THEMATIC REVIEW

Epigenetic responses and the developmental origins of health and disease

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Abstract

Maternal and paternal factors influence offspring development and program its genome for successful postnatal life. Based on the stressors during gestation, the pregnant female prepares the fetus for the outside environment. This preparation is achieved by changing the epigenome of the fetus and is referred to as 'developmental programming'. For instance, nutritional insufficiency *in utero* will lead to programming events that prepare the fetus to cope up with nutrient scarcity following birth; however, offspring may not face nutrient scarcity following birth. This discrepancy between predicted and exposed postnatal environments are perceived as 'stress' by the offspring and may result in cardiovascular and metabolic disorders. Thus, this developmental programming may be both beneficial as well as harmful depending on the prenatal vs postnatal environment. Over the past three decades, accumulating evidence supports the hypothesis of Developmental Origin of Health and Disease (DOHaD) by the programming of the fetal phenotype without altering the genotype *per se*. These heritable modifications in gene expression occur through DNA methylation, histone modification and noncoding RNA-associated gene activation or silencing, and all are defined as epigenetic modifications. In the present review, we will summarize the evidence supporting epigenetic regulation as a significant component in DOHaD.

Key Words

- maternal stress
- lincRNA
- DNA methylation
- IUGR
- FGR

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Introduction

Epidemiological studies in humans and experimental studies in laboratory animals have demonstrated a relation between intrauterine fetal stressors and the development of diseases in the adult offspring. These fetal stressors include maternal food excess and deprivation, hypoxia, drug addiction, alcohol and emotional stress (Limesand *et al.* 2006, Jansson & Powell 2007, Gluckman *et al.* 2008, Hanson & Gluckman 2008, Borengasser *et al.* 2013, Goyal & Longo 2013, Jang *et al.* 2015, Agarwal *et al.* 2018, Ducsay *et al.* 2018, Lecoutre *et al.* 2018). A factor that has received increasing attention, in this regard, is the idea of 'developmental programming' during fetal life, as a consequence of maternal stress or placental complications (Barker 2002, 2008, Barker *et al.* 2007, Goyal *et al.* 2009, Boehmer *et al.* 2017). One explanation behind developmental programming is that mothers prepare their babies to survive in the outside world. Based on the prenatal environment, fetal growth is modified

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to cope with the expected postnatal environment. For instance, maternal undernutrition will prepare the fetus for nutritional scarcity postnatally. This 'developmental programming' equips the organism with the capacity to store extra nutrition, if available, which may lead to obesity if dietary conditions are plentiful. Similarly, future development of diabetes mellitus is another mechanism to cope up with nutritional scarcity or overabundance because adaptations in glucose homeostasis can also be programmed *in utero*. Other stressors such as maternal obesity and overfeeding lead to adaptations in metabolism and adiposity in the offspring.

Several studies in humans and experimental animals have demonstrated that early growth restriction due to antenatal maternal stress or placental insufficiency can result in the development of hypertension, stroke, depression, schizophrenia, obesity, diabetes and other conditions (Fig. 1) (Hoek *et al.* 1996, Susser *et al.* 1998, Vickers *et al.* 2000, Vehaskari *et al.* 2001, Brawley *et al.* 2003, Goyal *et al.* 2010, Goyal & Longo 2013, Longo *et al.* 2014). The placenta forms the connection between mother and fetus and is responsible for the transfer of nutrients and oxygen. The placenta is also an important endocrine organ (Evain-Brion & Malassine 2003). Placental hormones play an essential role in fetal development and are a significant factor in programming. For instance, maternal stress has been shown to reduce maternal progesterone concentrations and methylate placental heme oxygenase 1 promoter (Solano *et al.* 2015). Reduction in heme oxygenase 1 expression slows fetal growth through immune-related actions, illustrating endocrine-related epigenetic changes due to maternal stress. Thus, changes in placental hormone initiate mechanisms that initiate a cascade of events that cause fetal growth restriction and may result in developmental programming. Of note, placental pathologies (such as placental insufficiency, or abnormal placental growth and insertion) may lead to fetal stress and developmental programming without maternal stress.

The question arises, how can a stressor during antenatal life be linked to so many multifaceted disorders in the adult? It is possible that maternal stress programs the embryonic cell mass; these cells then migrate and lead to the formation of the various organs with abnormal cell metabolism. Altered 'programming' of these embryonic cells, may manifest as different clinical disorders through the life course of the individual. Furthermore, the precise

