REVIEW ARTICLE

Nongenomic memory of foetal history in chronic diseases development

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Abstract

Foetal growth from conception to birth is a complex process predetermined by the genetic configuration of the foetus, the availability of nutrients and oxygen to the foetus, maternal nutrition and, various growth factors and hormones of maternal, foetal and placental origin.

Maintenance of the optimal fetal environment is the key factor of the future quality of life. Such conditions like inadequate nutrition and oxygen supply, infection, hypertension, gestational diabetes or drug abuse in the mother expose the foetus to nonphysiological environment. In conditions of severe intrauterine deprivation, there is a potential loss of structural units within the developing organ systems affecting their functionality and efficiency. Extensive human epidemiologic and animal model data indicate that during critical periods of prenatal and postnatal mammalian development, nutrition and other environmental stimuli influence developmental pathways and thereby induce permanent changes in metabolism and chronic disease susceptibility.

The studies reviewed in this article show how environmental factors influence a diverse array of molecular mechanisms and consequently alter disease risk including diseases such as metabolic syndrome and cardiovascular diseases, insulin resistance and diabetes mellitus, neuropsychiatric disorders, osteoporosis, asthma and immune system diseases.

Abbreviations

ACE	- angiotensin converting enzyme
ATR	- angiotensin type receptor
CVD	- cardiovascular disease
DOHaD	- developmental origin of health and disease
FOAD	- fetal origin of adult disease
HPA	- hypothalamic-pituitary-adrenal axis
ICAM-1	- Inter-Cellular Adhesion Molecule 1
IGF	- insulin-like growth factor
I-R	- ischaemia-reperfusion
IUGR	- intrauterine growth restriction
RAS	- renin-angiotensin system
ROS	- reactive oxygen species
T2DM	- type 2 diabetes mellitus

INTRODUCTION

Foetal growth from conception to birth is a complex process predetermined by the genetic configuration of the foetus, the availability of nutrients and oxygen to the foetus, maternal nutrition and various growth factors and hormones of maternal, foetal and placental origin. Suboptimal foetal environments due to poor or inadequate nutrition, infection, anaemia, hypertension, inflammation, gestational diabetes or hypoxia in the mother expose the foetus to nonphysiological hormonal, growth factor, cytokine or adipokine cues (Fernandez-Twinn and Ozanne, 2006). In conditions of severe intrauterine deprivation, mother's drug abuse or poisoning, there is the capacity to lose structural units such as neurons, cardiomyocytes, nephrons, or pancreatic β-cells within developing organ systems. The foetus adapts to an adverse intrauterine milieu by optimising the use of a reduced nutrient supply to ensure survival. However, favouring the development of some organs over that of others, leads to persistent alterations in the growth and function of developing tissues (Simmons 2005, Mach *et al*., 2006; Foltinova *et al*., 2006). These adaptive measures have short-term benefits to the embryo and foetus, so that the newborn will be better prepared for the adverse environment (e.g. undernutrition). However, adequate nutritional support during postnatal life that enables catch-up growth may create metabolic conflicts that predispose the adult to aberrant physiological functions and, ultimately, increased risk of disease (Lau and Rogers, 2004). Disturbed intrauterine growth and development has a negative influence on the development of the cardiovascular system and favours the occurrence of hypertension, insulin resistance, hypercholesterolaemia and hyperuricaemia in adult life (Barker's hypothesis) (Barker, 1998). Diverse factors, including intrinsic foetal conditions as well as maternal and environmental factors, can lead to intrauterine growth restriction (IUGR). The observations of associations between indices of foetal growth and later risk of cardiovascular disease have been attributed to 'programming' or 'imprinting'. Programming was originally defined by Lucas (1992) as a permanent response to an insult or stimulus, experienced during a critical period of development. The phenomenon termed "foetal programming", has led to the theory of "foetal origins of adult disease". Epigenetic reprogramming is the process by which an organ genotype interacts with the environment to produce its phenotype and provides a framework for explaining individual variations and the uniqueness of cells, tissues, or organs despite identical genetic information. The main epigenetic mediators are histon modification by DNA methylation, and non-coding RNAs. They regulate crucial cellular functions such as genome stability, gene imprinting, and reprogramming of non-imprinting genes (Tang and Ho, 2007). Epigenetics is defined as heritable changes in gene expression that does not alter DNA sequence but are mitotically and transgenerationally inheritable. Developmental epigenetics is believed to establish adaptive phenotypes to meet the demands of the later-life environment. Resulting phenotypes that match predicted later-life demands will promote health, while a high degree of mismatch will impede adaptability to later-life challenges and elevate disease risk (Gluckman and Hanson, 2007).

