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Perinatal Malnutrition and Epigenetic Regulation of Long-term Metabolism in the Liver and Adipose Tissue

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Abstract

Maternal malnutrition in perinatal life can have long-lasting adverse effects on glucose and lipid homeostasis in the offspring, culminating in dyslipidemia, insulin resistance, and obesity. Understanding the molecular mechanisms underlying how these nutritional deficits during perinatal life lead to permanent changes in hepatic and adipose function will provide efficacious therapeutic strategies to mitigate these metabolic defects short and long term. This chapter addresses how epigenetic mechanisms mediate alterations in hepatic and adipose gene expression identified from clinical studies and different experimental models of maternal malnutrition. These include DNA methylation, posttranslational histone modifications, and microRNAs.

Keywords

DOHaD • Dyslipidemia • Maternal low-protein diet • Liver • Adipose • Obesity • Plasticity • Sexual dimorphism • Posttranslational histone modifications • DNA methylation • MicroRNAs

List of Abbreviations

11β-HSD1	11β-hydroxysteroid dehydrogenase type 1
ABCA1	ATP-binding cassette transporter 1
ABCG5/8	ATP-binding cassette transporter 5/8

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ACCα	Acetyl-CoA carboxylase-α
ADP	Adenine diphosphate
APOE	Apolipoprotein E
CpG	Cysteine-phosphate-guanine
CVD	Cardiovascular disease
Cyp7a1	Cytochrome P450 7a1
DOHaD	Developmental origins of health and disease
ER stress	Endoplasmic reticulum stress
FBPase	Fructose bisphosphatase
G6Pase	Glucose-6 phosphatase
GDF3	Growth differentiation factor-3
HDL	High-density lipoprotein
HMG-COA	3-hydroxy-3-methylglutaryl-coenzyme A
HNF4α	Hepatocyte nuclear factor 4α
IGF-1	Insulin growth factor 1
IGF-2R	Insulin growth factor 2 receptor
IUGR	Intrauterine growth restriction
JMJD	Jmj-domain-containing histone demethylation protein
LDL	Low-density lipoproteins
LP	Low protein
LXR	Liver X receptor
LXRE	Liver X receptor element
miRs	MicroRNAs
MPR	Maternal protein restriction
PCK1	Phosphoenolpyruvate carboxykinase 1 (soluble)
PEPCK	Phosphoenolpyruvate carboxykinase
PND	Postnatal day
SCD-1	Stearoyl-CoA desaturase
SMAD4	SMAD family member 4
WAT	White adipose tissue

Contents

The Role of the Liver and Adipose in the Development of Dysmetabolism and Long-Term CVD

Collectively, the liver and adipose are critical for proper lipid and glucose metabolism in mammals. Impaired development and functioning of either of these tissues result in dyslipidemia leading to obesity and insulin resistance, culminating in the metabolic syndrome (Mathieu et al. 2006; Wilson et al. 1998). Specifically, the liver regulates cholesterol, glucose, and fatty acid homeostasis. With respect to cholesterol, the liver plays a role in cholesterol synthesis (i.e., HMG-CoA), metabolism (i.e., CYP7A1, APOE, LDL receptor), and/or transport (i.e., ABCA1, ABCG5/8) (Repa and Mangelsdorf 1999). The liver also plays an essential role in regulating glucose via the breakdown of glycogen (i.e., glycogen phosphorylase) versus the de novo production of glucose from noncarbohydrates (i.e., PEPCK, G6Pase, and FBPase) (Postic et al. 2004). Finally, the hepatic fatty acid biosynthesis pathway facilitates the storage of energy surplus as cytosolic lipid droplets or circulating triglyceride-rich lipoproteins (Jensen-Urstad and Semenkovich 2012). These triglycerides can later be oxidized to provide energy during times of deficiency. However accumulation of excess intracellular triglycerides, as occurs during obesity (Bosello and Zamboni 2000; Riediger and Clara 2011), is characteristic of atherosclerosis and hepatic steatosis (Bansal et al. 2007; Donnelly et al. 2005; Nordestgaard et al. 2007). The three main sources of free fatty acids that contribute to increased hepatic triglycerides are dietary, circulating, and de novo synthesis (Jensen-Urstad and Semenkovich 2012). Increased de novo lipogenesis in the liver occurs via transcriptional activation of genes for enzymes including acetyl-CoA carboxylase-α (ACCα), fatty acid synthase (FAS), and stearoyl-CoA desaturase (SCD-1) (Katsurada et al. 1990a, b; Ntambi 1992).