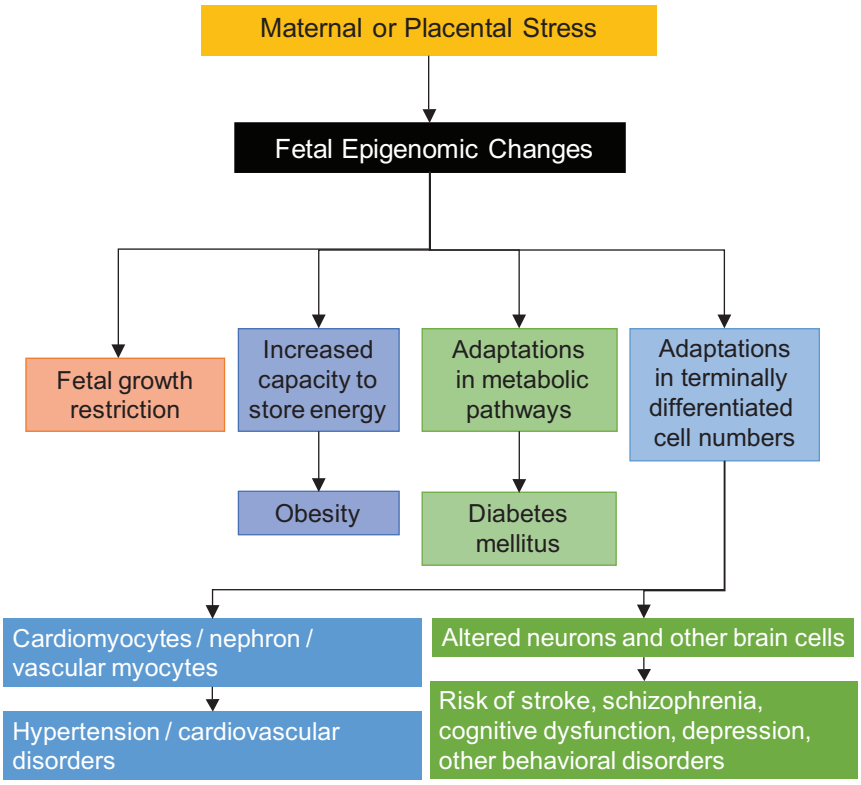

Figure 1
Maternal and placental stress-mediated changes in fetal epigenome responsible for developmental programming and differential adaptation responses in the fetus which can ultimately lead to phenotypic changes and disorders in adult offspring.

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timing and severity of the antenatal stress may make individuals susceptible to different disorders observed in the epidemiological studies by Barker and other groups. Importantly, the evidence demonstrates that developmental programming occurs from day 0 following fertilization. A study (Kwong *et al.* 2000) demonstrated that rat dams fed low-protein diet only during the preimplantation period following fertilization of the ovum (0–4.25 days after mating), induced programming of altered birth weight and organ/body-weight ratios, accelerated postnatal growth rate and development of hypertension in both female or male offspring. Also, preimplantation embryos collected from dams after 0–4.25 days of maternal low-protein diet (MLPD) displayed significantly reduced cell numbers in the inner cell mass (ICM) of the early blastocyst. This reduction in cell numbers was induced by a slower rate of cellular proliferation, rather than by increased apoptosis (Kwong *et al.* 2000). Thus, evidence indicates that maternal malnutrition during the peri-implantation period can lead to long-term programming of postnatal growth and physiologic function.

Mechanism of DOHaD

Given these findings, it is crucial to elucidate the mechanisms of *in utero* programming of adult diseases. As we know, germ cells store information that has been handed down from their ancestors and that will be transmitted to their descendants. For the most part, this 'memory' is encoded in the sequence of nucleic acids that comprise the DNA of the genome, the genotype, which provides stability and accurate heritability from generation to generation. Much traditional research has explored the effects of the environment on germline mutations of the coding and promoter regions of genes. Alternatively, cells can inherit and transmit information that is not part of the genomic sequence. These 'epigenetic' (beyond conventional genetic) modifications involve the heritable transmission of the regulatory components of gene expression patterns that are passed to the daughter cells during cell divisions. The three important mechanisms known to regulate gene transcription epigenetically are DNA methylation, histone modifications and regulation by noncoding RNA (Fig. 2).