The environmental processes influencing the propensity to disease in adulthood operate during the periconceptual, foetal, and infant phases of life (Gluckman and Hanson 2004a, Gluckman and Hanson, 2004b). The intrauterine environment of the conceptus may alter expression of the foetal genome, and have lifelong consequences. When considering effects of the environment on development, it is important to distinguish between responses that might be adaptive later in life from those that merely disrupt development in a pathological manner (those causing foetal malformation). Gluckman *et al*. (2005) define predictive adaptive responses (PARs) as a form of developmental plasticity that evolved as adaptive responses to environmental cues acting early in the life cycle. PARs, therefore, are a form of phenotypic plasticity in which the resulting phenotype is likely to be advantageous in an anticipated future environment. The early life influences can alter later disease risk, the "developmental origins of health and disease" (DOHaD) paradigm. The DOHaD phenomenon can be considered as a subset of the developmental plasticity by which organisms adapt to their environment during their life course (Gluckman *et al*., 2007).

The characteristic principles of developmental programming were formulated by Nathanielsz (2006).

(1) The first major principle of developmental programming is that critical time windows exist during development when organs are vulnerable to challenges such as decreased oxygenation, nutrient supply, and altered hormone exposure. The period of vulnerability varies from organ to organ.

(2) Programming has permanent effects that alter responses in later life and can modify susceptibility to disease.

(3) Programming involves several different structural changes in important organs.

(4) Although the foetus is able to compensate, the mechanisms by which the foetus changes the trajectory of development may affect postnatal function and have positive or negative outcomes depending on the postnatal environment.

(5) Attempts made after birth to reverse the consequences of programming may have their own unwanted consequences.

(6) Foetal cellular mechanisms often differ from adult processes.

(7) The effects of programming may pass across generations by mechanisms that do not necessarily involve changes in the genes.

MECHANISMS OF FOETAL PROGRAMMING

The mechanisms of "foetal origins" or "programming" of disease phenomenon remain unexplained. Many known or suspected causes or conditions associated with adverse foetal growth or preterm birth have been associated with hypoxia and oxidative stress.

I. Hypoxia and oxidative stress

Intrauterine growth retardation is associated with increased oxidative stress in the human foetus. A major consequence of limited nutrient availability is an alteration in the redox state in susceptible foetal tissues leading to oxidative stress. The alterations of redox state in susceptible foetal tissues can have deleterious effects, especially in cells that have a high energy requirement, such as the pancreatic β-cells. Mitochondrial dysfunction can lead to increased production of reactive oxygen species (ROS), which will lead to oxidative stress. Overproduction of ROS initiates many oxidative reactions that lead to oxidative damage not only in the mitochondria but also in cellular proteins, lipids, and nucleic acids. The mechanisms of oxidative stress programming may be through directly modulating gene expression or indirectly through the effects of certain oxidised molecules (Huang *et al*., 2004). Beta-cells are especially vulnerable to attacks by ROS since expression of antioxidant enzymes is very low in pancreatic islets. Increased ROS impair glucose-stimulated insulin secretion, decrease gene expression of key β-cell genes, and induce cell death (Simmons, 2006). Experimental investigations demonstrated the important role of redox balance in modulating gene expression, and recent studies indicate that both the insulin functional axis and blood pressure could be sensitive targets to oxidative stress programming (Walker, 2006).

II. Endocrine mechanisms of intrauterine programming

Hormones are important organizers of the developing neuro-endocrine-immune network, which finally regulates all fundamental processes of life. When present in non-physiological concentrations during "critical periods" of perinatal life, induced by alterations in the intrauterine or neonatal environment, hormones can act as "endogenous functional teratogens" (Plagemann, 2005). A periconceptional and/or the preimplantation period are critical windows during which maternal undernutrition may act to alter the set point of the function of the hypothalamic-pituitary-adrenal (HPA) axis. Potential mechanisms for this effect include an impact of the maternal hormonal and metabolic responses to undernutrition on the epigenetic regulation of gene expression within the developing embryo (McMillen and Robinson, 2005). Alterations in HPA activity throughout life will impact on adult health because of altered tissue exposure to endogenous glucocorticoids. Elevated plasma cortisol has been associated with atherosclerosis, immunosuppression, depression and cognitive impairment, in addition to raised cholesterol levels and increased incidence of Type 2 diabetes melitus (T2DM) (Matthews 2002). The glucocorticoids, in particular, have a key role in intrauterine programming. They induce permanent changes in physiological systems by altering hormone bioavailability and the cellular expression of receptors, enzymes, ion channels, transporters and various cytoarchitectural proteins in the foetal tissues. Glucocorticoids act directly on genes and indirectly via other hormones and growth factors. Endocrine changes are, therefore, both the cause and the consequence of intrauterine programming (Fowden and Forhead, 2004). The insulin-like growth factor (IGF) system, and IGF-I and IGF-II in particular, plays a critical role in foetal and placental growth throughout gestation. Disruption of the *IGF1*, *IGF2* or *IGF1R* gene retards foetal growth. IGF-I stimulates foetal growth when nutrients are available, thereby ensuring that foetal growth is appropriate for the nutrient supply. The production of IGF-I is particularly sensitive to undernutrition. IGF-II plays a key role in placental growth and nutrient transfer (Gicquel and Le Bouc, 2006).

