpG islands in fetal liver</td>
<td>Obesity</td>
<td>27</td>
</tr>
<tr>
<td>HF Japanese macaque</td>
<td>Hyperacetylation of histone H3K9, H3K18, and H3K14 in fetal liver</td>
<td>Obesity</td>
<td>28</td>
</tr>
<tr>
<td>HF Mouse</td>
<td>Hypermethylation of proximal promoter of DAT, MOR, and preproenkephalin in brain</td>
<td>Obesity</td>
<td>29</td>
</tr>
<tr>
<td>HF Mouse</td>
<td>Increased DNA methylation, MeCP2 binding, H3K9 methylation, and decreased H3 acetylation in MOR promoter region of reward-related brain regions</td>
<td>Obesity</td>
<td>30</td>
</tr>
<tr>
<td>Surgical models IUGR (bilateral uterine artery ligation) Rat</td>
<td>Epigenetic changes along entire length of Igf1 gene</td>
<td>Diabetes</td>
<td>31</td>
</tr>
<tr>
<td>IUGR (bilateral uterine artery ligation) Rat</td>
<td>Deacetylation of histones H3 and H4 at the proximal promoter of PDX1 in pancreatic islets; hypermethylation of the PDX1 promoter in pancreatic islets</td>
<td>Diabetes</td>
<td>34</td>
</tr>
<tr>
<td>IUGR (bilateral uterine artery ligation) Rat</td>
<td>Altered methylation at 1400 loci in pancreas; hypermethylation of GTP cyclohydrolase 1 promoter in pancreas</td>
<td>Diabetes</td>
<td>35</td>
</tr>
<tr>
<td>Environmental toxin Arsenic Mouse</td>
<td>Global hypomethylation in liver by the methyl acceptance assay</td>
<td>Diabetes</td>
<td>40</td>
</tr>
<tr>
<td>Paternal effect LP Mouse</td>
<td>Hypermethylation of promoter region of PPARα in liver</td>
<td>Obesity</td>
<td>42</td>
</tr>
<tr>
<td>Neonatal diet feeding Leptin treatment Rat</td>
<td>Hypermethylation of the proopiomelanocortin promoter in hypothalamus</td>
<td>Obesity</td>
<td>44</td>
</tr>
<tr>
<td>Exendin-4 Rat</td>
<td>Hyperacetylation of histone H3 at the promoter of PDX1 in pancreatic islets</td>
<td>Diabetes</td>
<td>45</td>
</tr>
<tr>
<td>Transgenerational effect LP Rat</td>
<td>Hypomethylation of hepatic PPARα and GR promoter in F1 and transmitted to F2</td>
<td>Obesity</td>
<td>46</td>
</tr>
<tr>
<td>LP Rat</td>
<td>PEPCK promoter methylation altered out to F3 generation</td>
<td>Obesity</td>
<td>47</td>
</tr>
<tr>
<td>Reverse (folic acid) Methyl supplementation Aγ mouse</td>
<td>Increased CpG methylation at Aγ locus of Aγ/a offspring</td>
<td>Obesity</td>
<td>50</td>
</tr>
<tr>
<td>Genistein supplementation Aγ mouse</td>
<td>Hypermethylation of CpG sites</td>
<td>Obesity</td>
<td>51</td>
</tr>
<tr>
<td>Protein restriction + folic acid IU Rat</td>
<td>Prevented hypomethylation of PPARα and GR in liver</td>
<td>Obesity</td>
<td>16</td>
</tr>
<tr>
<td>Juvenile-pubertal Rat</td>
<td>Reverse the promoter hypomethylation of PPARα, GR and IR in liver, and PPARα and IR in adipose tissue</td>
<td>Obesity</td>
<td>52</td>
</tr>
<tr>
<td>Protein restriction + folic acid IU Rat</td>
<td>Reverse the promoter hypomethylation of PPARα in liver</td>
<td>Obesity</td>
<td>53</td>
</tr>
</tbody>
</table>
ternal caloric restriction (70% metabolizable energy) has been associated with several epigenetic changes. In a sheep model, it was associated with DNA hypomethylation of the proximal CTCF binding site in DMR of the IGF-II/H19 gene in the adrenal gland that is associated with decreased expression of IGF-II along with an increase in adrenal gland growth in both male and female offspring and an increase in the cortisol stress response in females (25). In SM of SD rats, calorie restriction resulted in increased histone H3K14 deacetylation, which is associated with increased recruitment of histone deacetylase (HDAC)1 and HDAC4 (26). Also reported was an increase in H3K9me2 that was associated with increased SUV39H1 methylase activity and reduced glucose transporter 4 mRNA and protein expression that correlated with insulin resistance, increased adiposity, hypertension, and alterations in immune response in male offspring (26). In fetal liver of sheep, maternal restriction of vitamin B12, folate, and methionine altered DNA methylation of 4% of the 1400 CpG islands examined, and more than half of these changes were specific to male offspring (27).

