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REVIEW ARTICLE

Mechanisms involved in the developmental programming of adulthood disease

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There are many instances in life when the environment plays a critical role in the health outcomes of an individual, yet none more so than those experienced in fetal and neonatal life. One of the most detrimental environmental problems encountered during this critical growth period are changes in nutrition to the growing fetus and newborn. Disturbances in the supply of nutrients and oxygen to the fetus can not only lead to adverse fetal growth patterns, but they have also been associated with the development of features of metabolic syndrome in adult life. This fetal response has been termed developmental programming or the developmental origins of health and disease. The present review focuses on the epidemiological studies that identified this association and the importance that animal models have played in studying this concept. We also address the potential mechanisms that may underpin the developmental programming of future disease. It also highlights (i) how developmental plasticity, although beneficial for short-term survival, can subsequently programme glucose intolerance and insulin resistance in adult life by eliciting changes in key organ structures and the epigenome, and (ii) how aberrant mitochondrial function can potentially lead to the development of Type 2 diabetes and other features of metabolic syndrome.

Key words: early growth, maternal diet, thrifty phenotype hypothesis, Type 2 diabetes.

INTRODUCTION

Growth and development *in utero* is a complex and dynamic process, requiring interacting components from the mother and fetus in order to sustain optimal growth and survival throughout pregnancy. Governed by its own genetic constitution, the growth trajectory of the fetus can only be met if maternal nutrition and placental function are sufficient to maintain high rates of proliferation, growth and differentiation. Depending upon the complex interactions between the mother, placenta and fetus, the supply of macro- and micro-nutrients, oxygen and endocrine signals are critical in this early phase of life. Disturbances in the supply of these necessary components impact not only on the growth of the fetus, but also, as current evidence suggests, can have adverse consequences on the future health of the offspring. As substantiated by a large body of epidemiological evidence, it is now evident that diseases traditionally perceived as influenced by adverse adult environmental lifestyles, such as Type 2 diabetes, obesity, hypertension and CVD (cardiovascular disease), can be 'programmed' early in life and that low birthweight, a crude marker of disturbed fetal growth, strongly associates with features of metabolic syndrome [1].

DEVELOPMENTAL PROGRAMMING: SUPPORTING EPIDEMIOLOGY AND HYPOTHESES

The terms 'developmental origins of health and disease' or 'developmental programming' reflect a scenario whereby a stimulus or insult during a critical period of growth and development, has entrained long-term developmental and physiological changes in key tissues or organ systems [2]. Although the concept of programming had been suggested prior to the work of Barker and colleagues, it was their epidemiological studies in the U.K. in the late 1980s that led to the proposal that events in fetal life could influence long-term risk of metabolic disease. Using a cohort of 64-year-old men, they identified an inverse relationship between systolic blood pressure and increased cardiovascular mortality and birthweight [3,4]. Using the same cohort of men, Hales et al. [5] demonstrated a similar inverse link between birthweight and glucose tolerance and insulin resistance. They demonstrated that the individuals with the lowest birthweights were 6-fold more likely to develop Type 2 diabetes or impaired glucose tolerance when compared with those who were heavier at birth. These findings have now been replicated in a variety of populations with differing ethnicities [1]. On the basis of these observations, Hales and Barker [6] proposed the 'thrifty phenotype hypothesis' to explain how fetal malnutrition sets in motion a series of physiological and/or metabolic adaptations to maximize chances of survival in conditions of poor postnatal nutrition. This includes sparing the development of vital organs (such as the brain) at the expense of other tissues and organs, such as the endocrine pancreas. In addition, it suggests that poor intrauterine nutrition would impact upon and permanently alter (or 'programme') whole-body metabolism, promoting storage of fat within the individual. Although beneficial for the offspring if it were to be born into and exposed to a poor postnatal nutritional

Abbreviations used: Agtr1b, angiotensin receptor, type 1b; ARC, arcuate nucleus; A^{vy}, Agouti viable yellow allele; CRH, corticotropin-releasing hormone; CVD, cardiovascular disease; GDM, gestational diabetes mellitus; GLUT, glucose transporter; GR, glucocorticoid receptor; 11β-HSD2, 11β-hydroxysteroid dehydrogenase 2; IGF, insulin-like growth factor; IRS, insulin receptor substrate; IUGR, intrauterine growth restriction; LGA, large-for-gestational-age; Pdx-1, pancreatic duodenal homeobox-1; PI3K, phosphoinositide 3-kinase; PKC, protein kinase C; PVN, paraventricular nucleus; RAS, renin–angiotensin system; RNS, reactive nitrogen species; ROS, reactive oxygen species; SGA, small-for-gestational-age.

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environment, these physiological and metabolic changes would become maladaptive if it were to be exposed to a nutritionally rich postnatal environment [6].

The thrifty phenotype hypothesis has been supported by a number of human studies. Some of the most convincing evidence that a poor intrauterine environment, restricted fetal growth and increased adulthood disease risk are linked has come from studies of twins and individuals *in utero* during periods of famine [7,8]. In a study of middle-aged monozygotic and dizygotic twins from Denmark, who were discordant for Type 2 diabetes, it was revealed that the twin with Type 2 diabetes had a significantly lower birthweight when compared with their euglycaemic co-twin [7]. Following that study, similar findings were established in a younger population of twins from Italy [9]. The study of monozygotic twins in particular, given twins share the same genetic constitution, has demonstrated the importance of the intrauterine environment in the association between low birthweight and later development of Type 2 diabetes, by clarifying that this association was independent of the genotype of the offspring [10]. Further support for the thrifty phenotype hypothesis came from a study of individuals who were exposed to the short-term famine encountered in Holland between 1944 and 1945. During this famine, individuals were restricted to a daily calorific intake of 450–750 kcal (1 cal≈4.184 J); half the amount they had previously been receiving throughout World War II. Studying these 'children of the Dutch hunger winter' revealed that individuals who were *in utero* during the famine, when compared with those *in utero* the year before or after, demonstrated lower birthweights and impaired glucose tolerance by 50 years of age [8]. A similar study, conducted a year earlier, in individuals exposed to a famine during the siege of Leningrad, observed no relationship between early famine and later glucose tolerance [11]. However, it should be noted that the period of famine was longer than that experienced during the Dutch hunger winter and thus results may be confounded by a beneficial effect of reduced nutrition in early postnatal life (see below). Furthermore, this study only included 37 men within the malnourished group, and thus may lack statistical power [11].

In addition to the role of suboptimal nutrition *in utero* and perturbed fetal growth in the predisposition to adult disease, studies have also drawn attention to the significance of postnatal nutrition in this relationship; another critical component of the thrifty phenotype hypothesis. In both the Hertfordshire [5] and Dutch hunger winter studies [8], the individuals with the worst glucose tolerances were those who were born small and became obese as adults. More recently it has become apparent that growth in early postnatal life is also critical in the programming of metabolic disease [12–17]. A study by Crowther et al. [12] demonstrated, in a cohort of 7-year-old South African children, that those who had been born with a low birthweight and underwent rapid postnatal weight gain were most likely to develop Type 2 diabetes in adulthood as they had the poorest glucose tolerances. This evidence was later corroborated in two different populations in Finland [13] and India [14]. It is now evident that early growth restriction followed by accelerated postnatal growth also influences the risk of developing hypertension and coronary heart disease in adulthood [15–18]. The period in which accelerated postnatal growth can programme metabolic disorders still receives much deliberation, with some studies highlighting the immediate postnatal period [19] and others considering the first few years of growth as being vital for this relationship [20].

