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REVIEW

Molecular mechanisms underlying the fetal programming of adult disease

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Abstract Adverse events in utero can be critical in determining quality of life and overall health. It is estimated that up to 50 % of metabolic syndrome diseases can be linked to an adverse fetal environment. However, the mechanisms linking impaired fetal development to these adult diseases remain elusive. This review uncovers some of the molecular mechanisms underlying how normal physiology may be impaired in fetal and postnatal life due to maternal insults in pregnancy. By understanding the mechanisms, which include epigenetic, transcriptional, endoplasmic reticulum (ER) stress, and reactive oxygen species (ROS), we also highlight how intervention in fetal and neonatal life may be able to prevent these diseases long-term.

Keywords Fetal Programming · Epigenetics · microRNA · Posttranslational Histone Modifications · DNA Methylation · ER Stress · Nuclear Receptors

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Introduction

The incidence of low birth weight babies (defined as ≤2500 g or 5.5lbs) worldwide is estimated to be 15.5 %, and that number is greatly underestimated (Lopez et al. 2006). As a general indicator of public health, it is imperative that we study the etiology and outcomes of the individuals that develop as low birth weight babies. Similarly, the incidences of non-communicable diseases such as heart disease, type II diabetes, hypertension, obesity and the metabolic syndrome are on the rise in North America (Ford et al. 2004; WRITING GROUP MEMBERS et al. 2010; McGuire 2011). More than one in three Americans are obese (Ogden et al. 2012), compared to one in four in Canada (McGuire 2011). This trend is beginning to appear all over the world, including in developing nations (Grundy 2008; Nestel et al. 2007). Moreover, diseases such as cardiovascular disease are a leading cause of death in the United States (WRITING GROUP MEMBERS et al. 2010). Although the prevalence of these chronic and non-communicable diseases puts tremendous strain on the health care system and society, intervention with diet or drugs can play a significant role to reduce their incidence. For example, a meta-analysis prospective study, using data from 58 clinical trials as well as nine cohort studies, indicates that in patients with vascular disease, a 1.8 mM reduction in LDL cholesterol by statins resulted in a 17 % reduction in stroke and a 60 % reduction in the risk of ischemic heart disease (Law et al. 2003). Current treatment for these diseases, in addition to adopting a healthy lifestyle via alterations in diet and promoting exercise, relies on the use of pharmaceuticals. Unfortunately, these treatments are not efficacious for all individuals; for example, in some patients statin treatment can lead to rhabdomyolysis and hepatitis-associated liver failure (Law et al. 2003). Therefore, additional strategies in disease prevention are warranted.

The 'fetal origins' or 'Barker' hypothesis suggests that impaired growth of the fetus during gestation strongly correlates to the development of chronic disease in later life (Hockaday and Yajnik 2003; Barker 1990). Epidemiological studies have demonstrated strong correlation between low birth weight infants and the development of type II diabetes, cardiovascular disease, and hypertension (Jaquet et al. 2000; Hales et al. 1991; Huxley et al. 2007; Nilsson et al. 1997; Curhan et al. 1996a; Curhan et al. 1996b). It is postulated that the fetus is physiologically 'programmed' in utero to adapt to its environment (Barker et al. 2002; Desai and Hales 1997; Bateson et al. 2004). However, this adaptation becomes maladaptive when the infant is exposed to a different postnatal environment.

Experiments of intrauterine growth restriction (IUGR) in animal models provide further evidence to support the hypothesis that impaired growth in utero via various maternal deficiencies leads to impairment of glucose, cholesterol, and triglyceride metabolism in adulthood (Langley et al. 1994; Dahri et al. 1991; Lucas et al. 1996; Sohi et al. 2011a). In utero deficiencies that can lead to impaired growth in humans and animals include hypoxia (Wang et al. 2009), deficiencies in essential vitamins and minerals (Lewis et al. 2001), diminished protein (Sohi et al. 2011a), caloric restriction (Woodall et al. 1996), and excess glucocorticoids (Benediktsson et al. 1993; Reynolds 2010). Although the correlation between impaired fetal growth and the risk for developing chronic disease in adulthood is undoubtedly strong, the mechanisms behind these programming effects are only beginning to be elucidated. Studies have only begun to scratch the surface in understanding the molecular events leading to permanent changes to short- and long-term physiology and pathophysiology. This review aims to look at the current literature to highlight the possible mechanisms involved with 'fetal programming.' These mechanisms of interest include the role of epigenetics, nuclear receptors, reactive oxygen species (ROS) and markers of endoplasmic reticulum stress (ERS). Please see Fig. 1.

Epigenetics

The development of many complex and chronic diseases cannot be simply explained with genomic heritability alone (Manolio et al. 2009). Epigenetics has emerged as an important mechanism in adjusting the expression patterns of genes in a site and tissue specific manner as an adaptive response to insults during the developmental period. Epigenetic mechanisms essentially influence the long-term expression of a gene by altering the ability of the transcriptional machinery to interact with the chromatin environment. Moreover, they influence heritable changes in phenotype without altering the genetic sequence of an organism. Epigenetic changes can be both transient (Barth and Imhof 2010) and persist for long periods of time (Talens et al. 2010). Mechanisms of epigenetic action include DNA methylation, post-translational histone modifications, and more recently discovered microRNA-mediated repression and activation.