Aside from the contributions of de novo hepatic lipogenesis toward augmented triglycerides, compromised adipose tissue function also plays a major role in the dysregulation of lipid homeostasis and insulin sensitivity (Abate 2012). Normally, excess triglycerides are deposited in adipose tissue as a natural barrier to lipid and glucose toxicity, ectopic fat deposition, and, ultimately, CVD (Abate 2012). This is accomplished, in part, through proper adipocyte differentiation from precursor cells to the mature adipocyte capable of loading triglycerides (Abate 2012). However, if the adipocyte undergoes "maturation arrest," this reduces its triglyceride storage capacity and leads to greater fatty acid spillover in the plasma increasing substrate availability for triglyceride synthesis in other tissues, such as the liver (Perseghin 2011; van der Zijl et al. 2011). Ultimately this contributes to systemic abnormalities including dyslipidemia, insulin resistance, and various components of the metabolic syndrome (Aly and Kleiner 2011; Cali and Caprio 2009; Samuel et al. 2010; Volovelsky and Weiss 2011). Maturation arrest of adipose tissue can result from impaired adipocyte differentiation and/or proliferation (Moreno-Indias and Tinahones 2015). In addition to adipocyte maturation arrest, augmented adipose lipogenesis could also contribute to increased plasma fatty acid spillover (Moreno-Indias and Tinahones 2015).

To date, current therapeutic strategies are aimed at lifestyle modifications (i.e., healthy eating and physical activity) and/or pharmaceutical interventions to treat dyslipidemia and long-term adverse outcomes (i.e., CVD) (Bansal et al. 2007; Ishimoto et al. 2013; Kohli et al. 2010; Nordestgaard et al. 2007). While the risk of CVD can be reduced by pharmaceuticals, the long-term dependency on them can be dangerous for patients. For example, the risk of ischemic heart disease can be reduced by up to 60% by statins; however the existence of statin-induced rhabdomyolysis and hepatitis-associated liver failure can ensue (Law et al. 2003). Clearly additional studies are warranted for preventing dysmetabolism in the liver and adipose. One major preventative strategy is in elucidating the molecular (transcriptional and epigenetic) mechanisms involved in the developmental origins of health and disease (DOHaD) so that efficacious interventions can be targeted to prevent long-term dyslipidemia and its related comorbidities. For the focus of this chapter, we will review how maternal malnutrition (i.e., under- or overnutrition) during perinatal life alters epigenetic mechanisms in the liver and adipose leading to long-term metabolic disease.

Maternal Malnutrition and the Vulnerability of the Developing Liver and Adipose

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During the perinatal period, the liver continually grows, differentiates, and remodels becoming more hepatocyte-like by neonatal life (Gualdi et al. 1996). In rodents, the liver bud forms containing progenitor cells that differentiate into either hepatocytes or ductal cells; however liver mass triples by the end of gestation due to extensive proliferation (Cascio and Zaret 1991; Greengard et al. 1972). Neonatal life is then accompanied by high rates of replication, neogenesis, and apoptosis leading to great hepatocyte formation (Greengard et al. 1972). The course of liver development in humans is similar, but most of the liver has differentiated by birth (Kung et al. 2010). In human adipose tissue, growth and differentiation are evident from 5 to 29 weeks gestation, while in rodents this occurs from late gestation to 4 weeks in postnatal life (Greenwood and Hirsch 1974; Poissonnet et al. 1984). In both species, adipose tissue remains expandable throughout the course of life (Greenwood and Hirsch 1974; Spalding et al. 2008).