Obesity plays a critical role in the association between low birthweight, early childhood growth and adult disease [21–23]. However, the question that still remains is whether obesity is a manifestation of the intrauterine programmed changes, or if obesity itself engenders the expression of the thrifty phenotype. Several studies now suggest that catch-up growth is achieved through higher rates of weight gain in fat tissue than lean mass [22,24]. Termed 'catch-up fat', this phenotype has been observed in several cohorts of children born SGA (small-for-gestational-age) [25,26] and it has also been demonstrated that growth-restricted infants disproportionately deposit fat in the visceral stores rather that in subcutaneous depots [27,28]. In addition to this phenomenon, studies have also shown that maternal overnutrition and being born LGA (large-for-gestational-age) can also have detrimental health outcomes for the offspring. Common in pregnancies complicated by maternal obesity and/or GDM (gestational diabetes mellitus), not only do these LGA offspring demonstrate increased adiposity at birth, they are also at increased risk of developing features of metabolic syndrome [29–32]. Having originally identified low birthweight as a risk factor for metabolic syndrome, it is now evident that a U-shaped relationship exists between birthweight and increased risks of developing metabolic disorders later in life [33,34]. Although these studies have led to the expansion of the developmental origins of health and disease to include the role of early overnutrition, more significantly, they reiterate the importance of the early intrauterine environment on fetal growth and future risk of developing adulthood diseases. Very little mechanistically can be determined from these human studies; therefore in order to progress and identify the underlying mechanisms that mediate the association between the perturbed fetal environment and future disease, experimental animal models have been developed.

ANIMAL MODELS

Animal models have provided an invaluable resource in the elucidation of the mechanisms and outcomes elicited during developmental programming as not only can the conditions to which the fetuses are exposed be controlled, but also tissue sampling from the mother, fetus or offspring can be performed during any stages of the exposure. Many studies have been conducted in larger species, such as sheep [35,36], pigs [37,38] and non-human primates [39,40]; however, most animal studies use rodent models because of their shorter gestation and life-span. Using a variety of nutritional, surgical and pharmacological paradigms to challenge the growing fetus and newborn (Figure 1), we will now highlight the rodent models that have enabled investigators to study the developmental programming phenomenon and review the evidence for potential mechanisms involved in the relationship between perturbed fetal growth and adulthood disease.

Nutritional models: maternal undernutrition

Maternal calorie restriction

A number of animal studies utilizing global nutrient restriction in the fetal programming of adulthood disease have been reported. Not only have reductions in total food intake been documented as eliciting endocrine and metabolic abnormalities in rodent offspring, they also support the notion that the timing of nutrient restriction during gestation is critical in the programming of these disorders. Restrictions to 50% *ad libitum* in the last week of rat pregnancy results in low birthweight offspring with decreased pancreatic β-cell mass. Although these animals can regain their body and pancreatic weights upon normal feeding postnatally, they still demonstrate a reduced β-cell mass and insulin content in adulthood [41,42]. Extending this level

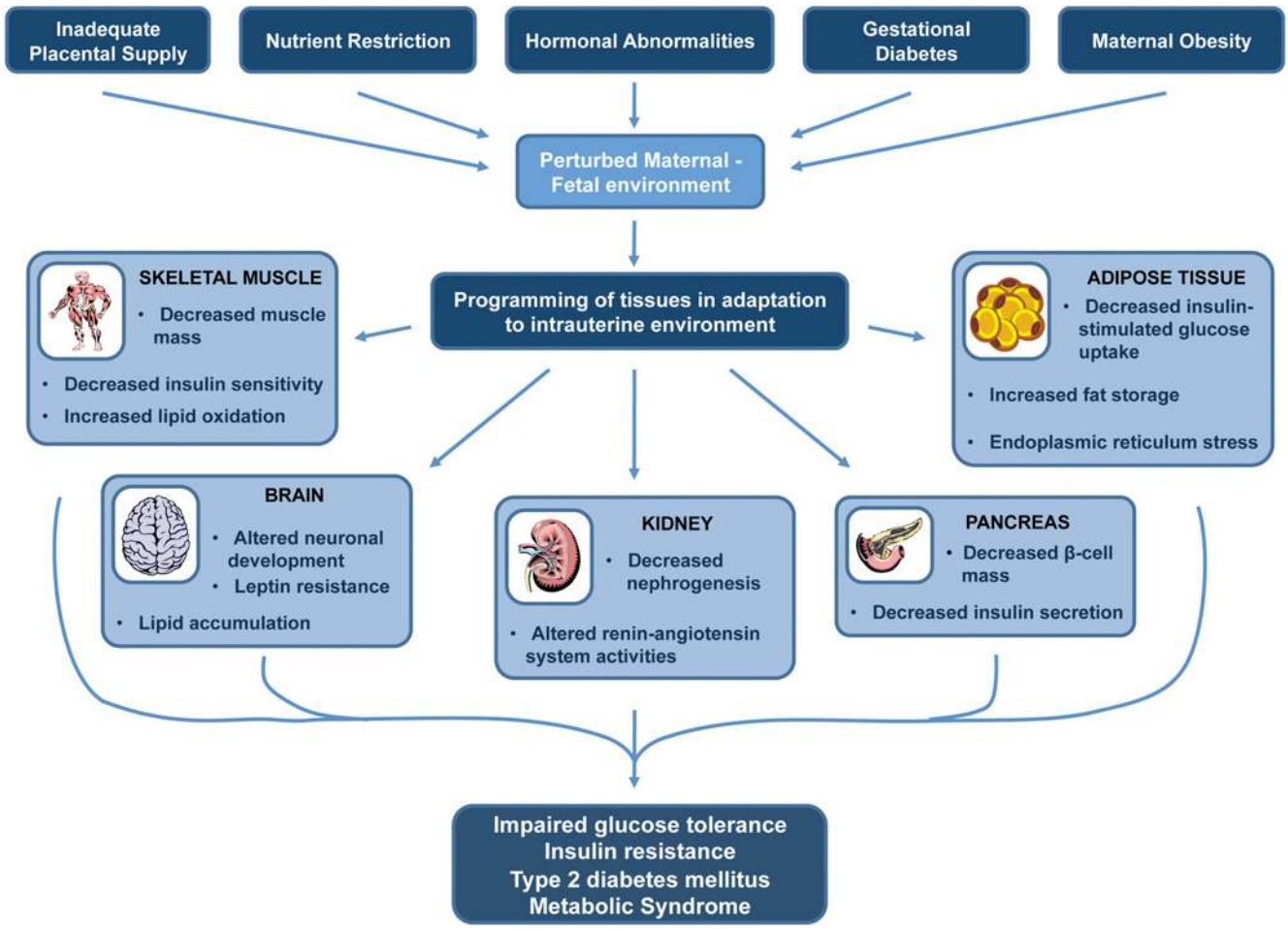

Figure 1 Summary of the structural and molecular adaptations made during the intrauterine programming of metabolic disease

A schematic representation of how a perturbed intrauterine environment, induced by a variety of physiological disturbances in animal models, can elicit changes in the structure and function of multiple organs, subsequently leading to the development of features of metabolic syndrome.

of nutrient restriction during suckling results in a permanent reduction of β-cell mass [43] and subsequent age-dependent loss of glucose tolerance in the offspring [44]. More severe reductions in food intake in dams (30 % *ad libitum*) results in growth-restricted offspring that demonstrate hyperphagia in adult life, and also develop hyperinsulinaemia, hypertension, hyperleptinaemia and obesity [45]. Administration of IGF1 (insulin-like growth factor 1), a potent anabolic hormone involved in fetal growth, in the offspring of malnourished dams alleviated the hyperphagic behaviour and obesity, while also normalizing blood pressure and reducing plasma insulin and leptin levels [46]. Similar findings were later demonstrated in these same offspring upon treatment of newborns with leptin [47]. More recently, a pilot study using nutrient-restricted dams (50 % *ad libitum*) revealed that not only were the offspring born lighter, but at 1 month of age, offspring already demonstrated reduced adiponectin and increased resistin concentrations; a pattern normally associated with the development of insulin resistance [48].