DNA methylation

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 essential to DNA methylation as it is the ultimate methyl donor for many methylation reactions. Similarly, folate/folic acid is involved

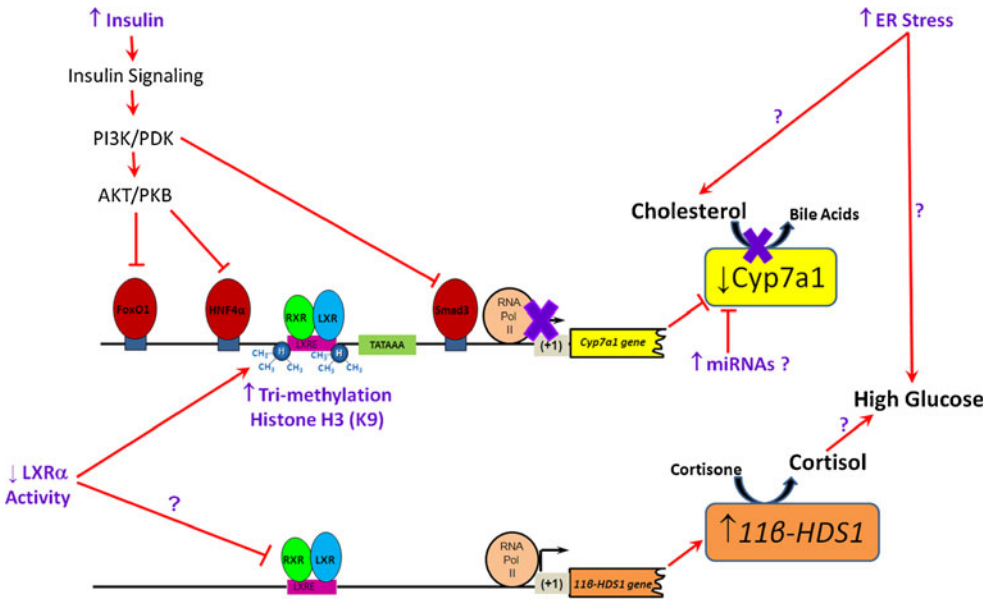

Fig. 1 Proposed molecular mechanisms of how maternal protein restriction (MPR) in the rat diminishes the expression of hepatic LXRα and LXR-target genes in postnatal life. MPR-induced effects are highlighted in purple

in methionine metabolism and is required for methylation reactions and DNA synthesis. Consequently, altered dietary intake of such nutrients may significantly affect DNA methylation profiles, and ultimately gene expression (Waterland 2006; Kim et al. 1997; Wilson et al. 1984). Traditionally, an increase in methylation across CpG sites can impair initiation, elongation or termination of a gene. However, this may not always hold true as is the case with expression of insulin growth factor 2 (Igf-2), which is increased in IUGR offspring due to intragenic methylation of its promoter (Murrell et al. 2001). Alterations in DNA methylation may be caused by changes in an organism's environment in order to adapt, however in cases of IUGR these DNA methylation responses may be maladaptive due to differing environments in utero and postnatally.

Recently it was demonstrated that during maternal protein restriction (MPR) in mouse pregnancy, expression of the Liver X Receptor (LXRα), a nuclear receptor involved in cholesterol homeostasis, is suppressed in the fetal liver as a result of methylation of the upstream region of the *LXRα* promoter (van Straten et al. 2010). However the effects in postnatal life were not investigated. Another recent study examining the effects of maternal protein restriction and maternal protein excess in porcine offspring found alterations in the expression patterns of a variety of genes involved in DNA methylation and methionine metabolism (Altmann et al. 2012). Beyond the realm of maternal protein restriction, Zhang et al. found that a high fat diet throughout pregnancy and lactation lead to alterations in methyl CpG binding protein-2, a protein involved in the silencing of genes via DNA methylation (Zhang et al. 2009). In addition, a study done by Nijland et al. (2010) that examined maternal nutrient restriction in baboon offspring found decreased methylation of CpG on the promoter of *PCK1* coupled with an increase in *PCK1* transcript in the neonate baboons (Nijland et al. 2010). Overexpression of PEPCK, the product of *PCK1* translation, has been implicated in hyperglycemia and type II diabetes (Valera et al. 1994; Gomez-Valades et al. 2008). Another study in baboon offspring of maternal nutrient restricted mothers found altered patterns of global DNA methylation in the brain, liver, and kidney between nutrient restricted offspring and offspring whose mothers received adequate food intake (Unterberger et al. 2009).

In humans, a recent double blind randomized control trial examining the effects of micronutrient supplementation during the pre- and periconceptual period found different methylation patterns at differentially methylated regions between the supplement group and the placebo group (Cooper et al. 2012). Another study done in humans by Einstein et al. (2010) indicated hypermethylation of the *HNF4A* gene, a nuclear receptor implicated in type II diabetes (Yamagata et al. 1996), in IUGR infants.

The current evidence suggests that DNA methylation may be a key player in modulating phenotypes in response to the environment. This applies especially to the mother and its newborn in less than ideal environments (*i.e.* situations of famine, poor nutrition or high altitude).

Post-translational histone modifications

The second major epigenetic mechanism involves influencing the chromatin environment via a number of post-translational modifications, including methylation, acetylation, phosphorylation, ubiquitination and ADP-ribosylation of histones (Jenuwein and Allis 2001). The combinatorial nature of these covalent modifications reveal a "histone code", which may serve critical as an adaptive regulatory mechanism that can also influence gene expression in a tissue- and gene-specific manner at times of insult during development. Interestingly, these histone modifications occur and are maintained by a diverse range of histone modifying enzymes including families of histone acetylases and methyltransferases (Marmorstein and Trievel 2009), whose levels may also be altered as a result of a developmental insult. It is important to realize that the different prenatal insults that lead to IUGR offspring seem to have both common and distinct adaptive responses initiated via epigenetic mechanisms. Therefore IUGR offspring derived from different insults may differ or be similar due to global, tissue, or site-directed epigenetic modifications.