Maternal malnutrition, as result of a poor maternal diet or placental insufficiency, has direct negative effects on fetal growth and development (Crosby 1991). During perinatal life comprised by malnutrition, nutrients are repartitioned to critical organs such as the brain and heart, at the expense of other organs including the liver and adipose (Valsamakis et al. 2006). Given the extensive differentiation of both tissues during perinatal life, they are very vulnerable to alterations by environmental cues (i.e., poor maternal diet) during this developmental window. Epigenetic forces can help an organism adapt to nutritional changes short term by influencing gene expression in a tissue-specific manner, but this can have dire consequences long term.

Epigenetic Mechanisms: Overview

The development of many complex and noncommunicable diseases cannot be simply attributed only to genomic heritability (Manolio et al. 2009). Epigenetics has emerged as an important mechanism for influencing the expression patterns of genes in a promoter- and tissue-specific manner in response to insults during the developmental period. Epigenetic mechanisms alter the long-term expression of a gene by influencing the ability of the transcriptional machinery to interact with the chromatin environment. Additionally, they influence heritable phenotypic changes without alterations to the genetic sequence of an organism. Epigenetic changes can be both transient and persist for long periods of time (Barth and Imhof 2010; Talens et al. 2010). Mechanisms of epigenetic action include DNA methylation, posttranslational histone modifications, and microRNA-mediated repression.

One way the chromatin environment can be altered is due to direct DNA methylation, via the addition of a methyl group to CpG sites on the DNA by members of the DNA methyltransferase family. In addition, the presence of methionine, an essential amino acid, is also critical to DNA methylation as it is the ultimate methyl donor for many methylation reactions. Folate/folic acid is involved in methionine metabolism and is required for methylation reactions and DNA synthesis. Therefore it is not surprising that altered dietary intake of such nutrients during perinatal life may significantly affect DNA methylation profiles and, ultimately, gene expression (Kim et al. 1997; Waterland 2006; Wilson et al. 1984).

Posttranslational histone modifications, a second major epigenetic mechanism, involve altering the chromatin environment via methylation, acetylation, phosphorylation, ubiquitination, and/or ADP-ribosylation of histones (Jenuwein and Allis 2001). The combinatorial nature of these covalent modifications reveals a "histone code," which serves as an important adaptive regulatory mechanism that can also influence gene expression in a tissue- and gene-specific manner during development – especially in suboptimal conditions. In general euchromatin is associated with histones which are acetylated on specific residues (e.g., lysine 9 and lysine 14 of histone H3), whereas heterochromatin contains predominately hypoacetylated and/or methylated histones (Marmorstein and Trievel 2009). These histone modifications occur and can be sustained by a diverse range of histone-modifying enzymes including families of histone acetylases and methyltransferases, whose expression levels may also be influenced by external environmental insults during these developmental windows (Marmorstein and Trievel 2009).

Aside from posttranslational histone modifications, which may govern the long-term expression of genes, microRNAs (miRs) may also play a key role in the perinatal programming of liver and adipose leading to dysmetabolism. miRs are short, noncoding RNA molecules of 20–25 nucleotides in length that regulate gene expression via degradation of mRNA species and/or repression of translation (Khorram et al. 2010; Xu et al. 2010). Consequentially, miRs alter a variety of physiological processes including cell cycle regulation, differentiation, metabolism, and senescence (Xu et al. 2010). They silence gene expression by binding to the 3′-untranslated region (3′-UTR) with partial sequence homology to induce cleavage

or repression of productive translation (Brennecke et al. 2005). Since they can bind to 3′-UTR with partial sequence homology, it is well established that a single miRNA may have numerous targets in the genome (Brennecke et al. 2005). Conversely, given the nature of miRNA targeting, a single mRNA transcript can theoretically be targeted by several miRs (Brennecke et al. 2005).

Overall, it is imperative to realize that the different nutritional insults that lead to IUGR offspring can have both common and distinct adaptive responses initiated via epigenetic mechanisms. Moreover, IUGR offspring derived from various models of maternal malnutrition may be different or similar due to global, tissue, or site-directed epigenetic modifications.