Maternal protein restriction

Many studies have shown that amino acids are key to fetal growth. Not only are these molecules beneficial, acting as substrates for the building of cellular proteins or precursors for hormones and other signalling molecules (e.g. nitric oxide and thyroid hormones), they can also be detrimental, as high concentrations of amino acids and their derivatives can act as pathogenic factors in oxidative stress and CVD (reviewed in [49]). The thrifty phenotype hypothesis postulated a key role for the supply of proteins [6] (although it did not exclude other nutritional deficits), thus a rodent maternal protein restriction model has been one of the most extensively studied models of IUGR (intrauterine growth restriction). Developed by Snoeck and colleagues [50,51], the low-protein-fed (5–8 %) dams give birth to growth-restricted offspring [50–54] and when suckled by the same low-protein-fed dams during lactation, they remain permanently growth-restricted, despite being weaned on to a control (20 % protein) diet [53]. This dietary manipulation recapitulates the levels of protein nutrition observed within developing countries, whereby economic and poor social-economic status limits the amount of protein consumed (reviewed in [55]). The physiological relevance of this model is supported further by the fact that reductions in placental weights, and endocrine and metabolic abnormalities, are also observed [51,56,57]. Despite young offspring (6 weeks to 3 months) of low-protein-fed dams demonstrating improved glucose tolerance [57,58], the male offspring in this model undergo an age-dependent loss in glucose tolerance, such that by 15 months of age they have impaired glucose tolerance, and

by 17 months of age they develop Type 2 diabetes and insulin resistance [59]. Female offspring only develop hyperinsulinaemia and impaired glucose tolerance at a much later age (21 months) [54]. Studies in this model have also demonstrated reductions in pancreatic β-cell mass [50], skeletal muscle mass [53], central adipose deposit weights [58,60] and metabolic changes in several insulin-sensitive tissues [60–62]. This IUGR model has also been associated with the development of hypertension and has potentially implicated the kidney and the RAS (renin–angiotensin system) as playing a role [63].

Maternal iron insufficiency

Iron-deficiency anaemia is a common problem encountered in pregnancy and is recognized as a significant risk factor for both the mother and fetus during gestation. Demonstrating a U-shaped relationship between maternal haemoglobin concentrations and birthweight [64], studies have identified that maternal anaemia results in complications in placental vascularization and deregulation of maternal and fetal hormones, including CRH (corticotropin-releasing hormone) and IGF1. Release of CRH can induce preterm labour and pre-eclampsia in the mother and subsequently inhibit the production of IGF1, potentially impacting on fetal development (reviewed in [64,65]). Using a rodent model of maternal iron restriction, not only were reductions in birthweight observed, but increases in blood pressure were also seen in the offspring from as early as 10 weeks of age [66–68]. These physiological and metabolic changes could be attributed to deficits in kidney nephron number [69] and also reduced hepatic expression of genes involved in bile/fatty acid synthesis [70]. Although no effects on glucose tolerance were observed by 14 months of age, having previously witnessed improved glucose tolerance in offspring of maternal iron-restricted dams at 3 months of age, it was suggested that these animals demonstrated an increased loss in glucose tolerance between these two time points [67,68].

Nutritional models: maternal overnutrition

Although the majority of animal models have addressed the undernutrition aspect, there are a growing number of studies that address the role of maternal overnutrition. Initial studies used models of high-fat feeding.

Maternal high-fat feeding

Prenatal overnutrition and changes in dietary fat intake during pregnancy have been demonstrated to increase the risk of developing Type 2 diabetes and CVD later in life [30,71]. Offspring of rat dams fed diets high in fat during pregnancy have been demonstrated to develop abnormal cholesterol [72] and lipid metabolism [73], hyperinsulinaemia [73,74], insulin resistance [74] and to have an increased risk of developing hypertension and CVD [75–78]. Howie et al. [79] revealed that offspring of rat dams fed a high-fat diet throughout their life were not dissimilar to offspring born from dams fed a high-fat diet only during pregnancy and lactation. When compared with offspring from control dams, the high-fat *in utero* offspring became obese in adulthood, and demonstrated hyperleptinaemia and hyperinsulinaemia, implying that a high-fat diet during pregnancy and lactation alone was sufficient to increase the risk of developing obesity in adulthood.

Maternal obesity

With the increased prevalence of maternal obesity in Westernized civilizations and the knowledge that this condition can be transferred through the generations [80], animal models of maternal obesity are now being used to investigate the mechanisms by which this propensity for adiposity and features of the metabolic syndrome are transferred in the offspring and into adulthood. In a study by Samuelsson et al. [81], offspring born to obese mouse mothers not only demonstrated an increased fat-to-lean-mass ratio and hyperphagic behaviour, they were also insulin resistant at 3 months of age, and by 6 months of age the male offspring had developed impaired glucose tolerance. This study also demonstrated that maternal obesity could predispose offspring to CVD, as these animals were hypertensive and showed signs of endothelial cell dysfunction. Nivoit et al. [82] demonstrated a similar phenotype in rat offspring from obese dams. Animals of both genders were found to develop a metabolic-syndrome-like phenotype, with increased adiposity, yet only male offspring demonstrated insulin resistance and poor glucose tolerance in comparison with the control offspring. These results have been corroborated by a number of different studies, documenting alterations in leptin levels and hyperphagic behaviour [83,84], insulin resistance [85] and also risks of developing CVD in adult offspring of obese dams [86].

Surgical models

Intrauterine arterial ligation

Uteroplacental insufficiency in humans is one of the most common causes of IUGR in Westernized societies [87] and is caused by abnormalities in placental development, maternal smoking and pre-eclampsia. Placental insufficiency results in a deprived fetal environment and subsequently low birthweight offspring who are predisposed to adult disease later in life [87,88]. A rat model pioneered by Wigglesworth [89] utilizes unilateral and bilateral uterine artery ligation to induce the perturbed intrauterine environment and asymmetric IUGR. Studies in the fetuses from these rats revealed that they were hypoxic, hypoglycaemic and showed reductions in fetal insulin and IGF1 [90]. Demonstrating many similarities with the human condition [90,91], studies in this model have shown that IUGR via uteroplacental insufficiency results in perturbations in the development of the pancreas [91,92], kidney [93] and liver [94], and also insulin resistance and insulin secretory defects early in life, and subsequently Type 2 diabetes [94,95] and a gender-specific development of hypertension in later life [96].

Pharmacological models

Diabetes during pregnancy

GDM is known to pose a serious health risk to both the mother and fetus [97,98] and is caused by either pre-gestational diabetes or the development of glucose intolerance during pregnancy. GDM can result in the birth of either a macrosomic or growth-restricted offspring depending on the severity of the maternal diabetes. Investigators have utilized the pharmacological agent, STZ (streptozotocin) to recapitulate maternal diabetes and demonstrated altered pancreatic development and increased risk of developing Type 2 diabetes in both fetal growth outcomes (reviewed in [99]). Mild induction of GDM during pregnancy resulted in offspring with fetal hyperinsulinaemia and impaired glucose tolerance and higher birthweights [100,101]. Conversely, exposure to severe maternal diabetes during pregnancy resulted

in growth-restricted offspring with fetal hyperglycaemia and hypoinsulinaemia [102,103]. With these data sets clearly indicating the similarities that this model shares with the human situation, these studies signify the importance of maternal glycaemia on fetal pancreas development during this period.