To date, there is very little known about the epigenetic alterations associated with expression of target genes in the fetal tissues, and how they are influence these genes throughout normal and abnormal fetal and postnatal development (Burdge et al. 2007a, b; Lillycrop et al. 2005; Rees et al. 2000). Using chromatin immunoprecipitation (ChIP), our laboratory recently demonstrated that MPR-induced IUGR rat male offspring had a decrease in postnatal Cyp7a1 expression, the critical enzyme involved in cholesterol catabolism, both short- and long-term (Sohi et al. 2011a). This was demonstrated to be 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 (*−128/−81* bp) of the *Cyp7a1* promoter. In contrast, MPR female offspring had normal cholesterol, restored levels of Cyp7a1 expression, RNA polymerase II binding, acetylation and trimethylation of Histone H3 (Lysine 9, 14) within the same promoter region (Sohi et al. 2011a).

microRNAs

Aside from post-translational histone modifications, which may govern the long-term expression of genes, microRNAs

(miRNAs) may also play a key role in the fetal programming of cholesterol homeostasis. miRNAs are short, non-coding RNA molecules of 20–25 nucleotides in length that regulate gene expression via mRNA degradation and/or translational repression (Khorram et al. 2010; Xu et al. 2010). By regulating the expression of target genes, miRNAs alter a variety of physiological processes including cell cycle regulation, differentiation, metabolism, and aging (Xu et al. 2010). miRNAs 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). Given their ability to bind 3′-UTR with partial sequence homology, a single miRNA may have multiple 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 miRNAs (Brennecke et al. 2005). While miRNAs likely play an important role in the etiology of adult diseases and cancer, their role in fetal development and programming remain elusive. Recent microarray studies employing primers for a variety of miRNAs have demonstrated that maternal nutrient restriction can permanently alter the expression of miRNAs in the aortas of newborn and aging rat offspring (Khorram et al. 2010). Moreover, circulating hypoxia-regulated miRNAs have been demonstrated to be increased in pregnant women with fetal growth restriction (Mouillet et al. 2010). The role and identification of miRNAs altering the expression of genes involved in the fetal programming of cholesterol, fatty acids, glucose, and insulin homeostais remain to be identified, but are the subject of great interest.

Nuclear receptors

Nuclear receptors are part of a family of ligand-mediated transcription factors involved in regulating transcription of genes responsible for growth, development, and differentiation (Mangelsdorf et al. 1995; Repa and Mangelsdorf 2000). Potential ligands for nuclear receptors include hormones, oxysterols, and lipophilic vitamins. There are four main classes of nuclear receptors, classified by their ligand-binding properties, DNA-binding properties, and dimerization properties (Repa and Mangelsdorf 2000). The four classes of nuclear receptors all have a similar mechanism of action through the activation and repression on promoter elements of genes; with slight differences (*i.e.* translocation between nucleus and cytoplasm differs between Class I and Class II nuclear receptors). Humans are thought to have 48 nuclear receptors while rats and mice have 47 and 49, respectively (Zhang et al. 2004). Examples of nuclear receptors include the estrogen receptor (ER), glucocorticoid receptor (GR), progesterone receptor (PR), retinoic acid receptor (RAR), retinoic X receptor (RXR), thyroid hormone receptor (TR), mineralocorticoid receptor (MR) and the liver X receptor (LXR). While some of these nuclear receptors have been implicated in IUGR and the development of chronic diseases, scientists have only begun to elucidate how nuclear receptors may be involved in the developmental origins of disease on a molecular level.

The liver X receptor

The LXRs (LXRα and LXRβ), part of the 1H subfamily of nuclear receptors, have long been implicated in the homeostasis of cholesterol and triglycerides (Janowski et al. 1996; Lehmann et al. 1997). Although, both LXRs share similar homology, they are expressed in different tissue and are differentially regulated in terms of nuclear and cytosolic trafficking (Repa and Mangelsdorf 2000; Prufer and Boudreaux 2007). Furthermore, both LXRs must heterodimerize with the retinoid X receptor (RXR), prior to binding with DNA (Willy et al. 1995). LXRα is mainly expressed in the liver, adipose tissue, spleen, and lungs (Willy et al. 1995; Apfel et al. 1994), while LXRβ is expressed ubiquitously (Song et al. 1994). Studies have also found that both isoforms may be involved in different pathways in the regulation of cholesterol and triglycerides (Lund et al. 2006). More recently, it has been found that LXR is also a glucose sensor and involved in the regulation of glucose homeostasis (Mitro et al. 2007b).

Given that LXRα plays a role in cholesterol (Repa and Mangelsdorf 2000), fatty acid (Repa and Mangelsdorf 2000; Lehmann et al. 1997) and glucose (Mitro et al. 2007b) homeostasis, it is an attractive candidate to elucidate the molecular mechanisms underlying the etiology of the metabolic syndrome. To date, few studies have demonstrated links between nutrition, hepatic LXRs and liver function. Both iron restriction and maternal protein restriction have been demonstrated to lead to decreased fetal LXRα (van Straten et al. 2010; Zhang et al. 2005), but less is known about the long-term effects in postnatal life. Our recent studies have demonstrated that in maternal protein restriction (MPR) in rats during pregnancy and lactation, the offspring are low birth weight offspring, with permanent elevation in circulating cholesterol and impaired glucose homeostasis (Sohi et al. 2011a; Vo et al. 2012). We have demonstrated that if MPR rat offspring were placed on a normal diet during lactation, hepatic LXRα was enhanced, preventing decreases in Cyp7a1 and hypercholesterolemia by three weeks of age (Sohi et al. 2011a). Further work on the role of LXRα, RXR, and other lipid-sensing nuclear receptors are warranted to understand the transcriptional mechanisms involved in cholesterol, glucose, and triglyceride homeostasis.