The Effects of Perinatal Nutrition on DNA Methylation and Downstream Targets in the Liver and Adipose Long Term

With the use of various animal models of perinatal malnutrition, several links between diet, DNA methylation, and long-term dysmetabolism have been identified. In several models of maternal undernutrition leading to IUGR, increases in DNA methylation across CpG sites impair gene expression leading to aspects of the metabolic syndrome in adulthood. For example, Zhang et al. found that a high-fat diet during perinatal life led to alterations in methyl-CpG-binding protein-2, a protein involved in the repression of genes via DNA methylation (Zhang et al. 2009). Moreover, maternal protein restriction (MPR) in mouse pregnancy led to increased DNA methylation and silencing of the promoter of the *liver X receptor (Lxrα)*, a nuclear receptor involved in cholesterol homeostasis in the liver (van Straten et al. 2010). In pregnant sheep changing the constitution of their maternal diet from one with fiber and protein to a strict corn diet (low in amino acids) led to decreased DNA methylation surrounding the promoter of *insulin growth factor 2 receptor* (*Igf2r*) in fetal white adipose tissue (Lan et al. 2013). While less is known about the links between poor maternal nutrition, IUGR, and long-term DNA methylation in humans, one elegant study has demonstrated that adipose-derived stem cells (ADSCs) derived from low-birth-weight adult men exhibited increased DNA methylation surrounding the promoter of *CYCLIN T2* associated with impaired leptin secretion (Broholm et al. 2016). Another study by Einstein et al. (2011) also indicated that IUGR infants exhibit hypermethylation of the *HNF4α* gene, a nuclear receptor which when impaired leads to type II diabetes (Einstein et al. 2010, p. 201; Yamagata et al. 1996).

It should be noted that undernutrition does not always manifest to increased DNA methylation. Nijland et al. (2010) demonstrated that maternal nutrient restriction led to decreased methylation of CpG sites on the promoter of *PCK1* in baboon offspring coupled with an increase in *PCK1* transcription (Nijland et al. 2010). This is significant as overexpression of PEPCK, the product of *PCK1* translation, has been implicated in hyperglycemia and type II diabetes (Gomez-Valades et al. 2008; Valera et al. 1994). Moreover, elegant studies in the baboon fetus have demonstrated that 70% undernutrition during pregnancy culminates to augmented

hepatic gluconeogenesis associated with both increased Pck1 mRNA and decreases in the methylation of CpG dinucleotides of the *Pck1* promoter (Nijland et al. 2010).

Obesity or alterations in individual nutrients during pregnancy have also been demonstrated to impact offspring adipose function via DNA methylation. For example, maternal obesity in rats decreases DNA methylation attributed to increased WAT differentiation and lipogenic gene expression in the offspring (Borengasser et al. 2013). Moreover, high levels of methyl vitamins (e.g., folate, vitamins B12 and B6) in rodent pregnancy led to increases in DNA methylation of the *leptin* promoter contributing to obesity and insulin resistance in the offspring (Cho et al. 2015). Too much folic acid in murine pregnancy results in offspring more vulnerable to obesity and insulin resistance due to greater methylation of DNA and lower adiponectin expression in white adipose tissue (Huang et al. 2014).

Animal studies have also implicated the transgenerational effects of maternal malnutrition on DNA methylation. For example, the offspring of uterine-ligated dams exhibit increased DNA methylation in the promoter of hepatic *Igf-1* at birth which persists into the F2 generation even if F1 IUGR offspring are adequately nourished (Fu et al. 2015; Goodspeed et al. 2015). It is noteworthy that supplementation of the diet in the F1 IUGR offspring with folic acid, choline, betaine, vitamin B_{12}, and other essential nutrients prevented the methylation of the *Igf-1* promoter in the F2 generation along with symptoms of the metabolic syndrome (Goodspeed et al. 2015). However caution is warranted in interpreting these studies as undernutrition-induced alterations in DNA methylation vary between sexes and within different CpG islands of the same promoter (Fu et al. 2015).