Glucocorticoid exposure

During early gestation, the fetus develops relatively free from glucocorticoid exposure as those of maternal origin become inactivated due to the actions of placental 11β-HSD2 (11β-hydroxysteroid dehydrogenase 2). Upon the activation of the fetal adrenal gland in late gestation [104,105], glucocorticoid synthesis increases and stimulates many fetal tissues to mature in preparation for postnatal life (reviewed in [106]). Given this importance in fetal maturation, it has become increasingly evident that fetal overexposure to maternal glucocorticoids, whether endogenous or exogenous, can result in IUGR in both humans and animals [107,108]. Mimicking this scenario through the administration of synthetic compounds, such as dexamethasone, or inhibitors of 11β-HSD2, such as carbenoxolone, investigators have replicated IUGR across multiple animal species, identifying multiple organs and tissues that can be affected through increases in maternal glucocorticoid exposure (reviewed in [109]). Studies in rodents have revealed that not only is the timing of the insult (increased glucocorticoids) critical during the development of the fetus, overexposure to glucocorticoids in pregnancy (especially during last third of gestation) can increase the offspring's risk of developing glucose intolerance, insulin resistance and hypertension [110–112]. In light of the vital role glucocorticoids play in fetal development and their effect on fetal growth, several studies addressed the possibility that increased exposure to glucocorticoids may mediate the programming effects of maternal undernutrition. Maternal protein restriction and maternal calorie restriction have both been demonstrated to result in fetal overexposure to glucocorticoids [113,114]. However, it should be noted that maternal exposure to dexamethasone, a synthetic glucocorticoid, can result in reduced maternal food intake [115,116], and some models of maternal undernutrition do not influence fetal glucocorticoid levels [117].

Despite the complex nature of these associated metabolic disorders, animal models of IUGR and fetal overgrowth are now beginning to highlight several key mechanisms underlying the developmental programming of adulthood disease. Although the methods employed in generating animal models of IUGR and fetal growth differ, they undoubtedly demonstrate that perturbations in the maternal–fetal environment can have significant consequences for the offspring in adult life (Figure 1).

MECHANISMS INVOLVED DURING DEVELOPMENTAL PROGRAMMING

Utilizing animal models of perturbed fetal growth, investigators have not only been able to focus on both the structural and functional changes observed in tissues and organs key to the development of metabolic disorders, but they have also been able to examine the molecular mechanisms underlying the development of these pathophysiological conditions. Although the structural and gene expression changes are interrelated, as development proceeds and critical windows of fetal organogenesis are passed, the flexibility to change organ structures and their subsequent homoeostatic functions becomes more limited. However, changes in gene expression can persist throughout life, both as a consequence of the remodelling of fetal and neonatal tissues and organ systems, and in response to the early and late postnatal environment.

Structural changes

During development, multiple phases of cell proliferation and differentiation have to occur in order to generate the large array of organs and tissues required for postnatal life. Following gastrulation and the generation of the three germ layers, organogenesis begins and allows progenitor cells to further differentiate and proliferate. With various organs and tissues forming during different periods of gestation and early postnatal life (reviewed in [118]), if a nutritional or hormonal challenge were to occur during these critical periods, this may result in the failure of a particular developmental process. If this process was not able to occur subsequently, this would have a profound effect on the numbers and types of cells within the tissue and impact on its structure and function in later life [119]. Studies in the animal models described above have identified changes in the anatomical structures of the brain, kidney and the pancreas.

Brain

With the current obesity epidemic in many affluent nations, much attention has been focused on elucidating the mechanisms that control energy homoeostasis and appetite control. As obesity results as a consequence of excess food intake in relation to energy expenditure, many studies on monogenic forms of severe obesity have shown that defects in appetite control mediate excess food intake (reviewed in [120]). Although insulin was the first peripheral circulating factor to be identified in the control of body weight by the central nervous system, a large amount of our understanding regarding how the brain controls energy homoeostasis comes from the work with the hormone leptin and its action on the ARC (arcuate nucleus) of the hypothalamus (reviewed in [121]). In 1953, Kennedy [122] proposed that a fat-derived factor signalled to the brain to report on the fat stores and subsequently control food intake. Studies in the hypothalamus have now revealed a complex neurological circuitry that responds to a variety of hormonal and nutritional signals [123]. Not only are these signals critical for the maintenance of energy homoeostasis in adult life, it is now evident that hormones, such as leptin, are vital in the development of the hypothalamic circuitry during early life.

At birth in rodents, this central system is in an immature state as the projections from the ARC do not reach their targets until the second week of life [124]. During this period, a surge in leptin production occurs, stimulating neurite extension from the ARC towards the PVN (paraventricular nucleus), LHA (lateral/perifornical hypothalamic area) and the DMH (dorsomedial nuclei) of the hypothalamus [125], i.e. the other hypothalamic structures involved in the regulation of food intake. Highlighting the neurotrophic action of leptin on the hypothalamus during suckling, several studies have now indicated that nutrition in pregnancy and in early life can affect this central axis of appetite control. Perinatal overnutrition in rodents via reductions in litter sizes following birth results in alterations in these key hypothalamic structures (ARC and PVN), as well as hyperphagia, hyperinsulinaemia and obesity [126,127]. Several studies have also shown that maternal undernutrition can either reduce the amplitude of the leptin surge [128] or result in a premature leptin surge and this subsequently impacts on the development of the ARC projections [129]. The critical timing of the leptin surge was addressed further by Yura et al. [129] who showed that mimicking this premature surge of leptin in animals

born from control dams resulted in offspring demonstrating accelerated weight gain and increased adiposity. This was later corroborated in a study demonstrating hyperphagia and leptin resistance in normal offspring given subcutaneous injections of leptin in early postnatal life [130].

These studies clearly demonstrate that a critical window of hypothalamic development exists in rodents and that perturbed nutrition during the first 2 weeks of life can impact on the development of the hypothalamus and the control of energy homoeostasis in the offspring. This may also be true in humans, as although development of the hypothalamus occurs *in utero*, and leptin expression begins after 19 weeks of gestation [131], cord leptin levels have been found to be reduced in SGA newborns [23].

Kidney

Owing to its role in regulating arterial blood pressure within the body [132], the kidney has long been studied in the aetiology of hypertension and CVD. Reduction in the numbers of nephrons was believed to lead to the development of hypertension and renal disease by causing an imbalance between excretory load and excretory capacity in the kidney [133]. Although the mechanism(s) underlying the relationship between nephron number and adult disease may be more complex than originally thought [134,135], numerous studies in animal models (and humans) have revealed that perturbations in the intrauterine environment and subsequent IUGR can result in decreased nephrogenesis (reviewed in [135]). Whereas the postnatal kidney can accommodate the reduction in nephron number through hyperplasia of the remaining nephrons and increasing the glomerular filtration rate, studies have revealed that nephropenia following IUGR can still confer an increased propensity to develop hypertension in adulthood by eliciting other disadvantageous consequences for the remaining nephrons [136–138]. This has been further supported by studies of rodents that were surgically uninephrectomized at a young age, which demonstrated signs of glomerular injury [139,140] and developed hypertension in adult life [141]. Although decreased nephrogenesis may not be the sole factor responsible for the generation of the hypertensive phenotype, it may contribute to its development [135,142]. These processes may potentially be compounded by catch-up growth, and the programming of the RAS in growth-restricted offspring, and may all co-ordinately work together in the development of hypertension in the adult [135]. Placental insufficiency, maternal protein restriction, glucocorticoid exposure and high-fat feeding *in utero* are all known to impact on the regulation of the RAS [63,77,143–145].

Endocrine pancreas

Development of the pancreas begins within the endoderm, wherein a small population of multipotent endodermal progenitor cells begins to proliferate and differentiate into the acinar and endocrine cell lineages (reviewed in [146,147]). As the β-cells differentiate from the pancreatic progenitor cells, rapid increases in β-cell mass are observed within the late fetal period in rodents [148]. Following this, and at birth, the newborn undergoes pancreatic remodelling and maturation, resetting the numbers of β-cells within the tissue [146]. Although there is some disparity between human and rodent pancreatic maturation, whereby fully functioning β-cells are attained by the end of the first trimester in humans [149], compared with them being acquired in early postnatal life in rodents [150], studies have demonstrated that the β-cell mass expansion slows down considerably in adulthood [151]. Having identified that islet mass can only be maintained through self-replication of already differentiated β-cells [152], if any *in utero* or postnatal challenge were to be encountered during these critical windows of pancreatic development, not only would it affect the proliferation and/or differentiation of the progenitor cells, but could also impact on both the early growth of the pancreas and the regenerative capacity of this tissue in adulthood [153].