The glucocorticoid receptor

The glucocorticoid receptor is a transcription factor part of the 3C subfamily of nuclear receptors. GR has two isoforms in humans and is expressed in all tissue, with pleiotropic effects throughout the body (Oakley et al. 1996; Lu and Cidlowski 2005). In conjunction with its natural ligand cortisol, GR is vital for the anti-inflammatory response, stress response, metabolism, and development (Barnes 1998; Sapolsky et al. 2000; Rhen and Cidlowski 2005). After ligand binding, GR exerts its actions via two main mechanisms: direct binding to DNA (Mangelsdorf et al. 1995) or through protein-protein interactions with other transcription factors such as NF-kappa B (Ray and Prefontaine 1994).

It has become common practice in medicine to give preterm fetuses glucocorticoids as a therapeutic agent to accelerate lung maturation and prevent fetal respiratory distress syndrome (Liggins and Howie 1972; Young et al. 1980; Knight et al. 1994). Common corticosteroids administered antenatally to prevent fetal respiratory distress syndrome include dexamethasone and betamethasone. However, glucocorticoid exposure during pregnancy has been strongly implicated in fetal programming and the development of chronic disease (Benediktsson et al. 1993; Reynolds 2010; Seckl 2004). Besides direct administration of glucocorticoids to the fetus, maternal undernourishment may also exhibit a similar effect of increased glucocorticoids in the mother and fetus (Blondeau et al. 2001; Lesage et al. 2001; Habib et al. 2011). Previous studies have implicated altered expression of GR in the brain (Levitt et al. 1996) and liver (Nyirenda et al. 1998) in the programming of hypertension and impaired glucose homeostasis in rat offspring when administered dexamethasone antenatally. Similarly, nutrient restriction leads to increased expression of GR in various tissues of rat and sheep offspring (Bertram et al. 2001; Whorwood et al. 2001). In a recent study done by Valtat and colleagues, offspring of dams fed a calorie-restricted diet one week prior to delivery displayed increased corticosterone levels, decreased beta-cell mass, and impaired glucose tolerance (Valtat et al. 2011). However, in offspring where their pancreatic precursor cells lacked GR expression, the deleterious effects were attenuated (Valtat et al. 2011). Thus, GR signaling was observed to play a critical role in the programming of beta-cell dysfunction. Other studies have also demonstrated the important role of corticosteroids on beta-cell development and proliferation (Blondeau et al. 2001; Gesina et al. 2004; Dumortier et al. 2011).

Evidence has emerged supporting the fact that the effects of GR expression on development are likely to be influenced at least partially by epigenetic modifications (Thomassin et al. 2001; Stevens et al. 2010; Begum et al. 2012). In 2005, Lillycrop and colleagues found that maternal protein restriction lead to increased expression of GR, coupled with decreased methylation of the GR promoter—decreased methylation of the promoter is presumed to lead to increased transcription of the gene (Lillycrop et al. 2005). Another study done by Lillycrop et al. (2007) found that methylation of the GR promoter in maternal protein restricted rat offspring may be due to a reduction in DNA methyltransferase-1 expression, leading to impaired methylation of DNA and histones (Lillycrop et al. 2007).

Interestingly, evidence even suggests these epigenetic modifications may even persist across generations. A study done by Burdge and colleagues (2007a, b) found that methylation of GR in adulthood persisted across the F1 generation into the F2 generation of offspring, likely through stable epigenetic modifications in the female gametes of F0 (Burdge et al. 2007a, b).

Peroxisome proliferator-activated receptors (PPARs)

The peroxisome proliferator-activated receptors (PPAR), part of the 1C subfamily of nuclear receptors, are another group of ligand-activated nuclear receptors that may play a vital role in fetal programming. Originally named for its role in peroxisome proliferation (Issemann and Green 1990), the PPARs are now known to be involved in wide variety physiological functions. Similar to the LXR, PPARs must heterodimerize with RXR prior to DNA binding and transcriptional regulation (Kliewer et al. 1992; Keller et al. 1993).

There are three isoforms of PPAR: PPARα, PPARβ/δ and PPARγ, which each have unique expression patterns (Michalik et al. 2006). The main functions of PPARα are maintaining energy homeostasis (Lefebvre et al. 2006) and modulating inflammatory responses (Chinetti et al. 2000). PPARβ/δ is also involved in maintaining energy homeostasis and is required for the development and maintenance of various tissues including the placenta (Barak et al. 2002; Schaiff et al. 2007), muscle (Luquet et al. 2003; Angione et al. 2011), skin and brain (Peters et al. 2000). Finally, PPARγ is involved in the differentiation and proper function of adipose tissue (Tontonoz et al. 1994; Imai et al. 2004; Farmer 2006). While there does not seem to be any clear endogenous ligands for the PPARs, it is thought that many different products of fatty acid metabolism are responsible for inducing the actions of these nuclear receptors (Michalik et al. 2006).