The Effects of Perinatal Nutrition on Posttranslational Histone Modifications and Downstream Targets in the Liver Long Term

While for a long time it was generally thought that environmental (i.e., oxygen, nutrition) insults leading to posttranslational modifications to histones were transient, several studies now suggest they can persist for long periods of time, including from fetal to postnatal life. Using chromatin immunoprecipitation (ChIP) to follow changes in posttranslational histone modifications from pregnancy to adulthood, our laboratory has monitored MPR offspring. We have demonstrated that MPR-induced IUGR rat male offspring exhibited hypercholesterolemia concomitant with a decrease in postnatal Cyp7a1 expression, the critical enzyme involved in cholesterol catabolism, both short and long term (Sohi et al. 2011). More importantly, this was associated with decreased recruitment of RNA polymerase II, enhanced trimethylation of histone H3 [lysine 9], and suppressed acetylation of histone H3 [lysine 9, 14], all markers of chromatin silencing, within the LXRE region of the *Cyp7a1* promoter (Fig. 1) (Sohi et al. 2011). Remarkably, this was sustained from 3 weeks to 4 months in postnatal life. In contrast, MPR female offspring exhibited normal cholesterol, restored levels of Cyp7a1 expression, RNA polymerase II binding, and acetylation and trimethylation of histone H3 [lysine 9, 14] all within the same region of the *Cyp7a1* promoter (Sohi et al. 2011). The trigger of these

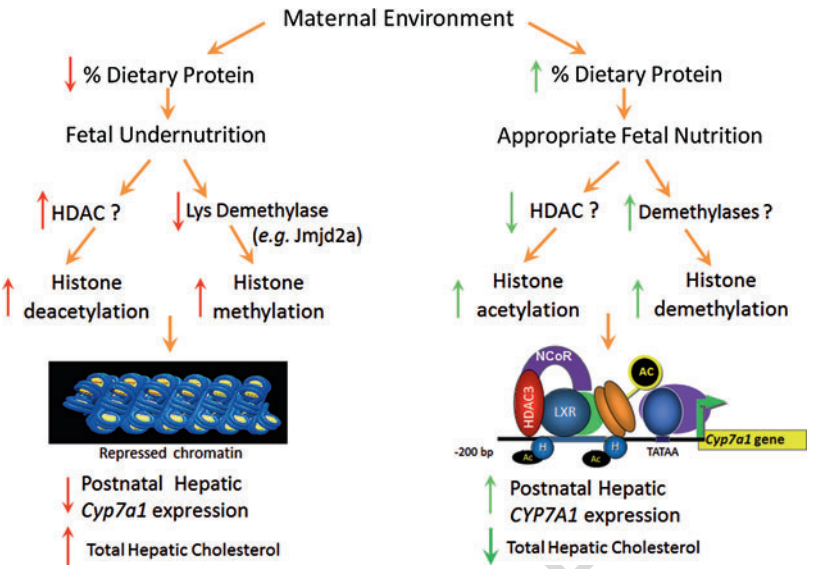


Fig. 1 Overview of how maternal protein restriction during perinatal life leads to long-term silencing of the *Cyp7a1* promoter and ultimately hypercholesterolemia via posttranslational histone modifications. A decrease in maternal proteins during fetal and neonatal life leads to diminished histone H3 [lysine 9,14] acetylation and increased histone H3 [lysine 9] trimethylation of the *Cyp7a1* rat promoter at 3 weeks and 4 months culminating in hypercholesterolemia. This is due, in part, to decreases in lysine 9 demethylase (e.g., Jmjd2a) expression in fetal life