III. Molecular mechanisms of foetal programming

Animal research shows that the processes occurring during early life growth restriction permanently change the level of gene expression including genes involved in the production of developmental regulatory factors, hormone receptors, signalling molecules and regulatory enzymes (Hales and Ozanne, 2003). Epigenetic alterations of gene expression through covalent modifications of DNA and core histones in early embryos may be carried forward to subsequent developmental stages. Two mechanisms mediating epigenetic effects are DNA methylation and histone modification (acetylation and methylation). DNA methylation and histone modifications may be altered by the overall availability of amino acids and micronutrients (Wu *et al*., 2004). Epigenetic reprogramming is the process by which an organism's genotype interacts with the environment to produce its phenotype and provides a framework for explaining individual variations and the uniqueness of cells, tissues, or organs despite identical genetic information (Tang and Ho, 2007). The main epigenetic mediators of histone modification, DNA methylation, and noncoding RNAs regulate crucial cellular functions such as genome stability, chromosome inactivation, gene imprinting, and reprogramming of non-imprinting genes, and work on developmental plasticity that exposures to endogenous or exogenous factors during critical periods permanently alter the structure or function of specific organ systems.

DEVELOPMENTAL ORIGIN OF CHRONIC DISEASES

A. Developmental origin of metabolic syndrome

The metabolic syndrome (MetS) involves combining disturbances in glucose, insulin metabolism, mild dyslipidemia and hypertension, with the subsequent development of obesity, T2DM and cardiovascular disease (CVD). It is arising in consequence of improper epigenetic programming during foetal/postnatal development, due to maternal inadequate nutrition and metabolic disturbances, and also during further life (Gallou-Kabani *et al*., 2005). The intrauterine substrate restriction and associated changes in neuroendocrine, haemodynamic, metabolic, and growth factors may alter patterns of cardiomyocyte hyperplasia, apoptosis and hypertrophy, myocardial development and vascularisation and result in programmed changes in cardiac structure and function (McMillen and Robinson, 2005). The effects of these factors on the pattern of heart growth during the perinatal period render the heart more vulnerable to infarction and damage in later life. Chronic hypoxia during pregnancy is one of the most common insults to foetal development and is thought to be associated with foetal intrauterine growth restriction. It was shown in a rat model that prenatal chronic hypoxia resulting in low birth weight significantly increased the susceptibility of the adult heart to I-R injury by increasing myocardial infarct size and decreasing postischaemic recovery of left ventricular function (Li *et al*., 2003). Chronic hypoxia during the course of pregnancy is a common insult to the foetus and results in foetal intrauterine growth retardation, which is independent of malnutrition (Zhang, 2005).

B. Developmental origin of hypertension

Animal studies and indirect evidence from human studies support the hypothesis that low birth weight, as a marker of adverse intrauterine circumstances, is associated with a congenital deficit in nephron number (Zandi-Nejad *et al*., 2006). Kidneys with lower nephron numbers maintain their haemodynamic and excretory functions through increases in local vascular resistance and blood pressure. Increased pressure within nephrons will lead to a progressive deterioration and loss of nephrons. The subsequent rise in pressure necessary to maintain function will then promote further nephron loss and advancing renal failure. Ultimately, the increases in single nephron pressure and vascular resistance will translate into elevated systemic blood pressure (Amann *et al*., 2004).