The role of PPARs in fetal programming involves a variety of tissues and organs, however altered muscle development and function appears to be a large contributing factor to insulin resistance and the metabolic syndrome based on previous studies. A study done by Bayol and colleagues in 2005 found that when pregnant rats were fed a “cafeteria diet” (high in fat and sugar), the offspring exhibited a 25 % reduction in muscle cross-sectional area concomitant with increased PPARγ (Bayol et al. 2005). The authors concluded that increased expression of PPARγ was a compensatory mechanism to preserve insulin sensitivity.

Moreover, another study done by Wang and colleagues in 2004 found that with targeted expression of PPARβ/δ in skeletal muscle, the mice were more resistant to developing obesity (Wang et al. 2004). Similarly, when PPARβ/δ was selectively ablated in skeletal myocytes, the mice were more prone to developing obesity and diabetes (Schuler et al. 2006). This is of great interest considering that hypoxia, associated with IUGR, increases PPARδ expression in cultured C_2C_{12} muscle myoblasts (Regnault et al. 2010). A more recent study has found that maternal obesity leads to altered insulin signaling in muscle of sheep offspring along with increased intramuscular triglycerides, however they did not examine the role of PPAR (Yan et al. 2011). Overall, these studies provide strong evidence for the role of PPAR and its interaction with muscle in the development of impaired glucose and fatty acid metabolism.

PPAR expression in adipose tissue may also play a key role in the programming of obesity. Muhlhausler and colleagues (2007) found that offspring of ewes fed a high nutrition diet (155 % versus 100 % control) lead to increased expression of PPARγ along with other lipogenic and adipogenic factors in perirenal fat (Muhlhausler et al. 2007). Another group found increased PPARγ expression in adipose tissue coupled with hypertension, and increased adiposity in offspring of mice dams fed an obesogenic diet (Samuelsson et al. 2008). Evidence has also emerged demonstrating that PPAR-mediated programming of visceral obesity in IUGR offspring may be sex-specific (Duffield et al. 2009).

The estrogen receptor (ERα and ERβ)

Sex steroid hormones (*e.g.* estrogen acting through ERα) remain an important mediator in the fetal origins of adult disease. It is well established that the onset and severity of numerous adult onset diseases differ between exist in men and women. For example, men have higher 24-hour mean blood pressure, by approximately 6 to 10 mm Hg, compared to age-matched premenopausal women, but this trend reverses after women reach menopause (Reckelhoff 2001). In females, it is hypothesized that differences in sex hormones modulate regulatory systems leading to decreased hypertension and vascular dysfunction (Reckelhoff 2001). Given the widespread origins of the metabolic syndrome, it is difficult to assess whether gender and, more specifically, sex hormones influence physiological homeostatic mechanisms. Recent studies in animal models have suggested that perturbations to the maternal environment during pregnancy can lead to sex-specific, long-term consequences in postnatal life. For example, male offspring of rat dams exposed to 30 % global nutrient restriction during pregnancy develop hypertension earlier than their female counterparts, whereas severe protein restriction (5 % protein diet) during pregnancy results in programmed hypertension in both sexes(Woods et al. 2004). Moreover, an MPR diet during gestation and lactation results in pancreatic β cell dysfunction and visceral obesity exclusively in the adult male offspring at postnatal day 130 (Guan et al. 2005; Petrik et al. 1999).

The sex specificity exists even at the epigenetic level in IUGR offspring. For example, uteroplacental insufficiency induced IUGR rats at postnatal day 21 have a global increase in the females and decrease in the males with respect to acetylation of Histone H3 (Lysine 9, 14) at in the hippocampus and white matter (Ke et al. 2006). Our studies have demonstrated that circulating cholesterol in MPR offspring was increased associated with impaired Cyp7a1 expression in both sexes at three weeks (pre-weaning), but persists only in the males at 4 months of age (Sohi et al. 2011a). This was associated with male-specific silencing of the promoter of *Cyp7a1*. While the mechanisms underlying these sex-specific programming effects remain unknown, it has been hypothesized that sex steroids (*e.g.* estrogen) protect the female against development of these disease processes, including elevated blood pressure (Ozaki et al. 2001). Evidence for this comes from the aromatase knockout (ArKO) mouse, which cannot synthesize endogenous estrogens due to distruption of the *Cyp19* gene (Hewitt et al. 2003). ArKO females challenged with a high cholesterol diet have higher circulating cholesterol and lower Cyp7a1 expression compared to wildtype females and males of either genotype (Hewitt et al. 2003), and estrogen replacement reversed the hepatic steatosis (Hewitt et al. 2004). However, the effects of estrogen may be only part of the reason for the sexual dimorphism observed in MPR offspring. Given that MPR males have reduced levels of circulating testosterone compared to control males (Chamson-Reig et al. 2009), it is possible that loss of this androgen may also underlie male-specific impairment of Cyp7a1 and cholesterol catabolism. In addition, MPR male offspring at 130 days of age have two-fold higher levels of circulating insulin (Chamson-Reig et al. 2009), which inhibits Cyp7a1 transcription in both rat hepatocytes and streptozotocin (STZ)-induced diabetic rats via decreases in the binding of transcription factors Fox01 and Smad3 to the promoter of *Cyp7a1* (Li et al. 2008). Furthermore, studies have now demonstrated that sex steroid hormones can influence epigenetic mechanisms, including post-translational histone modifications (Leader et al. 2006). Therefore, gender-specific differences in the fetal programming of cholesterol homeostasis may be due in part to alterations in their "histone code".

