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The developmental origins of adult disease

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Abstract

Purpose of review—Intrauterine growth restriction (IUGR) is associated with an increased propensity to develop adult onset disease and is described by the developmental origins of adult disease hypothesis. Sequelae of fetal growth restriction include metabolic disease as well as nonmetabolic disorders. Although it has become clear that the morbidities associated with IUGR are complex and result from disruptions to multiple pathways and multiple organs, the mechanisms driving the long-term effects are only just beginning to be understood.

Recent findings—IUGR affects most organ systems by either interrupting developmental processes such as apoptosis or producing lasting changes to levels of key regulatory factors. Both of these are associated with an often persistent change in gene expression. Epigenetic modulation of transcription is a mechanism that is at least partially responsible for this. IUGR is accompanied by changes in the quantity and activity of enzymes responsible for making modifications to chromatin as well as global and gene-specific modifications of chromatin.

Summary—The subtle adjustments needed to ensure developmental plasticity in IUGR are provided by epigenetic modulation of critical genes. Translating the messages of the epigenetic profile and identifying the players that mediate the effects remains one of the major challenges in the field. An understanding of the mechanisms driving the epigenetic changes will facilitate identification of dietary and pharmaceutical approaches that can be applied in the postnatal period.

Keywords

epigenetics; intrauterine growth restriction; programming

Introduction

The Developmental Origins of Adult Disease Hypothesis describes the origin of adult disease in terms of fetal developmental ‘plasticity’ or the ability of the fetus to respond to poor in-utero conditions [1]. A wealth of epidemiological evidence has provided a convincing link between a sub-optimal gestational environment and an increased propensity to develop adult onset metabolic disease [2,3]. Intrauterine growth restriction (IUGR) provides a useful model for examination of the developmental origins hypothesis and may result from perturbations in placental blood flow, poor maternal nutrition or maternal exposure to toxins [4–6].

To effectively manage IUGR infants postnatally and to minimize the adult consequences of poor prenatal growth, it is essential to understand the mechanisms by which a prenatal insult results in adult disease. This will facilitate interventions to identify a postnatal ‘window’ in which positive changes can be made and allow development of evidence-based assessments of the effects of specific macronutrients and micronutrients. This review will focus on recent

advances in understanding of the mechanisms by which the perinatal environment can have a lasting impact on adult phenotype.

Outcomes of intrauterine growth restriction

The development of adult morbidities as a result of IUGR is complex and involves multiple pathways and multiple organs. Generally speaking, the majority of morbidities associated with IUGR can be split into metabolic and nonmetabolic effects (Table 1 Table 1). The search for one specific organ or pathway that is disrupted by IUGR has been futile. Given the metabolic nature of the primary morbidities associated with IUGR, this is not surprising. Mammalian metabolism is a highly complex, finely choreographed interaction between many interconnected pathways and intermediates. IUGR affects many of these pathways and intermediates, and these effects are dependent on sex, the specific nature of the insult, the gestational timing of the insult and the rate of postnatal growth.

Metabolic effects of intrauterine growth restriction

Adult onset metabolic disturbances in IUGR individuals involve the adipose tissue, liver, β -cells kidney and vascular system. Disruption of lipid metabolism in the adipose tissue and liver contribute to dyslipidemia, fatty liver and obesity. Increased hepatic glucose production, β -cell dysfunction and impaired peripheral glucose uptake contribute to impaired glucose homeostasis in IUGR. Changes in structure and function of the kidney and vasculature contribute to hypertension and other cardiovascular morbidities. An important and interesting consideration is the impact of sex on the development of metabolic disease in IUGR, with men appearing to be more severely effected [7–10].

The prevalence of obesity, particularly visceral obesity, as an outcome of poor fetal growth is well documented [11–13] and can arise as a result of altered adipogenesis or increased energy intake or both. Increased visceral adiposity and increased visceral levels of pro-adipogenic transcription factors such as peroxisome proliferator activated receptor γ (PPAR γ) are seen as a result of lower birth weight in sheep regardless of whether the low birth weight is the result of IUGR [14*] or simply the result of natural population variation [15]. Increased visceral adiposity is also associated with the rate of postnatal growth in offspring that were previously growth restricted [16**,17]. Interestingly, minimizing postnatal growth in IUGR rat pups alleviates the obesity and metabolic consequences of IUGR [16**].