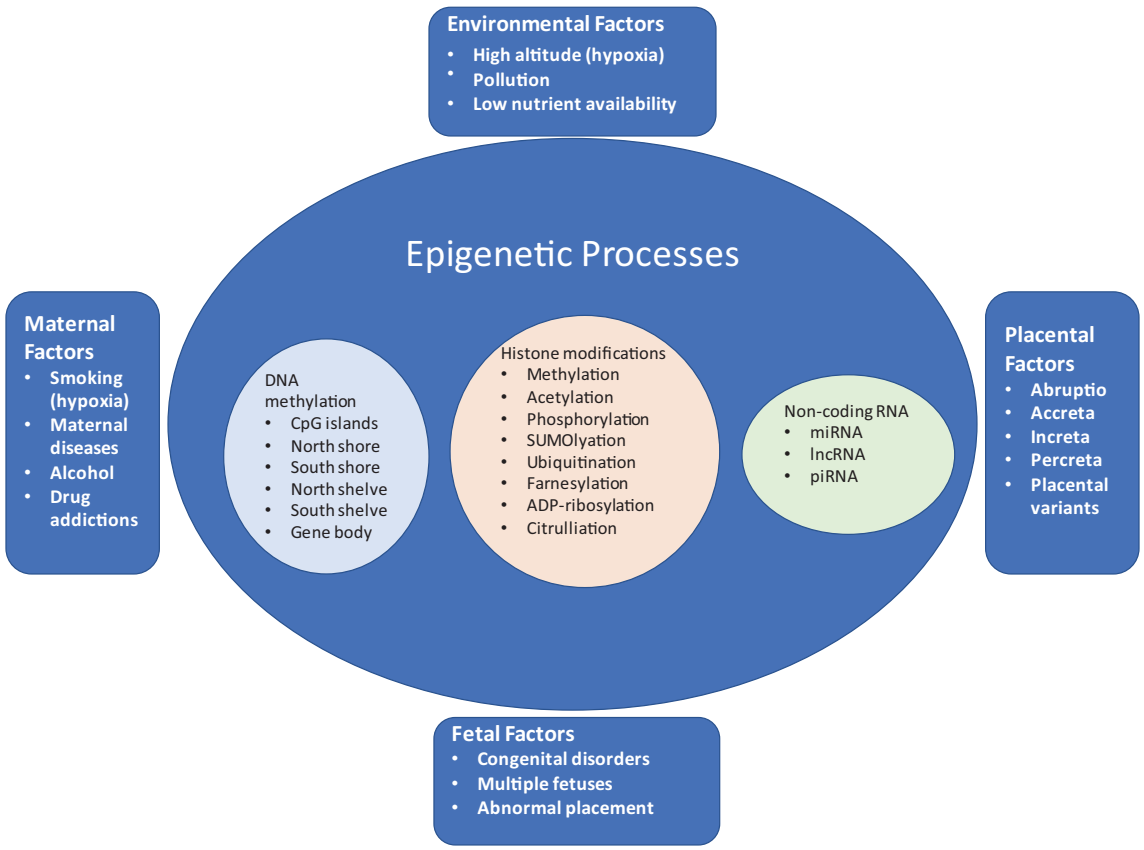

Figure 2
Various environmental, maternal, placental and fetal factors which can alter different epigenetic processes in the fetus.

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DNA methylation and DOHaD

Of all the epigenetic mechanisms, the most extensively studied is the control of gene expression by the alteration in the methylation of cytosine nucleotides in the promoter region of genes. Any cytosine in the DNA can be methylated; however, the chief regulatory cytosines are the ones which are adjacent to the guanosine. As the phosphodiester bonds join the nucleotides, these cytosine and guanosine are commonly referred to as CpG dinucleotides. Accumulating evidence during the past couple of decades indicate that DNA methylation and demethylation are key regulators of gene expression, as a consequence of environment–gene interactions. Methylation of cytosine changes DNAs hydrophobic property and inhibits its interaction with other transcription activators or suppressors. Hypomethylation of the cytosine bases in CpG islands located in a DNA promoter sequence allows increased (activates) gene expression, and hypermethylation results in decreased (silences) gene expression. Of note, DNA methylation in the gene body is associated with increased transcription (Yang *et al.* 2014). This can occur directly by inhibiting the binding of specific transcription activators or repressor and/or indirectly by recruiting methyl-CpG-binding proteins with repressive chromatin remodeling activities (Fig. 3).

Hypertension (Bogdarina *et al.* 2007, Goyal *et al.* 2009, 2013), type 2 diabetes mellitus (Williams *et al.* 2008), cancer (Schmutte & Jones 1998), neurodegenerative disorders (Obeid *et al.* 2009) and other clinical conditions are related