Early studies in the maternal protein restriction model revealed that protein restriction *in utero* resulted in a decreased β-cell mass, accompanied by reduced pancreatic vascularization, and insulin content and secretion in offspring [50,51,154]. It has also been documented that if protein restriction is applied during the last week of pregnancy, greater reductions in β-cell mass can be observed [155]. Upon further investigation, islets from the maternal-protein-restricted offspring were found to have a lengthened cell cycle, with a longer G_1-phase and increased levels of apoptosis [156]. The maternal calorie restriction model also demonstrated a decrease in β-cell mass; however, in contrast with the above phenotype, this was not attributed to increased rates of apoptosis, but rather to altered β-cell neogenesis [41]. It was later demonstrated that if maternal calorie restriction was extended to weaning, this significantly stunted β-cell growth in the offspring [44]. Upon being weaned on to a control diet, these animals demonstrated only a partial recovery of β-cell mass by 3 months of age, whereas those animals nursed by control mothers following malnourishment *in utero* demonstrated catch-up growth of β-cell mass so that, by 3 months of age, they were identical or larger than control animals. However, as the animals aged, neither of the malnourished groups (fetal and early postnatal, or fetal only) demonstrated increased β-cell mass when compared with the control animals, highlighting the impact intrauterine calorie restriction has on β-cell growth in adult animals. This impaired growth of the endocrine pancreas led to the development of hyperglycaemia and impaired glucose tolerance with insulinopenia in the animals that were calorie-restricted until weaning, and an increased fasting glycaemia in those only restricted during gestation [44].

Reductions in β-cell mass have also been observed in the intrauterine arterial ligation model [92,95]. However, there are some differences between these two studies as Styrud et al. [92] reported that IUGR led to a 35–40 % reduction in β-cell mass and insulin content in the offspring, whereas Simmons et al. [95] documented that their growth-restricted offspring showed no decreases in β-cell mass and islet size at 1 week of age and that these reductions were only evident in adulthood (demonstrated by an age-dependent decline in β-cell mass and glucose tolerance). These discrepancies may be accounted for by the differences in how IUGR was implemented, the duration of the nutrient restriction and when the animals were investigated.

Although it is still debated whether perturbations in the maternal–fetal environment, and the resultant IUGR, are mediated by changes in the levels of glucocorticoids, studies have revealed that excess glucocorticoids can have adverse consequences on the fetal pancreas [157–159]. Using a model of maternal calorie restriction, it was shown that there was a negative correlation between glucocorticoid levels and β-cell mass [157]. In addition, glucocorticoids are known to influence the expression of genes important for generating the endocrine pancreas [158,159].

Cellular and molecular changes in metabolism and gene expression

Although the studies mentioned above clearly demonstrate that a perturbed intrauterine and/or early postnatal environment can

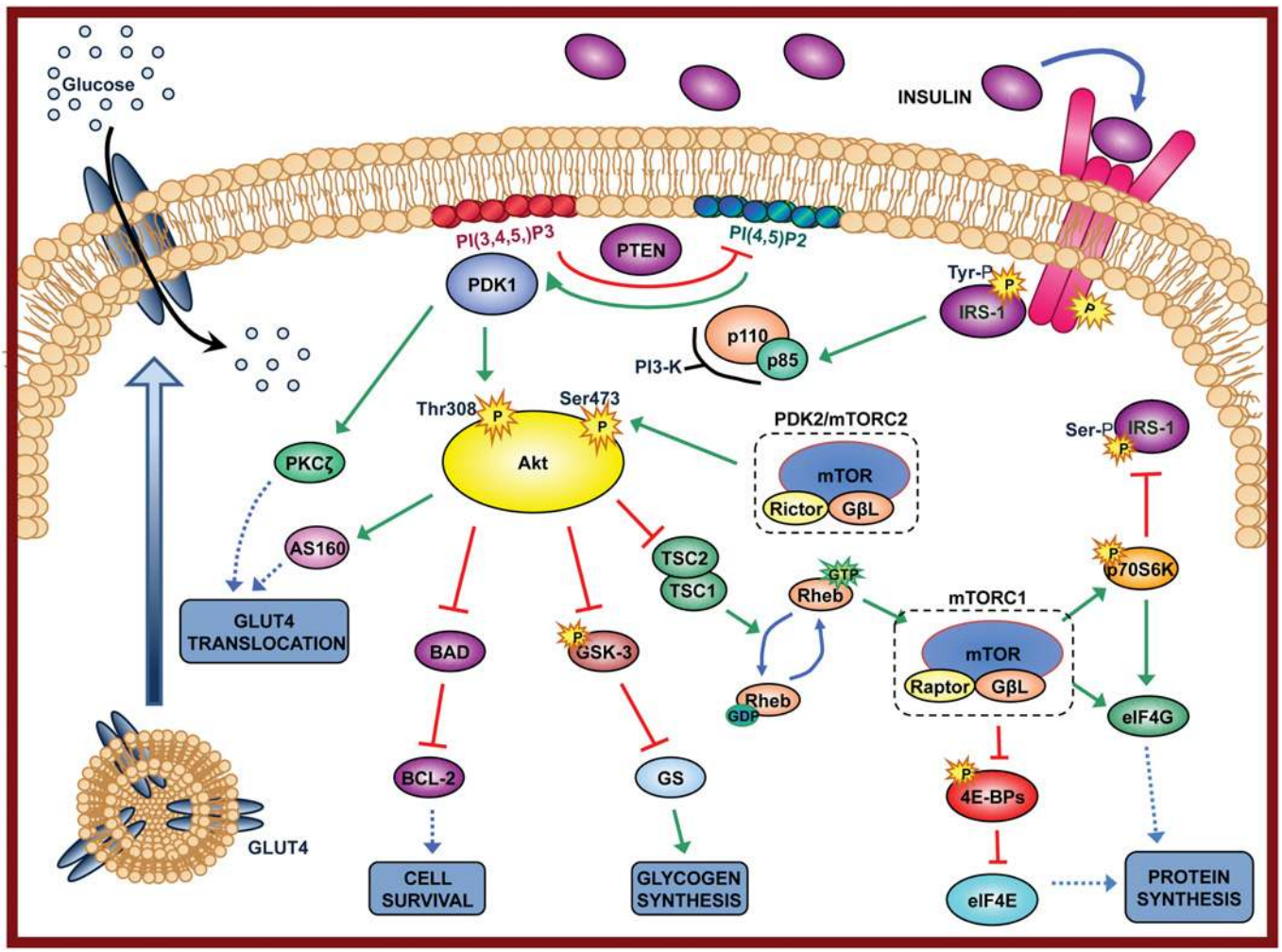

Figure 2 Metabolic actions of insulin signalling

Propagation of the signal from the insulin receptor begins with its own autophosphorylation, followed by the tyrosine phosphorylation (Tyr-P) of the IRS proteins. This results in the activation of PI3K, converting PIP_2 (phosphatidylinositol 4,5-bisphosphate) into the second messenger PIP_3 (phosphatidylinositol 3,4,5-trisphosphate), a process which can be attenuated by the actions of the PTEN (phosphatase and tensin homologue deleted on chromosome 10) phosphatase. Increased levels of PIP_3 activate PDK1 (phosphoinositide-dependent kinase 1), followed by activation of Akt/PKB (protein kinase B). Activation of PDK2 following this step further phosphorylates Akt at residue Ser^{473}, fully activating this kinase. Downstream of Akt, multiple intracellular signalling pathways are activated in order to mediate all of the processes that insulin controls. Several of these processes have been highlighted, most importantly the translocation of GLUT4 containing vesicles to the plasma membrane, stimulation of protein synthesis through the actions of mTORC1 [mTOR (mammalian target of rapamycin) complex 1], and the subsequent negative-feedback loop mediated by the downstream effector of mTOR, p70S6K/S6K1 (ribosomal protein S6 kinase 1). BAD, Bcl-2/Bcl-X_L-antagonist, causing cell death; 4E-BP, eIF4-binding protein; eIF, elongation initiation factor; GS, glycogen synthase; GSK-3, glycogen synthase kinase 3; Raptor, regulatory associated protein of mTOR; Rictor, rapamycin-insensitive companion of mTOR; TSC, tuberous sclerosis complex.

have adverse consequences on the structural properties of organs, these adaptations will also impact on gene expression.