Impaired hepatic lipid regulation and the development of fatty liver are associated with the metabolic syndrome and altered plasma lipids. Maternal food restriction in rats produces IUGR offspring with smaller hepatic lobules and sex-specific alterations in hepatic lipid regulation. In male rats, IUGR increases hepatic triglyceride and cholesterol content, whereas in female rats, IUGR decreases hepatic cholesterol. In addition, male rats have increased hepatic expression of genes involved in lipogenesis as well as increased markers of inflammation [18,19].

The liver is also an important site for glucose homeostasis. Hepatic glucose production, along with β -cell function and insulin sensitivity are affected by IUGR and result in the insulin resistance and type 2 diabetes observed in IUGR adults [11,20–22]. Late gestational fetal hypoglycemia in sheep increases gluconeogenic enzymes and gluconeogenesis without a concomitant change in liver glycogen [23**]. Pancreatic β -cells are also structurally and functionally affected by IUGR, again with a sex-specific difference and men being more severely affected [24].

A propensity toward renal insufficiency and adult onset hypertension is also associated with IUGR and accompanied by altered renal development and reduced nephron number in IUGR

offspring [25,26]. These changes are associated with altered expression of renal transcription factors driving development [27], altered glucocorticoid signaling molecules [28] and increased apoptotic processes [29]. In an attempt to elucidate the cause of sex effects in IUGR, recent studies have examined the effect of estrogen and testosterone on hypertension and vascular dysfunction and shown that estrogen can be associated with a protective effect [30] and testosterone with a deleterious effect [31].

Nonmetabolic effects of intrauterine growth restriction

Structural changes in organs not directly associated with the metabolic syndrome are also induced by IUGR. Although not as well documented as the metabolic effects, IUGR also predisposes human infants to an increased risk of chronic lung disease (CLD) at birth [32–34]. Animal models of IUGR have shown that impaired lung development during late gestational fetal growth results in altered lung morphology at birth, consistent with that seen in CLD [35,36]. These changes are accompanied by decreased active p53, as well as decreased mRNA of other pro-apoptotic targets downstream of p53, and increased mRNA levels of Bcl-2, an antiapoptotic gene downregulated by p53 [36].

Finally, although the asymmetric nature of IUGR induced by late gestational insults was once considered to have a ‘brain-sparing’ effect, the brain is also affected both structurally and functionally by IUGR. In humans, MRI analysis of adolescents who were born preterm shows altered brain structure, with decreased caudate volume and a corresponding decrease in IQ scores [37]. Interestingly, this cohort can be separated into groups that received either a standard or high nutrient postnatal diet, with the infants receiving high-nutrient diet displaying improved cognitive performance at 18 months and at 7–8 years compared with those who received the standard-nutrient diet. The effect was particularly pronounced in male infants [38]. Although these studies address the nutrient content of the postnatal diet, others have examined the association of cognitive function and BMI with postnatal rate of growth in term IUGR infants. Rapid weight gain over the first 4 months postnatally after IUGR predicts both increased BMI and decreased cognitive scores at 7 years of age [39*]. It is important to note, however, that poor postnatal growth was also associated with decreased cognitive scores [39*].

These studies show that, on a molecular level, IUGR can affect tissue in two ways. First, IUGR can produce structural changes in tissue. This reflects early interruptions in developmental processes, particularly those involving apoptosis. Second, IUGR results in altered levels of homeostatic regulating factors and subsequent changes to intercellular and intracellular signaling. Both these phenomena result from alterations in gene expression that occur in response to IUGR. A key mechanistic concept arises from the observation that many of the changes in gene expression that are observed in the neonatal period persist into adulthood. These persistent changes in gene expression have lead investigators to deduce that epigenetics is an underlying mechanism in the developmental origins of disease.

Epigenetics

The information stored in the genetic material predicts the potential phenotype of an organism; it is, however, the transcription of that information that produces the phenotype. Transcriptional regulation can be provided in the short term by signal transduction and transcription factor activation or over the long term by epigenetics. The persistent nature of altered mRNA levels of key genes in IUGR suggests epigenetic regulation of gene transcription.

Epigenetics refers to heritable changes in gene transcription caused by mechanisms other than changes in the underlying DNA sequence. One of these mechanisms involves modifications to chromatin; the DNA and protein complex that forms the fundamental structure of chromosomes. The reversible epigenetic modifications include direct methylation of DNA as

well as a vast array of histone modifications that include acetylation and methylation [40]. In the context of chromatin, these modifications can be read collectively as an epigenetic 'profile' or 'code'. The epigenetic profile of chromatin regulates the transcription of genes by affecting DNA interactions with the transcription machinery and other regulatory moieties. In addition to the already well explored functions of epigenetics in imprinting and gene silencing, epigenetics provides a means of modulating gene transcription; that is, adjusting the level of expression of genes already being transcribed. This will elicit subtle modifications in the phenotype and provide the 'plasticity' necessary for the fetal genotype to respond in the face of IUGR.