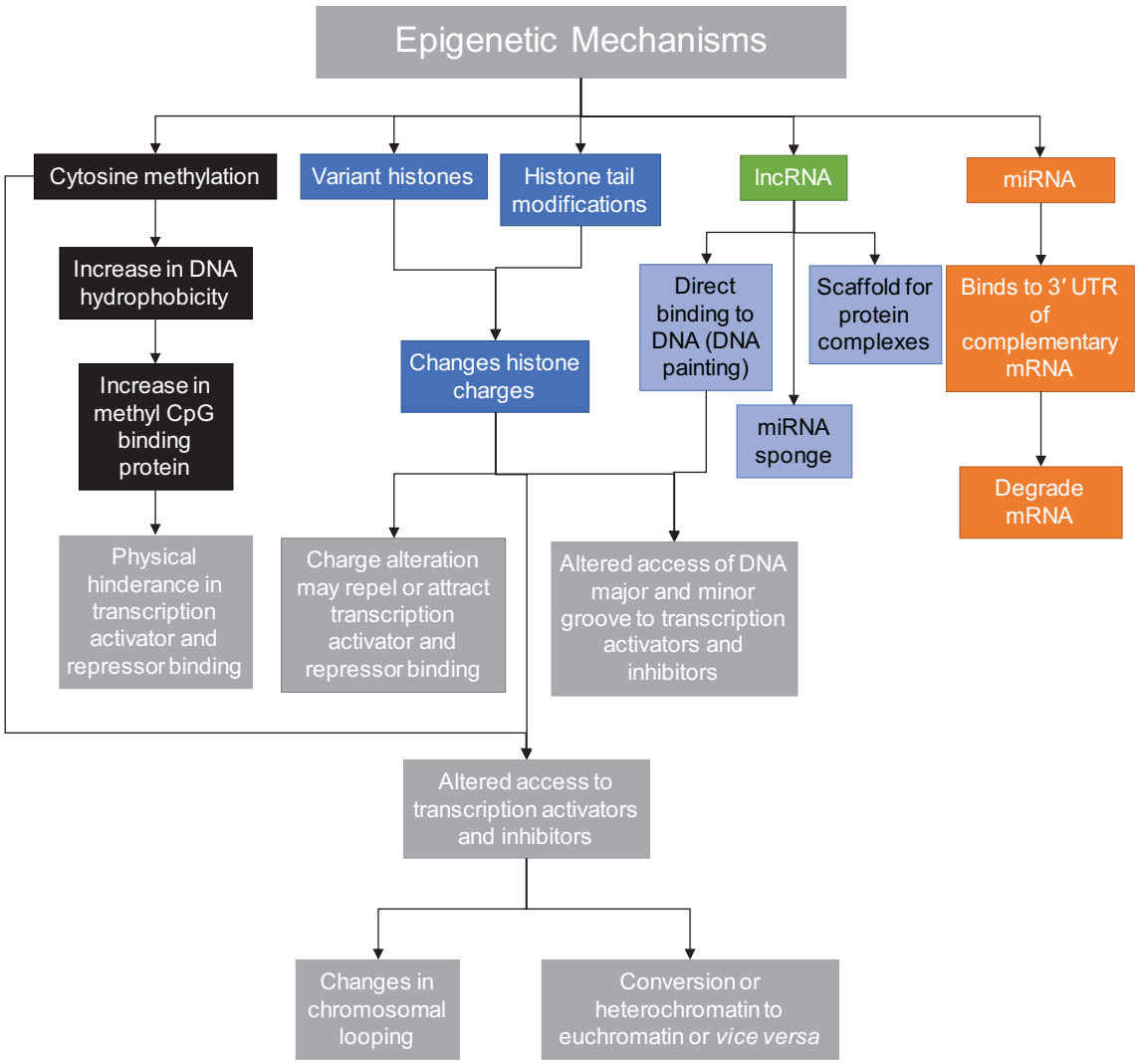

Figure 3
Different epigenetic mechanisms and underlying downstream processes which regulate gene expression.

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to altered DNA methylation. In the antenatal protein-deprived mouse fetus, we observed hypomethylation (activation) of the promoter region of the angiotensin-I-converting enzyme (ACE) and increased ACE mRNA expression in the lung and brain (Goyal *et al.* 2010, 2011*a*). In hypertension ACE is an important enzyme target for pharmacological inhibitors (enalapril, lisinopril). Therefore, offspring from the antenatal protein-deprived mice also developed hypertension, hyperglycemia and obesity in adulthood, and the hypertension is associated with hypomethylation of the ACE gene promoter (Goyal *et al.* 2009, Goyal & Longo 2013). Collectively, several experimental studies have established that environmental factors can lead to changes in DNA methylation, with altered gene expression. This is a mechanism in the pathogenesis of many disorders.

Enzymes critically associated with changes in DNA methylation are DNA methyltransferases (DNMT) and ten-eleven translocation methylcytosine dioxygenases (TET). DNA methyltransferases are a broad class of enzymes found in all groups of prokaryotic and eukaryotic organisms. There are four independently encoded mammalian DNMTs. DNMT1s are the classical maintenance methyltransferase, responsible for maintenance of methylation pattern during DNA replication (Bestor 2000). DNMT2 are now known to catalyze mainly RNA (Schaefer & Lyko 2009, Jeltsch *et al.* 2017), whereas two other enzyme families, DNMT3a and DNMT3b (Leonhardt & Bestor 1993, Poh *et al.* 2016), participate in the establishment of *de novo* methylation patterns during early embryonic development (Pradhan & Esteve 2003). Importantly, DNMT1 knockdown is embryonic lethal in both heterozygous and homozygous mice (Li *et al.* 1992). However, both heterozygous Dnmt3a+/− and Dnmt3b+/− mice were apparently healthy and fertile. Homozygous Dnmt3a−/− mice appeared normal at birth but their postnatal growth is stunted, and these mice died at about 4 weeks of age (Okano *et al.* 1999). In contrast, homozygous Dnmt3b−/− mice are not viable and die around embryonic day 9.5 (Okano *et al.* 1999). Hypoxic stress is known to regulate DNMT expression (Watson *et al.* 2014, Hu *et al.* 2017); however, how much of hypoxia-mediated developmental programming is controlled by DNMTs is currently not known.

DNA methylation is reversible, and DNA can be demethylated by TET enzymes (Tahiliani *et al.* 2009, Guo *et al.* 2011, Mohr *et al.* 2011). These enzymes play an essential role in embryonic stem cell maintenance and ICM specification (Ito *et al.* 2010). There are three known TET genes (*TET1*, *TET2* and *TET3*). Genetic mutations of TET enzymes have demonstrated that *TET1* and *TET2* homozygous knockout mice are viable; however, TET1-knockout mice have a small body size (Dawlaty *et al.* 2011, 2013). Double knockout of both TET1 and TET2 genes in mice, increased their DNA methylation status and abnormal methylation was observed at various imprinted loci. Moreover, a small number of these double TET1 and 2-knockout mice demonstrated mid-gestation abnormalities with perinatal lethality (Dawlaty *et al.* 2013). TET3 gene knockout in mice has shown that it localizes in both the maternal and paternal pronucleus and plays some role in active demethylation. However, the TET3 gene knockout had no significant effect on fertilization or other aspects of embryonic and fetal development, but it resulted in neonatal lethality. Although individual knockdown of TETs did not produce much impact on *in utero* development, the triple knockout of all the three TETs led to impaired embryonic stem cell differentiation and complete arrest of embryonic development (Dawlaty *et al.* 2014). Thus, these studies demonstrate the redundant nature of these enzymes and their mechanistic involvement in vital developmental processes. The effect of hypoxia on TET and its impact during development is not well studied, but the function of TET enzymes is significantly reduced under hypoxic conditions and are linked to various malignancies (Thienpont *et al.* 2016). Thus, it is entirely reasonable to speculate that intrauterine hypoxia may dysregulate TET activities and may be associated with developmental abnormalities. However, further investigation is required to know how fetal stressors affect changes in DNA methylation of particular loci.