Mitochondrial function and the role of reactive oxygen species

Reactive oxygen species (ROS) are free radicals that are byproducts of normal physiological reduction-oxidation reactions carried out by eukaryotic cells. Furthermore, ROS are involved in many cellular and physiological functions

including: proliferation, differentiation, apoptosis, and morphogenesis (Covarrubias et al. 2008). Common ROS include: nitric oxide (NO), superoxide (O_2^-), and hydrogen peroxide (H_2O_2). Oxidative stress occurs when ROS levels exceed certain threshold levels and begin to impair physiological functions. Given that ROS signaling and the maintenance of appropriate ROS levels plays a vital role in a diverse range of cellular processes, especially development, it is likely that ROS may mediate some of the programming effects of IUGR. Some studies have already begun to shed some light on the correlation between IUGR and increased ROS in the fetus (Karowicz-Bilinska et al. 2002; Raab et al. 2009).

One of the main cellular organelles involved in the production and regulation of ROS levels is the mitochondria. Studies have demonstrated that IUGR can lead to increased oxidative stress in rat hepatic mitochondria and impaired hepatic mitochondrial function (Peterside et al. 2003). A similar result was found in the pancreases of IUGR rat offspring (Simmons 2005). Considering pancreatic islet cells have been shown to express much lower antioxidant enzymes compared to other tissues, islet cells are likely to be more prone to ROS-related damage (Lenzen et al. 1996; Tiedge et al. 1997). Consequently, ROS-mediated damage and oxidative stress is thought to be one of the leading contributions to β-cell damage (Robertson et al. 2003). Thus, if IUGR lead to increased ROS in the pancreas, this could lead to impaired development of β-cells and predispose the fetus to impaired glucose tolerance and diabetes in later life (Simmons 2005; Simmons et al. 2005).

Another area of the body in which oxidative stress appears to cause long-term impairment is the cardiovascular system. Previous studies have established links between impaired vascular endothelial function and the presence of ROS (Nakazono et al. 1991). A study done by Franco Mdo and colleagues (2002) found that offspring of nutrient-restricted dams developed hypertension concurrent with increased oxidative stress in mesenteric arterioles(Franco Mdo et al. 2002). In addition to vascular dysfunction, IUGR also seems to induce ROS-mediated damage in the heart (Franco Mdo et al. 2002). von Bergen and colleagues (2009) found that the offspring of ewes administered dexamethasone during pregnancy displayed increased H_2O_2 in cardiac mitochondria as well as increased catalase activity (von Bergen et al. 2009). A more recent study found that rat offspring suffering from prenatal hypoxia developed oxidative stress in the fetal heart by the end of pregnancy (Giussani et al. 2012). The offspring also developed impaired NO-dependent relaxation of peripheral arteries and altered contractility of the heart in adulthood (Giussani et al. 2012). Hence, oxidative stress might not only impair the programming of metabolic pathways in IUGR offspring, but vascular formation and function as well. Concurrent destruction of metabolic pathways and vascular function provide higher risk to the development of diseases such as the metabolic syndrome.

Endoplasmic reticulum stress

Maternal insults such as hypoxia and low nutrition can force developing cells and tissues to reduce protein synthesis both short and long-term. This makes sense considering that ~30 % of total placental oxygen consumption is used for the oxidative process of protein folding (Carter 2000). In placental insufficiency, the associated deprivation of amino acids and oxygen leads to an increase in ROS and ATP resulting in the accumulation of misfolded proteins (Yung et al. 2008). This in turn leads to activation of the endoplasmic reticulum (ER) stress pathway or the uncoupled protein response (UPR) (Yung et al. 2008). In high altitude pregnancies, whereby pO_2 is reduced in association with a fall in birthweight of 100 g/1000 m (Moore et al. 1998; Giussani et al. 2001; Keyes et al. 2003), ER stress and protein synthesis inhibition was activated (Yung et al. 2012). In fetal tissues, decreased maternal dietary protein has also been demonstrated to lead to protein synthesis (increased phosphorylated $eIF2_\alpha$) in the rat liver (Parimi et al. 2004), while paradoxically in IUGR sheep messenger ribonucleic acid translation initiation occurred without increases $eIF2_\alpha$ (Thorn et al. 2009). Bispham and colleagues (2005) found that maternal nutrient restriction led to offspring with more adipose tissue associated with increased expression of uncoupling protein (UCP)-2, a hallmark of ER stress and protein synthesis inhibition (Bispham et al. 2005). While ER stress is associated with short-term adaptations in fetal life to maternal insults, the long-term effects ER stress on overall offspring health is less understood. This is of great interest considering that IUGR is associated with long-term insulin resistance and obesity, and that various components of the ER stress pathway have been linked to insulin resistance. For example, activation of the uncoupled protein response (UPR) in obesity leads to increases in phospho-IRS1 (p-IRS1), a marker of insulin resistance (Ozcan et al. 2004). In addition, a loss of weight leading to increased insulin sensitivity was associated with a reduction in markers of UPR activation (Gregor et al. 2009). In the rat, we and others have previously demonstrated that maternal protein restriction (MPR) in pregnancy and lactation results in impaired fetal growth, decreased liver to bodyweight ratio, insulin resistance, and hypercholesterolemia in adulthood (postnatal day 130) (Sohi et al. 2011a; Chamson-Reig et al. 2009). This is associated with a significant decrease in the hepatic phosphorylation of AKT1 (Serine 473) and increased levels of p85 protein, both indicative of impaired insulin signaling (Sohi et al. 2012). This coincided with elevation of established ER stress markers in the liver, including an increase in X box binding protein 1 (XBP-1) mRNA splicing levels and elevated ER chaperones (Glucose regulated protein 94 and 78) (Sohi et al. 2012). It was also concomitant with attenuated protein synthesis inhibition (increased phosphorylated $eIF2_\alpha$). Interestingly, fetal hepatic GRP94 and 78 protein levels were found

elevated in LP offspring at embryonic day 19, suggesting that ER stress may persist from fetal life into adulthood in low birth weight offspring. Future studies will be aimed at uncovering the underlying molecular mechanisms behind the long-term elevation of ER stress in this and other fetal programming models of insulin resistance and obesity.