Consumption of a HF diet during gestation (35–60% of calories from fat) is associated with phenotypic changes in offspring such as obesity, hypertension, abnormal cholesterol metabolism, and cardiovascular disease (13). HF diet has been associated with epigenetic changes in several animal models. In Japanese macaques that consumed a HF diet during gestation (35% calories from fat), hyperacetylation of histone H3K14, H3K9, and H3K18, along with an increase in DNMT1 expression, a decrease in HDAC1 expression, and an increase in hepatic triglycerides, was observed in fetal offspring liver (embryonic d 130 of 167 d) (28). In the brain of mice (C57BL/6j x DBA/2j F1 hybrids), a HF diet was associated with global and gene-specific promoter DNA hypomethylation, including the dopamine reuptake transporter, the µ opioid receptor (MOR), and preproenkephalin that was associated with altered dopamine and opioid gene expression as well as a change in feeding behavior (29). During the postnatal period of these mice, HF diet exposure was associated with increased DNA methylation and MeCP2 binding in the MOR promoter region of reward-related brain regions as well as increased H3K9 methylation and decreased H3 acetylation. These epigenomic changes were accompanied by decreased MOR expression in the ventral tegmental area, nucleus accumbens, and prefrontal cortex but not the hypothalamus and a decreased preference for sucrose in offspring (30). At present, it is unclear whether the abundance of reported epigenetic alterations, secondary to altered fetal nutrient availability, is critical for metabolic well being or if this is the most studied IU perturbation.

Surgical Models

Bilateral and unilateral uterine artery ligation of the pregnant rat has been used to generate a model of fetal growth restriction (31). This procedure is performed at d 18 or 19 of gestational age and is a model of both nutrient restriction as well as one of hypoxic exposure. These maternal manipulations have been associated with insulin resistance, glucose intolerance, hyperglycemia, hyperinsulinemia, and the development of diabetes in adulthood (32, 33).

Bilateral uterine ligation is associated with epigenetic changes in several organs. In liver, it resulted in epigenetic changes in the histone code along the entire length of IGF-I gene, resulting in decreased IGF-I levels in male and female SD rat offspring (31). In pancreatic islets, bilateral uterine ligation caused reduced expression of pancreatic and duodenal homeobox 1 (PDX1), which was accompanied by a general deacetylation of histone H3 and H4 in the PDX1 proximal promoter of male SD rats (34). Similarly, after birth, there was a decrease in histone H3K4me (3) and an increase in H3K9me2 followed by methylation of the CpG island in the proximal promoter of PDX1, resulting in gene silencing after the onset of diabetes (34). Additionally, in pancreatic islets, a genome-wide survey of male SD rat offspring showed altered DNA methylation of approximately 1400 loci that occurred predominantly in intergenic regions (35). The uterine artery ligation model of programmed metabolic disease yields a robust metabolic phenotype in offspring, yet there is a paucity of alterations in the epigenome. One may have assumed that epigenetic changes seen in this model might be overlapping with the nutrient restriction models discussed above. However, no overlap has been reported among these models, suggesting the hypoxia component of the uterine artery ligation model may be a dominant factor.

Environmental Toxins

Environmental exposure to toxins, such as heavy metals like arsenic, has been associated with increased risk for development of type 2 diabetes (36, 37). These toxins cause mitochondrial damage and increases oxidative stress in SM, as well as causing altered glucose and cholesterol metabolism, insulin resistance, and obesity (38, 39). Arsenic exposure during development is associated with global DNA hypomethylation of GC-rich regions as well as altered expression of genes in the insulin-like growth factor signaling pathway such as IGF-1, IGF receptor 2, and IGF binding protein 1, as well as the stress response genes metallothionein 1 in liver of male C3H.
offspring (40). Despite the correlation between toxin exposure and programmed metabolic disease, little is known about the epigenomic alterations associated with this model.

**Paternal Effect**

Paternal diet can also affect the health of his offspring. As shown by Ng et al. (41), paternal HF diet exposure programs pancreatic β-cell dysfunction that leads to metabolic abnormality in F1 female offspring of SD rats, illustrating a sexually dimorphic response. The underlying mechanism for this could be dependent upon the hormonal differences between offspring or other mechanisms that have yet to be described. Paternal LP diet exposure programmed elevated hepatic mRNA expression of genes involved in lipid and cholesterol biosynthesis and decreased levels of cholesterol esters in C57BL/6J mice. These changes were associated with a modest increase in DNA methylation of the upstream region of the PPARα gene (42). Considering that the father’s diet condition is inherited without changes to the DNA code itself, these findings suggest that sperm can undergo epigenetic alterations that are passed on to the offspring.