One may argue, however, why is DNA methylation so important for developmental programming? Of great importance, after fertilization, and through the blastocyst stage, male DNA undergoes complete demethylation (Abdalla *et al.* 2009). Subsequently, the genome undergoes *de novo* remethylation process to establish the basic bimodal methylation pattern observed at the time of implantation. This methylation organizes a fixed expression pattern in the genome, by which tissue-specific genes are either activated or repressed (based on the tissue expression pattern), while the genes required in vital functions are active in all types of the cells. Deficiency in amino acids may interfere with genomic demethylation and *de novo* methylation. In animal models, genome-wide demethylation is observed during early murine and bovine embryonic development, reaching a nadir at the blastocyst stage (Monk *et al.* 1987, Kafri *et al.* 1992).

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During this stage, the gametic methylation marks are erased (demethylation). Later, these are replaced with embryonic marks that are important for cellular differentiation and organismal development (Reik *et al.* 2001, Meehan 2003). Recent studies indicate that mechanisms for paternal DNA demethylation differ from those responsible for maternal genome demethylation. Moreover, the paternal genome is subjected to replication-independent, genome-wide active demethylation during the first few hours after fertilization (Mayer *et al.* 2000, Oswald *et al.* 2000). In contrast, the maternal genome maintains its methylation pattern until the beginning mitotic division stage, when both maternal and paternal genome undergo replication-dependent, passive demethylation due to the absence of DNMT1 (methylation maintenance enzyme). Furthermore, the maternal environment may modify the methylation at this stage, in an attempt to regulate fetal development in accordance with available nutrient and other conditions. The methylation marks may also be reprogrammed, so that the offspring may be prepared to face adverse conditions long after birth. As may be appreciated, many aspects of embryonic methylation and its regulation are unknown (Wilkins 2005, 2006). For instance, what are the effects of maternal stress on these processes and the resulting long-term sequelae?

DNA methylation has emerged as a primary epigenetic mechanism involved in DOHaD. Studies demonstrate that maternal stress leads to increased stress hormones such as a glucocorticoid and catecholamines (Jensen Pena *et al.* 2012). Our studies demonstrate that maternal protein deprivation or hypoxic stress can lead to significant increase in epinephrine and norepinephrine and can lead to permanent changes in cerebral blood flow and arterial contractility with associated obesity, hypertension, blood glucose dysregulation, fetal growth restriction and changes in DNA methylation (Goyal *et al.* 2009, 2010, 2011*a*,*b*, 2013, 2014, Ducsay *et al.* 2018). Moreover, reports demonstrate that increased cortisol and catecholamine secretion is also associated with gene expression changes in their receptors which are mediated by changes in DNA methylation (Jensen Pena *et al.* 2012). Furthermore, studies have demonstrated that paternal cold exposure can lead to differential DNA methylation of sperm and lead to protection from diet-induced obesity in the offspring (Sun *et al.* 2018). Similarly, maternal obesity has also been shown to modify DNA methylation and lead to increased adiposity in mice offspring (Borengasser *et al.* 2013). Of note, a recent study demonstrated that violence during pregnancy in human leads to changes in five CpG sites involved in circulatory system process (Serpeloni *et al.* 2017). Another study in human placenta demonstrated three important clusters of DNA methylation regions related to metabolic pathways are altered in response to increased maternal stress (Brunst *et al.* 2018). Thus, it appears that maternal stress irrespective of type (caloric malnutrition, an imbalanced diet with low protein, hypothermia, hyperthermia, maternal overfeeding, as well as psychological stressors due to domestic violence) can lead to changes in DNA methylation and fetal programming to make the offspring more resilient to future stress. However, the nuances of changes in DNA methylation and transcriptional control of gene expression during DOHaD are not completely understood.

Histone modifications and DOHaD

DNA with accompanying histones is packaged in nucleosomes, the core of which contains an octamer of histone proteins. Five basic forms of histones (H1, H2A, H2B, H3 and H4, as well as minor variants), are encircled by 146 base pairs of DNA (Smith *et al.* 1970, Luger *et al.* 1997). Histone modifications and DNA methylation confer a considerable increase in the information capacity of each nucleosome, allowing specific functions such as DNA repair and gene activation (Sarma & Reinberg 2005). Enzymes associated with histone modifications are histone acetyltransferases (HAT), histone methyltransferases (HMT), histone deacetylases (HDAC), histone demethylases (HDM) and others (Klose *et al.* 2006, Dodd *et al.* 2007). These enzymes modify histones, which alter gene expression to affect the phenotype by regulating promoter activity, chromatin structure, dosage compensation and epigenetic memory, without changes in the nucleic acid code *per se* (Wolffe & Matzke 1999, Martin & Zhang 2005). These molecular alterations may be responsible for several disorders in the offspring during adult life.

Strahl and Allis proposed the histone code hypothesis, stating '*… distinct histone modifications, on one or more tails, act sequentially or in combination to form a "histone code" that is read by other proteins to bring about distinct downstream events*' (Strahl & Allis 2000). Histone modifications change their interactions with DNA and shuttle the genes occupancy between hetero- and euchromatin (Fig. 3). Gene expression is regulated by switching to a variant form of histone and by post-translational modifications on histone tails (Bao & Bedford 2016). It is well established that variant histones played an essential role in the evolution of complex life forms (Malik & Henikoff 2003, Banaszynski *et al.* 2010).