Tissue plasticity: reversing the in utero origins of adult disease

The development of many organs occurs both pre- and postnatally. For example, in the liver, development consists of embryonic cell specification, budding, and then differentiation (Kung et al. 2010). Until birth, the liver has a major haematopoietic function (Gualdi et al. 1996), but by mid-gestation in rodents, the liver bud is formed containing bipotential progenitor cells that differentiate into either hepatocytes or ductal cells (Cascio and Zaret 1991). In the last 3 days of gestation in the rat, liver mass triples due to a high rate of fetal hepatocyte proliferation (Greengard et al. 1972), followed by a transition of fetal to adult rat hepatocytes in the first week of postnatal life (Gruppuso et al. 1997). Given that during this neonatal period there is a high rate of replication, neogenesis and apoptosis (Greengard et al. 1972) leading to extensive liver remodeling, this period represents a critical window for therapy designed to improve hepatic growth and function long-term. For example, it has been demonstrated in IUGR rats derived from uterine-ligated dams, that neonatal administration of Exendin-4™ (a GLP-1 analog) prevents the development of diabetes due to a restoration of the transcription factor Pdx-1, and ultimately β cell function (Stoffers et al. 2003). Moreover, Exendin-4™ treatment during this neonatal period also prevented the development of hepatic oxidative stress and insulin resistance (Raab et al. 2009). This indicates quite remarkably that neonatal intervention in rats can influence both pancreatic and liver development long-term. Therefore the goal of future studies is to understand how we can exploit this plasticity in organ development to correct the short- and long-term abnormalities resulting from an adverse in utero environment. While at birth the rat liver is less mature than the human liver (Kung et al. 2010), further insights into the reversibility of fetal programming effects on liver development offers promise in human IUGR pregnancies. Our recent studies indicate that restoration of maternal protein intake during lactation can rescue liver growth and prevent the development of hypercholesterolemia long-term (Sohi et al. 2011b). However the underlying epigenetic and transcriptional mechanisms are unknown. While LXR agonists have been demonstrated to activate acetylation of LXR-target promoters (Talukdar and Hillgartner 2006) and lower LDL cholesterol in atherosclerosis-prone adult mice (Talukdar and Hillgartner 2006), their use in neonatal life is limited (Fluhr et al. 2005). Given Cyp7a1 expression is enhanced by histone hyperacetylation (Mitro et al. 2007a), it is conceivable that LXR agonists in vivo could boost the expression of LXR target genes, via increases in both LXR binding and histone acetylation surrounding the LXRE sites. Preliminary evidence from our laboratory suggest that three-week old MPR offspring treated with an LXR agonist (GW3695) from postnatal day 5 to 15 had decreased circulating cholesterol:HDL ratios compared to vehicle treated MPR offspring (Sohi et al. 2011b). Moreover, three-week old MPR offspring treated with GW3695 from postnatal day 5 to 15 had increased hepatic expression of LXRα and Cyp7a1, concomitant increased the recruitment of RNA polymerase II and acetylation of histone H3 (lysine 9,14) surrounding the *Cyp7a1* promoter by 3 weeks of age (Sohi et al. 2011b). While the effects of LXR and RXR agonists on cholesterol homeostasis still need to be assessed long-term, preliminary data suggests that LXR and other nuclear receptor agonists may play a promising role in reversing the long-term adverse effects of impaired fetal development on offspring health.

Another interesting paper by Langley-Evans (1997) found that offspring of maternal protein restricted rats were "rescued" from developing hypertension when dams were administered metyrapone, an inhibitor of corticosterone synthesis (Langley-Evans 1997). A sex-specific effect was also seen when a replacement dose of corticosterone was administered with metryapone. Females responded to the replacement dose and developed hypertension, while males did not exhibit this effect. These results lend evidence to the role of corticosteroids in early programming and the possibility of reversal through pharmacological intervention.

Other studies have indicated that intervention with certain nutrients can reverse the insults to the fetus due to malnutrition. For instance, Jackson et al. (2002) found that when maternal protein restricted dams were supplemented with glycine, offspring hypertension was ameliorated, implicating that the availability of glycine is crucial for adequate development of the cardiovascular system (Jackson et al. 2002). Increased vitamin usage or ROS scavengers such as Vitamin C might also reverse ROS-mediated damage (Giussani et al. 2012).