**Effect of Neonatal Feeding**

Epigenetic changes have also been shown to occur during the neonatal period (43). Leptin treatment in male Wistar rats during the suckling period is associated with DNA hypermethylation of proopiomelanocortin promoter in the hypothalamus that is involved in appetite and body weight control (44). Similarly, exendin 4 treatment during the neonatal period modified the hyperacetylation of histone H3 in the proximal promoter of PDX1 in pancreatic islets of SD rats (45). These results illustrate that the diversity of epigenetic modifications that have profound effects on energy balance and pancreatic development, contributing to obesity and diabetes pathogenesis, can be programmed during the neonatal period.

**Transgenerational Effect**

In general, epigenetic modifications are cleared and reestablished with each generation. However, in some cases, the epigenetic state at these alleles can be transmitted between generations. Burdge et al. (46) reported that the PPARα and GR promoters are hypomethylated in liver of male Wistar rat offspring exposed to a LP diet, although the expression of these genes was not different between the reference diet group and the LP diet. Interestingly, using this LP diet model, DNA hypomethylation of the hepatic PPARα and GR promoters seen in the F1 generation were transmitted to the F2 generation (46). Another study demonstrated that relatively few of these changes are consistently transmitted to the F3 generation (47). Of these, PEPCK promoter methylation and mRNA expression, as well as expression of genes in the adherens junctions pathway, were altered out to the F3 generation along with increased fasting glycemia. These findings imply that transmission of the altered epigenetic modification associated with altered maternal nutrient intake can be transmitted for at least one additional generation; however, changes in the interaction between the maternal phenotype and the environment can alter the signals received by the developing fetus, emphasizing again the correlation between altered fetal nutrient availability and epigenomic change.

**Reversibility of Epigenetic Changes**

The viable yellow agouti (A<sup>v</sup>) mouse model, a sensor for nutritional and environmental alterations on the fetal epigenome (48), has been shown to cause variation in coat color, glucose tolerance, and tumor susceptibility according to the exposure to different nutrients during development (49). The A<sup>v</sup> allele is a metastable epiallele that can be modified by epigenetic modifications that are established very early during development. Several dietary manipulations have been used to determine the effect of nutrients on the fetal epigenome. These studies include methyl supplementation of nonagouti a/a females with vitamin B<sub>12</sub>, choline, and betaine, which affects the phenotype of the A<sup>v</sup>/a offspring by increasing CpG methylation at the A<sup>v</sup> locus (50), leading to the coat color distribution of the offspring being shifted toward the pseudoagouti phenotype. Similarly, maternal dietary supplementation with genistein (phytoestrogen found in soy) results in hypermethylation of CpG sites, causing a decreased ectopic agouti expression protecting the offspring from obesity (51).

In other animal models, epigenetic modifications can be reversed by the addition of methyl donors, such as folic acid in the diet. Epigenetic modifications are not observed in Wistar rats that received a LP diet containing folic acid supplementation from conception to delivery, suggesting that the DNA hypomethylation was due to a deficiency in folic acid or its reduced availability (16). As discussed above, the mother’s diet during pregnancy is the strong factor in deciding the epigenetic status of her offspring;

---

Endocrinology, March 2012, 153(3):1031–1038  
endo.endojournals.org  
1035

Downloaded from https://academic.oup.com/endo/article-abstract/153/3/1031/2423676 by guest on 29 January 2018
however, it is known that the period of epigenetic plasticity may extend beyond the IU or lactation period. In Wistar rat offspring exposed to a maternal LP diet IU, folic acid supplementation during the pubertal period prevented DNA hypomethylation of following loci: hepatic and adipose PPARα promoter and insulin receptor promoter (52) and hepatic GR promoter (53). The stability of the epigenome is decreased during the juvenile-pubertal period; therefore, dietary supplementation with folic acid or methionine during this critical period may have the effect of modifying the methylation status of the PPARα and GR promoters.