Gene expression changes following a perturbed intrauterine environment

Insulin resistance is a central component in many of the phenotypes observed in models of IUGR and human studies. Insulin acts upon a variety of tissues within the body; however, those of particular interest are the skeletal muscle, liver and adipose tissue, as these are the primary sites of insulin action for regulating glucose homoeostasis. As shown schematically in Figure 2, insulin is known to mediate a multitude of cellular events following its release from the endocrine pancreas; most importantly the translocation of vesicles containing the facilitative GLUT4 (glucose transporter 4) protein in the adipose tissue and skeletal muscle. The dynamics of vesicle translocation, fusion and recycling are all important processes in the control of GLUT4 localization and function [160], and perturbations in this signalling system have been associated with insulin resistance and development of Type 2 diabetes [161]. β-Cell dysfunction is also a key feature of Type 2 diabetes so pancreatic islets have also been the focus of a number of studies.

Skeletal muscle and adipose tissue. Studies in male offspring from protein-restricted dams have demonstrated alterations in the expression of proteins downstream of the insulin receptor in both adipose tissue and skeletal muscle [162–164]. Insulin-stimulated glucose uptake was reduced in both these tissues and these animals also exhibited decreases in the association of the p110β catalytic subunit of PI3K (phosphoinositide 3-kinase) with its regulatory subunit, p85 (Figure 2) and this was associated with reduced activity of PI3K within the adipose tissue [162]. By contrast, in skeletal muscle, the reductions in glucose uptake were accompanied by decreases in PKCζ (protein

kinase C ζ) expression [163]. In light of these findings from this rodent model, it was later established that similar differences in the protein expression of insulin signalling components were also observed in muscle and adipose tissue from healthy adult humans who were born with a low birthweight [164,165]. These studies demonstrated a strikingly similar profile in insulin signalling protein expression, both in terms of the magnitude of changes and the specificity. In both humans and rodents, low birthweight subjects showed reductions of similar magnitudes in expression of GLUT4, PKCζ, and both the p85 and p110β subunits of PI3K in skeletal muscle [164]. The humans at the time of study were glucose tolerant and had similar adiposity and circulating insulin levels compared with normal birthweight individuals. Therefore, as these reductions in insulin signalling protein expression preceded the onset of Type 2 diabetes, they were proposed to be involved in the development of this disorder later in life [164]. Subsequent studies in adipose tissue from low birthweight individuals revealed that fetal growth restriction was associated with changes in the protein expression of GLUT4, p85, p110β and IRS (insulin receptor substate)-1 [165]. Upon examining the transcript levels of these proteins, no parallel reductions in their mRNA expression was observed, suggesting that post-transcriptional gene regulatory mechanisms were responsible for these changes in protein expression [165].

Several reports from Devaskar and colleagues have demonstrated that calorie restriction during pregnancy can also elicit changes in insulin signalling molecules in the offspring. IUGR due to maternal calorie restriction resulted in decreased amounts of GLUT4 mRNA and protein expression in skeletal muscle, with GLUT4 predominantly localizing to the plasma membrane, and that insulin was unable to stimulate further translocation of GLUT4 [166]. It was later determined that these changes in GLUT4 trafficking were a result of a heightened basal insulin sensitivity as, upon insulin administration, these animals were unable to activate PKCζ and stimulate GLUT4 translocation [167]. However, as the white adipose tissue retained its insulin responsiveness, it was speculated that absorption of nutrients into this tissue could contribute to the development of obesity in adulthood [166]. Continued investigations have now revealed that reduction in *GLUT4* mRNA expression can be attributed to altered transcriptional control of *GLUT4* [168]. Concomitant with this result, epigenetic modifications (see below) have also been reported at this locus [169].

Pancreatic islets. Using the maternal protein restriction model, Arantes et al. [170] demonstrated that protein restriction *in utero* impacted on the expression of the *Pdx-1* (pancreatic duodenal homeobox-1) gene. During development, this transcription factor is critical for the differentiation of the endocrine cell lineage and expansion of β-cell mass [147]. The study also demonstrated that expression of *Pdx-1* could be restored to control levels when offspring were suckled by control fed dams. *Pdx-1* expression changes correlated with both islet mass and levels of insulin secretion, demonstrating that protein restriction resulted in perturbed islet structure and function [170]. However, these changes were also noted to take place at the post-transcriptional level as the levels of *Pdx-1* mRNA transcript was not different between the groups. Reduced Pdx-1 expression levels have also been implicated in mediating the effects of fetal exposure to dexamethasone treatment [158]. This may suggest that regulation of Pdx-1 expression is a common pathway that mediates the effects of detrimental exposures *in utero* to the long-term risk of diabetes.

Epigenetics in the developmental programming of adulthood disease

Epigenetic modifications are a means of imposing on the fixed genome an additional level of gene regulation, which can be stably transferred throughout multiple rounds of mitosis, without changing the DNA nucleotide sequence [171]. Epigenetic modifications are achieved through both methylation of DNA CpG dinucleotides and post-translational modifications of histones and they control gene expression through the remodelling of chromatin. Therefore, with a fixed genotype, epigenetics can confer a degree of phenotypic plasticity, allowing the organism to respond to the environment and change its gene expression accordingly. Given this ability to establish heritable transcription states and control cell lineage specification during development [172], this mode of gene regulation is now receiving much attention in the field of developmental programming. The laying down of aberrant epigenetic marks in response to a perturbed intrauterine environment may confer an increased susceptibility to developing features of metabolic syndrome later in life.

Effects of DNA methylation. The first study to demonstrate that maternal diet could influence the epigenome in the offspring was by Wolff et al. [173]. This study was conducted in mice that carried the epigenetically sensitive A^{vy} (Agouti viable yellow) allele; offspring from dams that were fed a maternal diet enriched with methyl donors (supplemented with folate, vitamin B12, choline or betaine) showed hypermethylation of the retrotransposon element found upstream of this allele, subsequently silencing the expression of the A^{vy} gene. These offspring demonstrated a leaner phenotype and change in coat colour (pseudo-Agouti), in comparison with the obese, yellow-coat offspring born when the A^{vy} gene is ubiquitously expressed in the animal [173]. The result has been replicated in other studies [174–176], with one report even demonstrating that these epigenetic processes were capable of preventing the transgenerational amplification of obesity seen in the model [176]. As well as these observations, studies in rodent models of IUGR have demonstrated changes in the epigenetic modification of genes involved in metabolism within the offspring.

Providing further support that maternal diet during pregnancy can elicit changes within the epigenome, studies in offspring of protein-restricted dams have identified changes in DNA methylation of the *GR* (glucocorticoid receptor) and the *PPAR*α (peroxisome proliferator-activated receptor-α) genes in the liver [177]. That study demonstrated that promoters of both these genes were hypomethylated in the maternal-protein-restricted rat offspring and this was associated with increased expression of their corresponding transcripts. Using a protein restriction model to study intrauterine programming of hypertension, Bogdarina et al. [178] also demonstrated decreased methylation in the gene promoter for *Agtr1b* (angiotensin receptor, type 1b). Correlating with an increase in the expression of the *Agtr1b* mRNA transcript, and receptor protein expression, these changes were suspected to augment the regulation of blood pressure and contribute to the development of hypertension later in life. A more recent study in mice has reported that a protein restrictive diet while *in utero* can differentially methylate over 200 promoter regions within the liver of fetuses, including the *Lxra* (liver-X-receptor α) gene [179].