Given that folic acid/folate is a crucial source of methyl donors for methylation; it may play a role in epigenetic-mediated effects long-term. Supplementation of folic acid following protein restriction appears to alter the growth curve of offspring depending on the fat and protein content of their diet (Burdge et al. 2008). Maternal folic acid/folate supplementation in maternal protein restricted dams also appears to reverse the programmed effects of hypertension in offspring (Torrens et al. 2006). Folic acid supplementation also attenuated altered mRNA expression of various genes in IUGR piglets (Liu et al. 2011). Moreover, evidence suggests that folic acid supplementation may exert its effects

through epigenetic mechanisms, involving reduced methylation of gene promoters such as GR and PPARα (Lillycrop et al. 2005; Burdge et al. 2008; Lillycrop et al. 2008). A further study done by Burdge et al. (2009), in which folic acid supplementation was given to juvenile-pubertal (postnatal day 56) rats of maternal protein restricted mothers lead to favourable epigenetic changes in the promoters of hepatic GR and PPARα (Burdge et al. 2009). Further studies are warranted to determine whether intervention in the offspring diet is comparable to dietary intervention in the mother and whether plasticity lasts longer than we have anticipated. For a review of intervention strategies in the rat, please see Fig. 2.

Conclusion

This review presents only a small piece of the puzzle with regards to the molecular mechanisms underlying the fetal programming of chronic adult diseases. Undoubtedly, there exist many other key players involved that we have not discussed and many mechanism that have yet to be elucidated. However, we have come a long way in terms of understanding the hypothesis that Barker postulated decades ago. As we come to understand the molecular mechanisms behind the programming of adult disease, we come closer to not only understanding the development of these diseases but preventing their onset as well.

Elucidating the processes of integral, multifaceted proteins provides significant promise in treating complex, systemic diseases such as the Metabolic Syndrome. The most promising targets for the investigation of fetal programming in the near future will likely be transcription factors and nuclear receptors involved in multiple pathways. These include LXRα and the PPARs, among others. The role of LXR in cholesterol metabolism, lipid metabolism and glucose metabolism make it an auspicious candidate for linking the three pathways together.

Our recent understanding of epigenetics has shed light on many of the possible mechanisms that may be responsible for the long-term programming of disease. Though traditional genetic inheritance increases the disposition for developing disease, it is ultimately epigenetics and the environment that will determine the outcome of that disease. This provides great hope for therapeutic intervention, as one's future is no longer determined only by what is passed on by their parents. By understanding how our diet, lifestyle, and external environment can affect our DNA methylation profiles, chromatin remodeling, and such, we can learn to take control of our internal environment. This holds true especially for expectant mothers and what they can do for their future children. The evidence underlying the importance of a proper diet during pregnancy has never been so strong. Furthermore, investigation using pharmaceutical therapies provides more support for how the early life environment can be manipulated. Current studies investigating the efficacy of early life intervention are encouraging. For example, work by Pinney et al. (2011) remarkably found that intervention during neonatal life with a transcription factor agonist (*Exendin-4)* lead to permanent changes in later

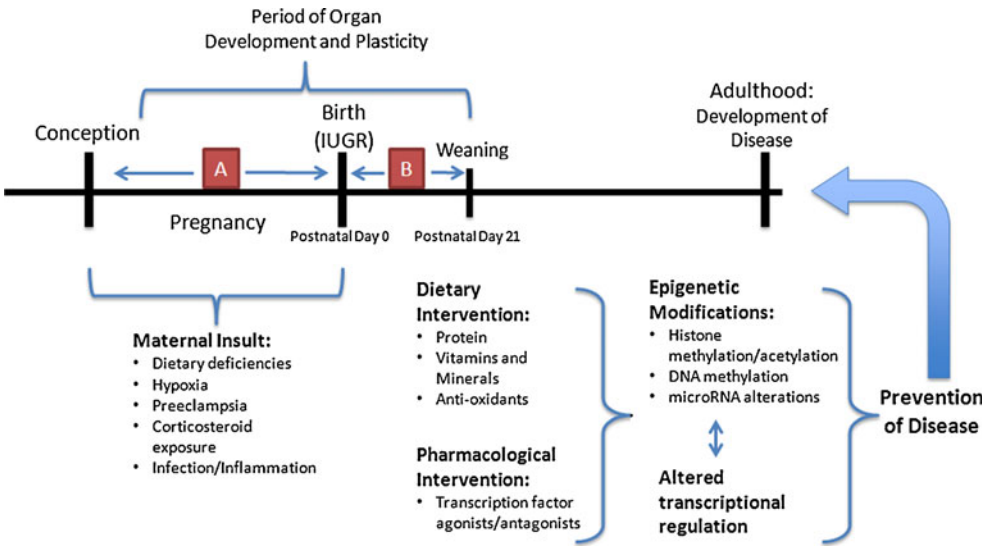

Fig. 2 Windows of opportunity for therapeutic intervention to prevent IUGR related development of chronic disease in rats and possible mechanisms of action. **a** The period of gestation, beginning at conception is an opportune moment for the prevention and intervention of IUGR. Dietary supplementation and proper nutritional intake are likely to be the most effective forms of prevention and intervention of IUGR during this period. **b** The period right after birth until weaning is a period of rapid development and high plasticity. At this moment IUGR has already occurred and programming may have taken its toll, however organ plasticity still allows for intervention—especially with pharmaceuticals that modulate transcription factor activity. Dietary intervention in the offspring may reverse the effects of IUGR. Dietary intervention in the mother may also be effective as the offspring still rely on the mother for milk as well

life and ultimately a reversal of the programmed phenotype, likely mediated through epigenetic mechanisms such as histone acetylation and DNA methylation. Currently, *Exendin-4* is already used to treat diabetic patients. However, if we can determine its efficacy and safety during the neonatal period, we can develop therapies to prevent the development of disease in IUGR infants. As well, these studies warrant further investigation with other transcription factor agonists and antagonists.

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