IUGR is accompanied by changes in the quantity and activity of enzymes responsible for making modifications to chromatin. In the IUGR rat brain at birth, global decreases in DNA methylation and increases in histone 3 (H3) acetylation on lysine 9 (K9) and K14 are observed [41]. These changes are accompanied by a concomitant decrease in the DNA methyltransferase Dnmt1, the methyl-CpG binding protein MeCP2, and the histone deacetylase HDAC1 [41]. Interestingly, the modifications to chromatin in IUGR rat brains are sex dependent, with a divergence in global acetylation occurring at d21 when female brains continue to be characterized by increased site-specific acetylation, whereas male brains become characterized by decreased acetylation at K9 and K14 of H3 [41]. Liver chromatin modifications are also affected by IUGR with persistent increases in acetylation of H3K9 and K14 [42], as well as reduced hepatic expression of Dnmt1 [43]. IUGR is also associated with specific changes in the IUGR promoter histones of skeletal muscle GLUT4 and β -cell Pdx1 [44,45*]. Interestingly, modified histones are not only associated with limited fetal nutrition, a non-human primate model of maternal obesity also results in hyperacetylation of specific lysines of histone 3 and reduced mRNA, protein levels and activity of HDAC1 [46**].

The search for altered epigenetic phenomena in IUGR has shown that the modulation of transcription required for subtle adjustments may utilize the epigenetic profile in a slightly different manner than that used to produce absolute gene silencing or activation. In other words, once a gene is being expressed, IUGR appears to alter the epigenetic profile in a unique manner that results in a subtle adjustment to the level of transcription. This information is supported by studies that look at regions of the gene traditionally considered important for transcriptional regulation and studies that have examined the entire gene.

In studies examining the proximal promoter region of the homeobox 1 transcription factor, Pdx1, IUGR results in increasing methylation of CpG dinucleotides as the offspring age and this is accompanied by a decrease in the expression of Pdx1 mRNA. What is interesting in this study is that even though IUGR offspring have reduced Pdx1 transcription at birth and 2 weeks of age, the appearance of methylation in the promoter is not detectable until 6 months of age [45*,47]. Histone modifications in the region of the promoter are, however, present at birth and presumably precipitate the presence of promoter methylation in later life. The hepatic dual specificity phosphatase, DUSP5, gene is also affected by IUGR in an interesting manner. IUGR decreases mRNA levels of hepatic DUSP5 in conjunction with decreased methylation of five CpGs contained within exon 2 of DUSP5; this apparent paradox of decreased transcription being associated with decreased methylation is supported by evidence that downstream methylation may be involved in promoting transcription [48].

The subtle adjustments needed to ensure developmental plasticity in the context of a fixed genotype are provided by epigenetics. The progression of understanding of the role of epigenetics in the developmental origins hypothesis began with the observation that IUGR induced lasting changes in gene expression and that this was accompanied by changes in levels and activities of chromatin-modifying enzymes. This was followed by characterizations of changes in global DNA methylation and histone modifications. The examination of chromatin

associated with specific key genes is now yielding a wealth of information about IUGR-induced modifications to chromatin. The next step is to understand how IUGR results in these changes and to interpret the language of the chromatin modifications. This will require detailed analysis of entire genes in the context of multiple models of IUGR and in multiple tissues.

Conclusion

The consequences of poor in-utero growth are relatively constant. Although the details may vary, depending on the timing and severity of insult, the overall mechanism appears to involve epigenetic modifications to chromatin associated with critical genes. The developmental origins field is in an exciting time with studies now beginning to characterize changes to the epigenetic profile of chromatin in response to IUGR. This should be followed by identification of the environmental and nutritional signals that result in these changes. Translating the messages of the epigenetic profile and identifying the players that mediate effects remains one of the major challenges in understanding the manner in which epigenetics link a perinatal insult to an adult phenotype. Such an understanding will facilitate identification of dietary and pharmaceutical approaches that can be applied in the postnatal period.

Acknowledgement

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Table 1

Adult phenotypes of intrauterine growth restriction

Metabolic	Nonmetabolic
Dyslipidemia	Attention deficit disorder
Hypertension	Chronic lung disease
Insulin resistance	Immunodeficiency
Poor postnatal growth	Neurodevelopmental delay
Renal insufficiency	Schizophrenia