histone modifications in fetal life is due, in part, to MPR-mediated decreases in Jmjd2a and Jmjd2c, demethylases involved in removing trimethyl groups of histone H3 [lysine 9]. While both male and female MPR offspring exhibited decreased Cyp7a1 expression at 3 weeks, female MPR offspring at 4 months are protected from the posttranslational histone modifications silencing the *Cyp7a1* promoter. MPR has also led to silencing of the promoter of *liver X receptor* (*Lxrα*) in the liver at 4 months due to decreased histone H3 acetylation [lysine 9,14] (Vo et al. 2013). The decrease in this repressive glucose sensor led to glucose intolerance in these offspring due to augmented expression of hepatic LXR-target gluconeogenic enzymes (e.g., G6Pase and 11β-HSD1) (Vo et al. 2013). In a model of maternal hypoxia leading to decreased maternal food intake and IUGR, we have also demonstrated that the 12-month IUGR male offspring display hypoglycemia concomitant with decreased hepatic G6Pase mRNA and protein (Osumek et al. 2014). Chromatin immunoprecipitation revealed that these IUGR offspring exhibit increased histone H3 trimethylation [lysine 9] of the *G6Pase* promoter (Fig. 2). Aside from undernutrition, this may originate, in part, to the direct effects of hypoxia to induce global hepatic histone H3 trimethylation [lysine 9] coupled with decreased G6Pase expression (Osumek et al. 2014). Given undernutrition in pregnancy also leads to tissue-specific increases in hypoxia, oxygen may be an underlying factor in mediating the long-term posttranslational histone modifications and physiological

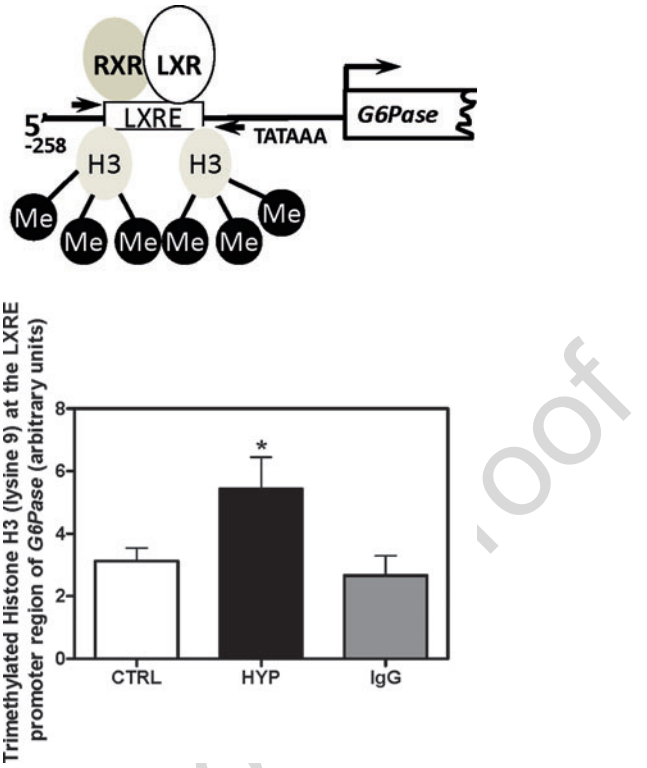
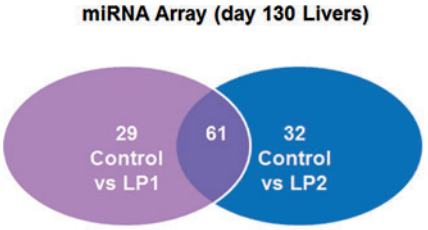


Fig. 2 Levels of trimethylated histone H3 (lysine 9) association with the LXRE-containing region of the *glucose-6-phosphatase* promoter are increased in 12-month males from hypoxemic pregnancies. Hepatic tissue from 12-month male control (CTRL, 20%) or hypoxic (HYP, 11.5%) offspring was subjected to cross-linking, lysis, and sonication. Solubilized chromatin was immunoprecipitated with a specific antibody for trimethylated histone H3 [lysine 9] or IgG control. After immunoprecipitation, DNA was analyzed for the promoter region containing the LXRE region of *G6Pase* utilizing real-time PCR. After analysis with an unpaired two-tailed t-test, it was determined the 12-month male offspring from hypoxemic dams had significantly increased histone H3 [lysine 9] trimethylation to the LXRE region of *G6Pase* relative to CTRL offspring (*$p < 0.05$) (Reprinted from Osumek et al. (2014), with permission from SAGE publications)

outcomes in these malnourished offspring (Elias et al. in revision; Peterside et al. 2003).