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Thus, it is not surprising that modification to histones plays an important role in developmental programming. Studies have demonstrated that maternal and paternal stress induce histone modifications that affect phenotypes related to DOHaD (Zheng *et al.* 2011, Kilcoyne *et al.* 2014). Histone methylation of testicular germ cells during fetal life programs the generation of Leydig cells at puberty, which is responsible for testosterone secretion in adult men (Kilcoyne *et al.* 2014). Similarly, a high-starch diet in rats has been demonstrated to increased histone acetylation of genes associated with carbohydrate metabolism (Inoue *et al.* 2011) and may predispose adiposity. The chromatin (DNA and protein skeleton) of mature mammalian spermatozoa differs markedly in composition and structure from somatic chromatin. DNA is not associated with histones and arranged in nucleosomes. Instead, spermatozoa DNA is condensed with protamine, a highly basic protein possessing an arginine-rich central domain (Wouters-Tyrou *et al.* 1998). Following fertilization, the spermatozoa DNA is decondensed and remodeled into the transcriptionally competent chromatin of the male pronucleus. The chromatin is dispersed by removal of protamine, and the naked paternal DNA is acted upon by demethylase enzyme and undergoes active demethylation along with rewinding of the male DNA with maternal acetylated histones (Adenot *et al.* 1997). In contrast, oocyte DNA does not undergo any histone exchange or active demethylation. Of great importance, maternal protein deprivation reduces fetal amino acid availability, and this inactivates the mTOR signaling pathway, which is known to have significant histone deacetylase activity (Nishioka *et al.* 2008). Importantly, following fertilization, there are dynamic epigenetic changes in both paternal and maternal alleles in the zygote which are highly susceptible to maternal stressors. Balanced nutrient with adequate vitamins has been demonstrated to lower the thioredoxin-interacting protein expression, which has been proposed as a preimplantation stress marker and lead to better development of blastocysts by changing histone methylation (Ikeda *et al.* 2018). Moreover, studies have demonstrated that perinatal stressors such as protein deprivation can also alter histone acetylation (Sun *et al.* 2015). Similarly, high-fat diet is also known to alter histone acetylation as well as methylation which may lead to changes in gene expression in adipose tissue, liver, skeletal muscle and other fetal tissues (Masuyama & Hiramatsu 2012, Suter *et al.* 2014, Bansal & Simmons 2018). In contrast, a recent study showed that providing better environmental conditions during gestation reduced risk of Alzheimer's disease in the offspring by histone hyperacetylation (Liu *et al.* 2019). Additionally, studies demonstrate that extracellular histones secreted in the uterus may play a role in blastocyst implantation and increased nutrient supply to the growing embryo (Van Winkle & Ryznar 2018). Furthermore, there is a cooperative mechanism between DNA methylation and histone acetylation, which leads to switching between hetero- and euchromatin (Mochizuki *et al.* 2017). It has been demonstrated that in FGR fetuses, the development of diabetes mellitus involves a reduction in pancreatic homeobox domain 1 (pdx1), which is a result of cooperative regulation of gene expression by changes in histone acetylation, demethylation and DNA methylation (Park *et al.* 2008). Nonetheless, this is a much less studied mechanism as compared to DNA methylation and requires further investigation.

miRNA and DOHaD

Apart from DNA methylation and histone modifications, miRNAs have emerged as essential players in post-transcriptional gene regulation. These are subtypes of small, noncoding RNA, 21–25 nucleotides in length. miRNAs are capable of base pairing with mRNA, and fine-tuning gene expression during development and differentiation, by suppressing their expression in a sequence-specific manner. Following the discovery of first miRNA 'lin4' in 1993, as a small temporal RNA (Lee *et al.* 1993), there has been enormous growth in this family, and identification of their targets. Although miRNAs are similar to siRNA in their generation pathway and molecular characteristics, unlike siRNA, miRNA does not degrade the target mRNA. Instead, they target the 3′ untranslated regions (UTR) of mRNAs with which they share partial sequence complementarily, thereby silencing post-transcriptional gene translation. In this way, the biological system increases or decreases miRNA production, which up or downregulate gene expression according to the biological need, thus producing desired morphologic and physiological response. miRNA can cross the placental barrier (Chang *et al.* 2017) and their regulation may occur in maternal, placental or fetal tissues to regulate the growth and development of the maternal–placental–fetal unit. Furthermore, placental miRNA (miR-141, miR-149, miR-229-5p and miR-135b) are secreted in maternal circulation and their concentrations decline after parturition (Chim *et al.* 2008). This indicates that placental-derived miRNAs in addition to regulating gene expression in the placenta are

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capable of regulating maternal conditions with obscure etiology, such as preeclampsia or related hypertensive disorders. Studies reveal differential expression of miRNA (miR-210 and miR-182) in placenta from patients with preeclampsia and with small for gestational age newborn infants (Pineles *et al.* 2007). A study also demonstrated that a very diverse and dynamic set of miRNA is expressed in the embryonic chick at 11 days of incubation (Hicks *et al.* 2008). Another valuable study in silkworm (*Bombyx mori*) demonstrated several stage-by-stage changes in expression of miRNA with specific time points during embryogenesis. For example, upregulation of miR-1 and bantam in late embryos, increased miR-34b expression was associated with stage transition between instar and molt larval stages, miR-274 expression was associated with silk gland growth and spinning activity and so forth. Studies from our laboratory demonstrate miR-27 involvement in the regulation of the renin-angiotensin pathway in lungs in response to maternal stressors such as hypoxia and protein deprivation (Goyal *et al.* 2011*a*, 2015). Moreover, with maternal hypoxia, we observed downregulation of miR-199b in placenta, which increases renin translation and downregulates miR-27a and miR-429. These miRNAs increase ACE1 and ACE2 protein concentrations in lungs (Goyal *et al.* 2010, 2011*b*). Studies from several other laboratories have also demonstrated that miRNAs are associated with developmental programming of various organs (Zucchi *et al.* 2013, Casas-Agustench *et al.* 2015). The organs and tissues investigated include heart (Yan & Jiao 2016, Lock *et al.* 2017), brain (Petri *et al.* 2014) and several endocrine glands (pancreas, ovary, testes, hypothalamus and pituitary) (Kredo-Russo *et al.* 2012, Voglova *et al.* 2016). Of note, exposure to environmental toxins during human pregnancy affects miRNA expression in cord blood, which lead to increased disease susceptibility in offspring (Rager *et al.* 2014, Gillet *et al.* 2016). In the future, it will be important to study how maternal and placental stressors regulate particular miRNA expression to produce phenotypic alterations in the fetus.