Recent studies in humans have also shown long-term effects of maternal diet on the epigenome of the offspring. These demonstrated that individuals exposed to the Dutch hunger winter had lower levels of methylation at the *IGF2* gene in adulthood [180]. Furthermore, Tobi et al. [181] have identified an additional six loci that were differentially methylated after prenatal exposure

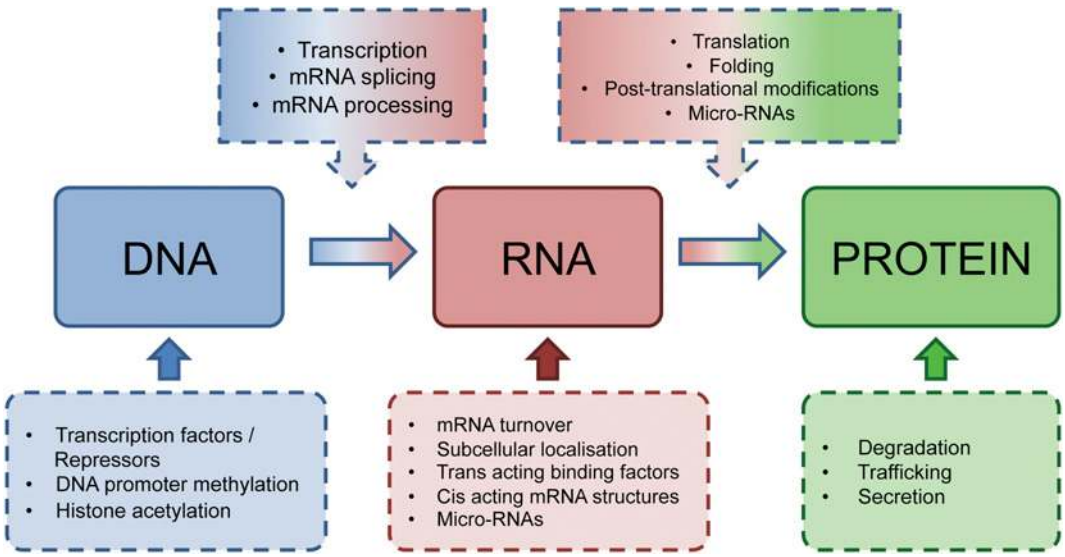

Figure 3 Mechanisms involved in the control of gene expression

An illustration of the regulatory mechanisms involved in the control of gene expression and the sites at which they act. These mechanisms can either be employed during the transition of one state to the next (i.e. DNA to RNA or RNA to protein; arrowed boxes) or upon its production, controlling the levels of this gene product.

to the famine, with all of them being implicated in either growth or metabolic and cardiovascular phenotypes.

Effects of histone modifications. Although initial focus was directed towards the role of changes in DNA methylation, there is now growing evidence to suggest that changes in histone modifications are as important, if not more important, in controlling gene expression in relation to nutritional/environmental stimuli.

Pdx-1 has been shown to be epigenetically regulated following IUGR resulting from intrauterine arterial ligation [182]. Upon parturition, these animals displayed a normal β-cell mass, but a reduced expression of *Pdx-1*. However, by adulthood, the IUGR offspring demonstrated decreased β-cell mass and *Pdx-1* mRNA expression was almost absent [183]. Park et al. [182] illustrated that the early reductions in *Pdx-1* expression were associated with deacetylation of core histones, and a reduction in USF-1 (upstream transcription factor-1) binding. With age, IUGR animals exhibited further changes in the histone marks and increased DNA methylation of the *Pdx-1* locus, changes that were associated with a progressive reduction in *Pdx-1* expression [182].

Changes in histone modifications have also been demonstrated in maternal calorie restriction models of IUGR. Raychaudhuri et al. [168] demonstrated that such IUGR was associated with changes in modifications of histones at the GLUT4 locus. This included losses in acetylation and increases in dimethylation of histone H3. These changes persist into adulthood, and were proposed to lead to the development of Type 2 diabetes in the adult female IUGR offspring [168].

Following on from their studies showing a reduction in the levels of hepatic DNA promoter methylation at the *GR* gene, Lillycrop et al. [184] demonstrated that intrauterine protein-restricted rat offspring had changes in histone modifications at this locus. This included a reduction in histone H3 dimethylation and increases in H3 acetylation, which would be associated with increased transcription.

Despite the evidence that gene expression changes can be achieved by variety of means, it should be noted that other mechanisms of regulating gene expression might underpin the developmental programming of adulthood disease (Figure 3). Considering the multifactorial nature of the associated metabolic diseases, continued efforts to determine the mechanisms mediating developmental programming may reveal some unexpected 'players' in the future development of these adulthood diseases.

Programming of mitochondrial function

Mitochondria are central to both normal and pathogenic processes within the cell, as not only are they responsible for the generation of the cells' primary energy source, ATP, they are also the principal source of highly destructive ROS (reactive oxygen species). Large quantities of ATP are generated through the tricarboxylic acid cycle and oxidative phosphorylation. Electrons generated within this system are eventually used to reduce oxygen and generate water. However, some incompletely reduced forms of oxygen, such as superoxide anions ($O_2^{\bullet -}$), can be produced [185]. If left unchecked, $O_2^{\bullet -}$ can react with other molecules within the cell, generating other ROS, such as the hydroxyl radical ($^{\bullet}OH$). $^{\bullet}OH$ is a highly reactive molecule that can cause damage to macromolecules within the cell, including proteins, lipids and DNA. Proteins can also be damaged by over-production of RNS (reactive nitrogen species), such as nitric oxide ($NO^{\bullet}$). $NO^{\bullet}$ is generated by NOSs (nitric oxide synthases). Reactions between $O_2^{\bullet -}$ and $NO^{\bullet}$ can produce an extremely volatile RNS, peroxynitrite ($ONOO^-$), which causes damage to both lipids and DNA (Figure 4) [185].

Embodied by the terms oxidative stress and nitrosative stress, the generation of high levels of these molecules and the damage they cause is thought to be involved in the aetiology of many features of metabolic syndrome. Levels of oxidative stress are normally kept to a minimum within cells and tissues via endogenous antioxidant defence mechanisms and maintenance of the redox state of the respiratory chain (reviewed in [186]). However, in states of calorific excess, such as those observed in obese and diabetic individuals, this can lead to an altered redox state within the mitochondria, generating more and prolonging the life of $O_2^{\bullet -}$ [186].