The Role of MicroRNAs in the Fetal Programming of Metabolic Disease

The concept that miRs could be programmed long term by the perinatal environment seemed very unlikely until the recent discoveries that their expression can be regulated via both transcriptional and epigenetic mechanisms. Elegant long-term



Control vs LP2 (day 130)

miRNA	fold change	pvalue	Target Gene
miR-140	6.79	<0.001	HDAC-4
miR-29a	5.11	<0.001	IGF-1
miR-29b	5.0	<0.001	IGF-1
miR-322	5.0	<0.01	FGF-2
miR-33	1.75	<0.05	IGF-1
miR-29c	1.48	<0.05	IGF-1

Fig. 3 Top six hepatic microRNAs exclusively upregulated in 4-month low-protein IUGR offspring with postnatal catch-up growth. Affymetrix™ microRNA microarray analysis of hepatic rat microRNAs derived from control, LP1 (low-protein diet all life), and LP2 (low-protein diet during pregnancy and weaning) dietary regimes in postnatal day 130 offspring. mirBase™ coupled with Partek® Genomics Suite™ software was used to identify the significant microRNAs altered versus control for each LP group, along with their postulated target genes (Unpublished data)

studies in rodents have revealed that maternal nutrient restriction can permanently alter the expression of aortic miRs in newborn and aging rat offspring (Khorram et al. 2010). Unpublished data from our laboratory using Affymetrix™ miRNA microarray has demonstrated the MPR IUGR offspring with postnatal catch-up growth exhibit exclusive alterations in hepatic miRs compared to control or MPR IUGR offspring without catch-up growth (Fig. 3). This suggests that the low-protein diet alone may not be the only trigger in the long-term regulation of miRs. In addition, catch-up growth in these IUGR offspring associated with augmented endoplasmic reticulum (ER) stress also likely contributes to the augmented expression of hepatic miRs observed (Nolan et al. 2014, p. 201; Sohi et al. 2013). MPR during pregnancy and lactation has been demonstrated to increase the expression of hepatic miR-29a, miR-29b, and miR-29c by 3 weeks and 4 months of age which silences the expression of *Igf-1* attributing to the decreased insulin sensitivity observed (Sohi et al. 2015). Remarkably, protein restriction during lactation alone had a more profound effect to augment the miR-29 family and suppress *Igf-1*, while restoration of maternal dietary proteins in MPR offspring at birth prevented miR-29-repression of *Igf-1* (Sohi et al. 2015). This demonstrates that MPR-induced expression of hepatic miRs could be reversed if the nutritional intervention occurred during a developmental window of tissue plasticity. In guinea pigs, uterine ligation during pregnancy led to the silencing of hepatic miR-146a expression in 5-month offspring, resulting in increases in its target *smad4*, a profibrotic gene (Sarr et al. 2015).

In either low-birth-weight humans or the offspring of undernourished rats, the expression of miR-483-3p is augmented in adipose tissue later in life, leading to decreased *growth differentiation factor-3* (*gdf3*) mediating the decreased lipid storage, enhanced lipotoxicity, and insulin resistance observed (Ferland-McCollough et al. 2012). Individual changes in maternal dietary lipids (i.e., soybean, olive oil, fish oil, linseed, or palm oil) in rodent pregnancy can have differential effects on programming the long-term expression of miRs in adipose and liver tissue (Casas-Agustench et al. 2015). It is of great interest that the maternal fish oil-exposed

offspring had the worst insulin sensitivity at 12 months linked to decreased expression of hepatic miR-192-5p, miR-10b-5p, miR-377-3p, and miR-215, all targets of insulin and glucose homeostasis (Casas-Agustench et al. 2015; Sardinha et al. 2013). Moreover, the changes in the expression of these miRs were specific both to pregnancy (vs. non-pregnancy) and to the liver (vs. adipose) (Casas-Agustench et al. 2015). Further studies are warranted to elucidate how the expression of these miRs in the liver and adipose are influenced by perinatal undernutrition via direct (i.e., regulation of 5′-UTR of miRNA promoters) and indirect (i.e., ER stress) mechanisms (Nolan et al. 2014).