Long noncoding RNA and DOHaD

Another important group of regulatory RNA is the lncRNA. These RNA molecules, unlike miRNA, can fold into a complex secondary and tertiary structure and serve as sponges for miRNA or provide a scaffold for proteins to form regulatory complexes (Fig. 3) (Rinn & Chang 2012, Kumar & Goyal 2017). Recent studies have demonstrated that lncRNAs regulate cellular differentiation and organismal development. For instance, lincRNA-RoR reprograms human-induced pluripotent stem cells (Loewer *et al.* 2010). The lincRNA ES1, ES2 and ES3 promote pluripotency and neuronal differentiation indicating a role in human brain development (Ng *et al.* 2012) and linc-MD1 regulates muscle differentiation by acting as competing endogenous RNA in mouse and human myoblasts (Cesana *et al.* 2011). Linc-MD1 'sponges' miR-133 and miR-135 to regulate the expression of transcription factors MAML1 and MEF2C that activate muscle-specific gene expression (Cesana *et al.* 2011). Additionally, lncRNAs have been implicated in cardiovascular development (Kurian *et al.* 2015), and stem cell-based studies have highlighted the involvement of lncRNA Braveheart (AK143260; Bvht) in cardiac development (Klattenhoff *et al.* 2013). Kcnq1 was also reported to be involved in heart development during embryogenesis (Korostowski *et al.* 2012). Additionally, lncRNA Fendrr a lateral-mesoderm-specific lncRNA has been shown to modify chromatin, and thereby control the developmental signaling in the heart of genetically engineered mice (Grote *et al.* 2013). This study showed that Fendrr is an essential regulator of heart and body wall development. Furthermore, lncRNAs have been shown to affect adipogenesis and β-cell formation (Sun *et al.* 2013, Arnes *et al.* 2016, Singer & Sussel 2018). Recent evidence indicates that lncRNAs are induced by hypoxia (Michalik *et al.* 2014), which provide new leads regarding their role in several physiological and pathological conditions where hypoxia is an associated factor. Growth arrest-specific transcript 5 (GAS5 lncRNA) is induced under conditions of nutrient deprivation (Kino *et al.* 2010). Thus, the current evidence supports important actions for lncRNA, which may only be in its infancy of scientific discovery but identifies new roles for noncoding genes to regulate the organism's development and function and potentially modify the developmental program in response fetal stressors. To decipher the lncRNA roles in DOHaD, further work is needed.

DOHaD and evidence from human studies

Evidence from human studies that contributed toward the formulation of DOHaD hypothesis came from observations following the 'Hunger Winter' that occurred during World War II. This human tragedy provides useful lessons on the effects of caloric restriction/malnutrition because during this seven-month famine, the caloric ration fell to less than 25% of the recommended

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intake for adults. Although to an extent, children, pregnant and lactating women, received extra rations, they too suffered severe dietary restriction (Roseboom *et al.* 2001). Upon reaching adulthood, those infants who experienced nutritional scarcity showed a higher incidence of cardiovascular disease, type II diabetes (Roseboom *et al.* 2001, Kyle & Pichard 2006) (Painter *et al.* 2005) and mood and personality disorders (Kim *et al.* 2015). Those fetuses exposed to maternal caloric restriction in mid-gestation had a much higher incidence of pulmonary disease, including bronchitis (Lopuhaa *et al.* 2000) and renal disease as evidenced by microalbuminuria (Painter *et al.* 2005). Females who were conceived during the famine also had a much higher prevalence of obesity as adults (Ravelli *et al.* 1999), and both males and females showed atherogenic lipid profiles (Roseboom *et al.* 2000). Concomitantly during WWII, the people of St. Petersburg and the surrounding area of Russia also were subjected to starvation due to the interdiction of food supplies by opposing forces. Although not as well documented as the Dutch experience, children born under these conditions were small for gestational age and developed health problems later in life (Neugebauer *et al.* 1999). Another example of the sequelae of antenatal food deprivation is that of the Biafran War in Nigeria (1967–1970) (Hult *et al.* 2010, Thurner *et al.* 2013). Again, records of these offspring are not as clear as those in Holland but reflect similar *in utero* transmission of metabolic diseases. Similarly, previous studies demonstrated that an increase in the incidence of diabetics in the population of the Pima Indians of Arizona was an evolutionary mechanism to survive chronic nutrient scarcity (Schulz & Chaudhari 2015). Furthermore, diabetic mothers with macrosomic babies can program obesity in the offspring (Yajnik 2014).