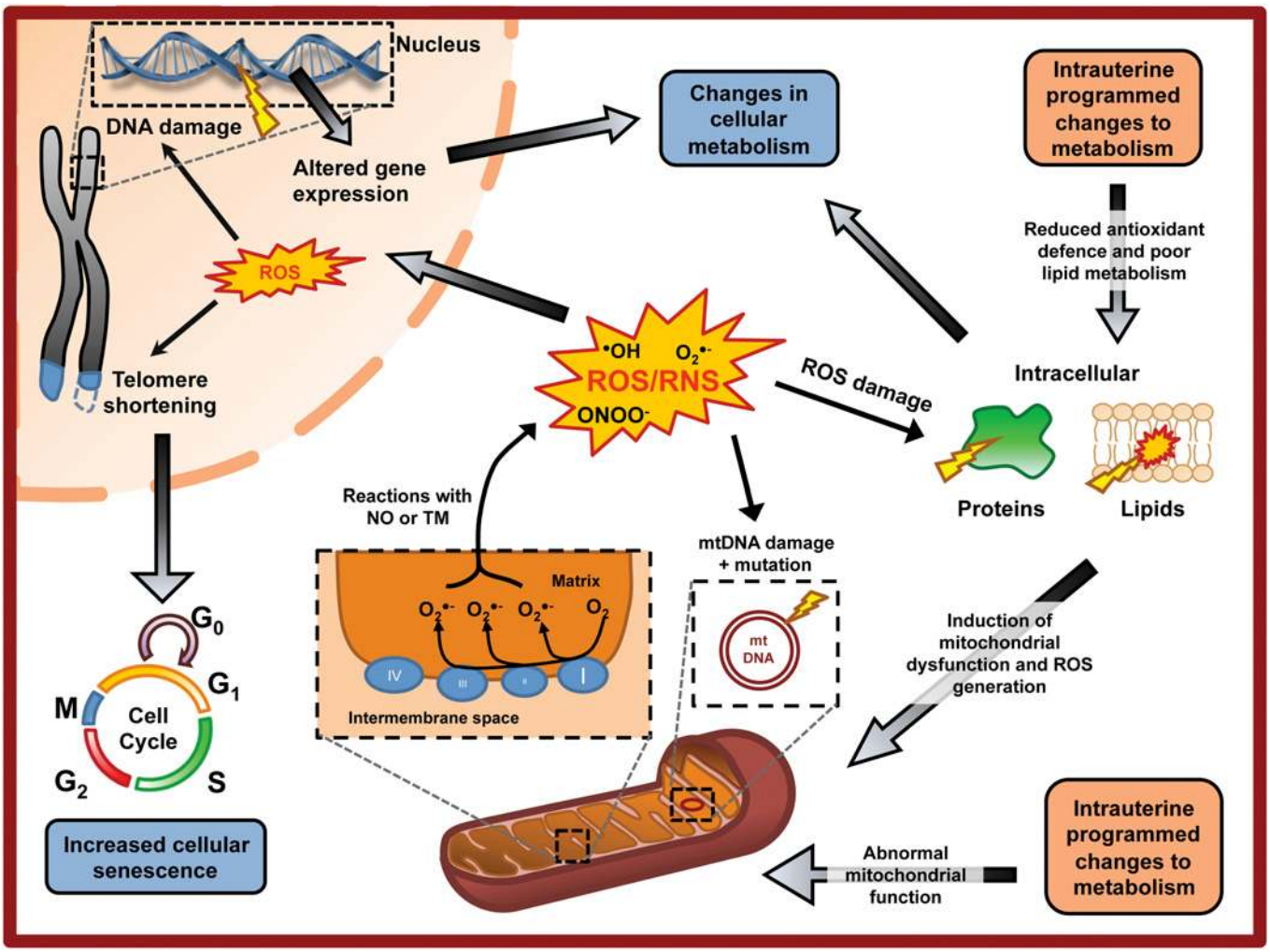

Figure 4 Potential programming of mitochondrial dysfunction and downstream processes altering cellular metabolism

Programmed changes in mitochondrial function, antioxidant defence pathways or resulting hyperglycaemia/poor lipid metabolism leads to the increased generation of the ROS, superoxide ($O_2^{•-}$). Superoxide reacting with other cellular components, generates more ROS (H_2O_2 and •OH) or reacts with $NO^{•}$ to form the RNS, peroxynitrite ($ONOO^-$). Excessive ROS/RNS leads to the damage of cellular proteins and lipids, genomic DNA and telomeres and also components of the mitochondria. These actions are also self-reinforcing, eventually causing impairments in mitochondrial function, cell-cycle control and potential induction of cellular senescence (following excessive telomere shortening). mt, mitochondrial; TM, transition metals (e.g. Fe and Cu).

Mitochondrial dysfunction is coupled with increases in oxidative stress. Several studies in humans indicate that mitochondrial dysfunction in skeletal muscle is intrinsically linked with diabetes [187–190] and increases in oxidative stress have been associated with IUGR in human fetuses [191–193]. Although this early exposure to oxidative stress impacts on a variety of tissues, it is suspected that certain tissues, such as the pancreas, may be more sensitive to mitochondrial dysfunction and ROS exposure when compared with other tissues. In order to maintain glucose-stimulated insulin secretion, β-cells require high levels of ATP [194]. Despite their high oxidative energy requirement, β-cells demonstrate very low levels of antioxidant defence enzymes [195,196], therefore any defects in mitochondrial function or increases in oxidative stress severely impact on β-cell function. Several studies have shown that increased levels of ROS can impair glucose-stimulated insulin secretion (e.g. [197], reviewed in [194]) and reduce the expression of key β-cell genes [198–200].

Use of the intrauterine arterial ligation model in the rat has demonstrated that IUGR pups experience increased oxidative stress and impaired mitochondrial function when compared with controls, a phenotype that progressively worsens with age. This was associated with an age-dependent decline in the activity of the oxidative phosphorylation pathway, and subsequently ATP production, as well as an accumulation of mitochondrial DNA damage [201]. This model has also demonstrated that mitochondrial dysfunction is not limited to just the β-cell, as mitochondria from both the liver and skeletal muscle exhibit decreased oxidation of pyruvate, subsequently leading to the development of features commonly found in Type 2 diabetes [202,203]. Decreases in liver pyruvate oxidation were predicted to predispose the animal to increased hepatic gluconeogenesis [202], while the changes in the muscle tissue led to a chronic reduction in ATP generation, subsequently reducing the levels of GLUT4 translocation and glucose transport into the tissue, contributing to the hyperglycaemia observed in Type 2 diabetes [203].

Studies have demonstrated that oxidative stress is not limited to just mitochondrial DNA damage, but also genomic DNA, impacting on cell-cycle regulation and gene expression [204]. Despite DNA being targeted throughout by ROS, there are particular regions that are known to be more sensitive to ROS-mediated damage, for example telomeres (reviewed in [205]).

Telomeres comprise GC-rich hexanucleotide repeat sequences and are found at the ends of each chromosome. They are known to shorten with each cellular division and, hence, can act as a 'mitotic clock', registering the number of replicative divisions to have taken place within the cell.

It has been hypothesized that increases in oxidative damage can lead to acceleration of telomere shortening and subsequently induce premature aging [206]. Recognizing that the risk of developing Type 2 diabetes and CVD increases with age, it has been hypothesized that telomere biology may form an important link between increases in oxidative stress and the development of these age-associated disorders. Studies have revealed that not only is telomere attrition associated with the development of these disorders [205–207], but increased losses in telomere length can be associated with IUGR. Investigations using a modified model of the maternal protein restriction paradigm have revealed that diet during gestation and early life can impact on telomere biology, significantly influencing the development of features of metabolic syndrome and longevity in offspring [208–213]. Through a method of cross-fostering in rodents, studies from our laboratory have shown that limiting dietary protein and growth during lactation increases the longevity of the offspring [208,209] and also confers increases in antioxidant defence enzymes in the kidney [210,211] and aorta [212] (with a higher proportion of larger telomeres within the aorta [212]). Conversely, if dietary protein and growth was limited during gestation, this results in a decrease in longevity in the offspring [208,209] accompanied by reductions in antioxidant defences in the kidney [211] and aorta [212], as well as mitochondrial antioxidant defences in pancreatic islets [213], and decreases in telomere length in both aorta and islets [212, 213].

CONCLUSIONS

There is now substantial evidence demonstrating the importance of the intrauterine environment on the development of the fetus and its predisposition to features of metabolic syndrome later in life. Although a few mechanistic studies have been conducted in humans, the majority of investigations into the mechanisms underlying the developmental origins of health and disease have used animal models. These mechanisms have shown similarities to the human situation and therefore suggest that these represent fundamental biological processes. They include permanent structural changes, epigenetic modifications leading to permanent changes in gene expression and mitochondrial dysfunction, leading to cumulative oxidative damage. The relative contribution of these various mechanisms still remains to be established. Once we have reached a comprehensive understanding of the mechanisms underlying developmental programming of disease, focus can then be directed towards strategies for therapeutic intervention.

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