Conclusion

The liver and adipose play an essential role for long-term lipid and glucose homeostasis. Given the growth and differentiation of these tissues occur in both fetal and postnatal life, alterations in maternal nutrition during these developmental windows can have short-term and long-lasting implications on metabolism. The present review illustrates how maternal malnutrition in pregnancy can influence epigenetic (i.e., DNA methylation, posttranslational histone modifications, miRs) mechanisms which dictate gene expression of key receptors, enzymes, transporters, and hormones in these organs in postnatal life. In many situations, while these epigenetic changes may serve as a compensatory adaptation during fetal life, it predominantly leads to dysmetabolism and dyslipidemia in mammals, contributing to the metabolic syndrome. Further studies are warranted to address safe and specific interventions (i.e., dietary or pharmaceutical) during neonatal of adult life to prevent these long-term deficits in metabolism. This is better achieved with further understanding of how nutrition during perinatal life influences the epigenome.

Mini-dictionary of Terms

- *Dyslipidemia*: An increase in plasma cholesterol, triglycerides, or both, leading to the development of cardiovascular disease.
- *Euchromatin*: Activated region of DNA leading to an increase in gene expression.
- *Hepatic steatosis*: Accumulation of fat in the liver.
- *Heterochromatin*: Repressed region of DNA leading to a decrease in gene expression.
- *Malnutrition*: Either an excess or deficiency in one or more nutrients.
- *Tissue plasticity*: A period of time in development whereby an organ is amenable to positive or negative environmental cues.

Key Facts Regarding Lipid Homeostasis

- Both the liver and adipose play critical roles in cholesterol, fatty acid, and glucose homeostasis. Moreover, these organs continually proliferate and differentiate from fetal to postnatal life in mammals, subjecting them to vulnerable windows of plasticity by nutritional changes in the environment.
- Altered maternal nutrition in pregnancy can lead to DNA methylation and silencing of critical metabolic genes from fetal life to adulthood and, in certain situations, from generation to generation.
- Posttranslational histone modifications resulting from a poor maternal diet can influence long-term gene expression of lipogenic genes in promoter- and sex-specific manner. Some of these changes in gene expression can be reversed in neonatal life, a period of tissue plasticity.
- Maternal malnutrition can influence the expression and secretion of various microRNAs in neonatal life and adulthood which can silence key enzymes and hormones involved in lipid homeostasis. Further understanding is warranted to elucidate how these microRNAs are regulated long term.

Summary Points

- The liver plays a key role in cholesterol synthesis, metabolism, and transport. It also is involved in fatty acid biosynthesis and glucose homeostasis.
- Adipose tissue plays an important role in lipid storage and insulin signaling.
- Altered hepatic or adipose function leads to dyslipidemia, obesity, and cardiovascular disease. Efficacious strategies are better warranted in preventing than treating dyslipidemia.
- During perinatal life in mammals, both the liver and adipose are vulnerable to maternal nutritional insults which can reprogram gene expression leading to long-term metabolic deficits in the offspring.
- Epigenetic mechanisms facilitate developing organs to adapt to short-term deficits in nutrition; however this has can have dire consequences long term.
- In models of maternal undernutrition, DNA methylation can be increased or decreased affecting long-term gene expression in a promoter- and/or tissue-specific manner.
- Alterations in DNA methylation have been implicated to occur in more than one generation; however developmental windows do exist which can prevent this from occurring.
- Animal models of maternal undernutrition demonstrate that posttranslational histone modifications (i.e., histone H3 acetylation and methylation) can be altered in early life that persists into adulthood. Moreover, this can occur in a sex-specific manner.

- MicroRNAs can also be influenced by maternal malnutrition short and long term which target and silence the expression of key endocrine factors in the liver and adipose.
- Changes in maternal diet during fetal and/or neonatal life can alter the trajectory of microRNA expression long term.

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