Conclusions

These studies demonstrate that the early life environment is very critical in determining disease susceptibility and that perturbations of the developmental milieu can have a profound impact on the age of onset and incidence of diabetes and obesity contributing to the current worldwide metabolic disease health crisis. Animal models of epigenetic changes during development are an effective and valuable tool in understanding the relationship between the fetal/neonatal environment and adult disease. We have to consider that the epigenetic transmission can occur in a sex or genetic background-dependent manner (54, 55), and although the complexities of the human condition cannot be thoroughly reproduced, animal models provide a useful tool that allow us the utilization of humane techniques that would be unethical to perform in humans. Although an array of animal models, as well as animal strains, has been used to induce fetal/neonatal/pubertal programming of adult metabolic disease, the epigenetic changes observed differ among the models (gene and tissue specific), yet each leads to similar metabolic phenotypic consequences (including obesity and/or diabetes), demonstrating that multiple factors contribute to the development of metabolic disease. Thus, it will be important to determine the most effective animal model for the study of the various aspects of epigenetic programming based on the recognition of the complex nature (background, sex, critical stage of development) of obesity and diabetes, which seems to be the common end stage of a number of interventions. In summary, the molecular results of these epigenomic studies characterized by alterations in DNA methylation and histone PTM suggest novel therapeutic interventions that may be used in managing the metabolic disturbances observed in diabetes and obesity. These findings also suggest that more care should be given to consumption of a healthy maternal diet and improved fetal nutrient availability that may lead to a more normal birth weight and early life growth, thereby reducing the risk for programmed metabolic disease.

Acknowledgments

We thank current and past members of the Charron laboratory for fruitful discussions on the subject of this review.

Address all correspondence and requests for reprints to: Maureen J. Charron, Ph.D., Department of Biochemistry, Albert Einstein College of Medicine, 1300 Morris Park Avenue, Room F312, Bronx, New York 10461. E-mail: maureen.charron@einstein.yu.edu.

This work was supported by National Institutes of Health [Grants R21 DK081194 (to M.J.C.) and KO8 HD042172 (to P.M.V.), Diabetes Research and Training Center Grant P60 DK020541, Epigenomics, Liver, O’Brien Kidney, and Comprehensive Cancer Centers of Albert Einstein College of Medicine, Diabetes Action Foundation, and American Diabetes Association (to M.J.C.).

Disclosure Summary: The authors have nothing to disclose.

References

18. Gong L, Pan YX, Chen H 2010 Gestational low protein diet in the rat mediates lgg2 gene expression in male offspring via altered hepatic DNA methylation. Epigenetics 5:619–626
31. Fu Q, Yu X, Callaway CW, Lane RH, McKnight RA 2009 Epigenetics: intrauterine growth retardation (IUGR) modifies the histone code along the rat hepatic IGF-1 gene. FASEB J 23:2438–2449
44. Palou M, Pico C, McKay JA, Sanchez J, Priego T, Mathers JC, Palou A 2011 Protective effects of leptin during the suckling period against later obesity may be associated with changes in promoter methylation of the hypothalamic pro-opiomelanocortin gene. Br J Nutr 105:1–10
47. Hoile SP, Lillycrop KA, Thomas NA, Hanson MA, Burdge GC 2011
Dietary protein restriction during F(0) pregnancy in rats induces
transgenerational changes in the hepatic transcriptome in female
offspring. PLoS One 6:e21668

48. Dolinoy DC 2008 The agouti mouse model: an epigenetic biosensor
for nutritional and environmental alterations on the fetal epig-

49. Morgan HD, Sutherland HG, Martin DI, Whitelaw E 1999 Epige-
etic inheritance at the agouti locus in the mouse. Nat Genet 23:
314–318

50. Waterland RA, Jirtle RL 2003 Transposable elements: targets for
early nutritional effects on epigenetic gene regulation. Mol Cell Biol
23:5293–5300

genistein alters coat color and protects Avy mouse offspring from
obesity by modifying the fetal epigenome. Environ Health Perspect
114:567–572

52. Burdge GC, Lillycrop KA, Phillips ES, Slater-Jeffries JL, Jackson
AA, Hanson MA 2009 Folic acid supplementation during the juve-
nile-pubertal period in rats modifies the phenotype and epigenotype
induced by prenatal nutrition. J Nutr 139:1054–1060

53. Lillycrop KA, Phillips ES, Torrens C, Hanson MA, Jackson AA,
Burdge GC 2008 Feeding pregnant rats a protein-restricted diet
persistently alters the methylation of specific cytosines in the hepatic
PPARα promoter of the offspring. Br J Nutr 100:278–282

54. Waterland RA, Travisano M, Tahiliani KG, Rached MT, Mirza S
2008 Methyl donor supplementation prevents transgenerational

55. Dunn GA, Morgan CP, Bale TL 2011 Sex-specificity in transgen-
erational epigenetic programming. Horm Behav 59:290–295

Members can search for other endocrinology professionals
around the world in the online Member Directory.
www.endo-society.org/directory