Contemporary epidemiologic data on the role of maternal nutrition in determining the long-term health of offspring derives from the studies of Barker and colleagues in the United Kingdom (Barker 1992, 2002, 2003, 2008). Professor David JP Barker formally proposed the modern concept of the DOHaD, in the late-1980s, where through detailed historical records he associated cardiovascular disease with reduced fetal growth (Barker *et al.* 1989). In a related analysis, impaired glucose tolerance was shown to be strongly associated with reduced growth in early life due to beta-cell dysfunction (Hales *et al.* 1991). These authors also demonstrated the high correlation of cerebrovascular accidents in the 1970s, to increased neonatal mortality six decades earlier during the years 1911–1914 (Barker & Osmond 1987). Besides, men born from 1911 to 1930, Barker and colleagues have shown an inverse correlation between the weights both at birth and at 1 year of age to coronary artery disease in adulthood (Barker *et al.* 1989, Barker 1993). A subsequent study disclosed a similar trend with birth weight among women, which illustrates both sexes are affected by developmental programming (Osmond *et al.* 1993).

Apart from the seminal studies on the Dutch Hunger Winter cohorts, there have been several human population studies which have reported that the nutritional state of individuals and other maternal stressors may have phenotypic consequences or their children and grandchildren (Lumley *et al.* 1985, Lumley & Bakoula 1993, Kaati *et al.* 2002). An example of maternal nutrition-induced changes in progeny phenotype and underlying DNA methylation status is evident in patients with hyper-homocysteinemia (Ingrosso *et al.* 2003). This disorder is characterized by increased levels of cellular adenosylhomocysteine, a potent inhibitor of S-adenosylmethionine-dependent methyltransferases, and possibility altered DNA methylation. In these offspring with increased homocysteine concentrations, folate supplementation restored global methylation levels, as well as appropriate methylation of imprinted IGF2-H19 locus (Ingrosso *et al.* 2003). Accumulated evidence underscores the importance of folic acid, an important component of DNA methylation reaction, as a vital dietary factor in fetal development, and the manner in which it modulates disease risks later in life (Torrens *et al.* 2006). However, further investigations are needed to determine (as in the case of hyper-homocysteinemia) if altered DNA methylation plays a causative role in these phenotypic effects (McKay *et al.* 2004).

Nonetheless, an optimal uterine environment is central to the establishment of embryonic epigenetic patterns and fetal development (Vickaryous & Whitelaw 2005). Because embryo culture and manipulation are used in the modern day assisted reproductive technologies (ARTs), the obvious concern is regarding the extent to which ART or related procedures affect DNA methylation patterns and other epigenetic modifications that lead to a higher risk of developing adult-onset diseases (Khosla *et al.* 2001, Vickaryous & Whitelaw 2005, Feil 2006). An issue of great importance is the extent to which the chemical composition of culture medium, the duration of culture or other factors, play a role in affecting changes in DNA methylation or histone modifications which may play an essential role in DOHaD (Doherty *et al.* 2000, Khosla *et al.* 2001, Young *et al.* 2001, Mann *et al.* 2004).

An additional consideration is the role of environmental toxins in producing alterations in the nucleosome with

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epigenetic consequences. A notable example from the mid-twentieth century is the administration of the estrogen-receptor agonist diethylstilbestrol (DES) to women to reduce the risk of spontaneous abortion. Subsequent studies demonstrated that DES was associated with increased incidence of vaginal clear cell carcinoma (Swan 2000), and altered limb development in the first generation and deafness in the second generation (Stoll *et al.* 2003). Not only environmental compounds but drugs may also alter the expression of specific genes, as well as the stress-related chaperone heat shock protein (HSP)-90, which plays a role in histone modifications (Rutherford & Lindquist 1998, Feil 2006).

In humans, many factors, genetic and epigenetic, can influence placental/fetal growth, development and long-term sequelae. Several hypotheses have been proposed to account for these phenomena. The initial thought was the environmental toxin/stressors lead to changes in genetic sequences (mutations), which may be the factor in the development of chronic disorders. Later on, single nucleotide polymorphism was a major area of investigation to understand the risk of these chronic disorders in adult life. However, the accumulating evidence indicates that epigenomic changes may be the primary factor in these disorders (Holness & Sugden 2006).

Summary

Epigenetic modifications play an important role in normal cellular function, as well as the development and differentiation of various cell types (Monk *et al.* 1987, Reik *et al.* 2001, Drake & Walker 2004, Rahnama *et al.* 2006). The epigenetic state can be disrupted by maternal environmental influences such as protein deprivation, caloric excess, hypoxia and so forth, which alter DNA methylation and modify histones. Also, a wide variety of environmental toxins, including low-dose radiation and psychological stress, have been demonstrated to be important in epigenetic mechanisms (Dolinoy 2007, Feinberg 2007, Jirtle & Skinner 2007). Increasingly, epigenetic changes are being recognized to be of importance in aging and the development of cancer and other diseases (Gopalakrishnan *et al.* 2008, Goyal *et al.* 2013, 2015, Goyal & Longo 2013). Despite the general understanding that DNA and/or histone modifications constitute a major mechanism in the pathogenesis of epigenesis, little is known of the molecular mechanisms whereby these chemical reactions/changes are regulated and/or how they are transmitted between generations (Longo & Goyal 2014, Longo *et al.* 2014, Ducsay *et al.* 2018). Nonetheless, the accumulating evidence suggests that the epigenetic basis of developmental origins of adult health and diseases is the primary factor in metabolic syndrome (hypertension, obesity and diabetes mellitus). A future challenge is to develop strategies to negate the long-term consequences of these molecular alterations.

Declaration of interest

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