Animal experiments demonstrated that relative hypertension induced by foetal exposure to low protein diet could be successfully treated by using the inhibitor of the renin–angiotensin system captopril. Studies of the effects of angiotensin converting enzyme inhibitors on programmed hypertension were broadly supportive of a role for the renin–angiotensin system in the programming mechanism linking an imbalance of maternal nutrition to later cardiovascular disease (Langley-Evans 2001, Langley- Evans *et al*., 2003). All components of the RAS, i.e. angiotensinogen, renin, angiotensin converting enzyme (ACE), angiotensin type I receptor (AT1R) and AT2R are highly expressed in the developing kidney in a pattern that suggests a role for angiotensin II in renal development (Guron and Friberg 2000). The strong association between birth weight and serum ACE suggests that ACE or the renin-aldosterone system may be linked to mechanisms controlling early human growth. Angiotensin II has a specific growth factor-like effect on target tissue, and the renin-angiotensin system has been proposed to have a pivotal role in foetal development and growth (Forsyth *et al*., 2004). Sympathoadrenal control of the activity of the renal RAS can be exerted either by circulating catecholamines or by catecholamines released from sympathetic nerve terminals. There is evidence that the developing sympathetic nervous system can amplify the reactivity of the developing RAS (Lumbers *et al*., 2001)

Glucocorticoids, potent regulators of the renin-angiotensin system, play a central role in foetal programming of adult disease. The developing foetal tissues are protected from the high levels of maternal glucocorticoids by the enzyme 11β-hydroxysteroid dehydrogenase, which converts naturally occurring glucocorticoids to inactive forms. Evidence suggests that upregulation of the renin-angiotensin system, particularly through changes in ATR expression, may play a role in foetal programming of high blood pressure (McMullen and Langley-Evans, 2005).

C. Developmental origin of insulin resistance and Type 2 diabetes

Foetal and neonatal life are known to be crucial periods for pancreatic β-cell development. Any deficiency in β-cell mass occurring *in utero* as a result of either genetic mutations, maternal malnutrition or placental dysfunction leading to inappropriate expression of transcription or growth factors, will have only a limited opportunity for correction postnatally. Shortly after birth a developmental apoptosis appears to delete many of these β-cells and they are simultaneously replaced with new islets derived from a second wave of neogenesis. Early environmental insults may alter the timing of developmental changes leaving the individual with a β-cell population poorly suited both quantitatively and qualitatively for postnatal life, and ultimately leading to glucose intolerance. Thus it is possible that perturbations of prenatal growth may lead to inappropriate β-cell ontogeny and will have life-long consequences for glucose homeostasis (Hill, 2005). An abnormal intrauterine milieu can induce permanent changes in glucose homeostasis after birth. The foetus adapts to an altered environment in utero that may enhance its short-term survival probability at the expense of its long-term

capacity for normal growth and development. In effect, the cells are reprogrammed to enable the foetus as a whole to survive under conditions of nutrient deprivation. However, this reprogramming persists throughout life, leading to the development of type 2 diabetes in adulthood (Simmons *et al*., 2001; Simmons, 2006). Studies in the IUGR rat demonstrated that an abnormal intrauterine environment induces epigenetic modifications of key genes regulating beta-cell development (Simmons, 2006).

In utero undernutrition in humans may be associated with insulin-resistance but not with abnormal β-cell development or β-cell dysfunction. In contrast to results in humans, findings from animal models strongly suggest that poor nutrition during foetal life may impair β-cell development, leading to β-cell dysfunction in late adulthood. Perinatal undernutrition affects islet neogenesis and permanently impairs β-cell mass in young adult rats. These discrepancies between results in humans and animals indicate a need for caution in extrapolating animal data to humans (Béringue *et al*., 2002).

D. Developmental origin of neuropsychiatric disorders

Foetal environment influences later life, particularly early programming may affect hormone and neurotransmitter secretions which may later influence psychological as well as physical health. A relationship was found to exist between birthweight and cognitive function; a lower birthweight was found to be associated with a lower IQ (Bellingham-Young and Adamson-Macedo, 2002; Bellingham-Young and Adamson-Macedo, 2003). Overviews of gestational biology and the postnatal physiologic, cognitive-affective, and behavioural effects of gestational stress were identified to play a central role for the hypothalamic-pituitary-adrenal axis. The autonomic nervous system and the HPA axis are key components of the neuroendocrine response to stress. An adverse early environment, as evidenced by reduced birth or infant weight, is associated with enhanced autonomic and HPA responses to experimental psychological stress (Phillips and Jones 2006; Worthman and Kuzara, 2005).

It is estimated that about 1–2% of all genes are regulated by hypoxia. It would appear reasonable to hypothesise that several genes important for neurodevelopment are regulated by hypoxia in a physiological manner. However, hypoxia could be involved also in a pathological manner. Excessive hypoxia could result in dysregulation of responsive genes, overexpression or underexpression, and in an imbalance of gene expression at critical stages of development. Two subsets of hypoxic-ischaemia-related foetal/neonatal complications were identified: 1) conditions of compromised foetal growth and development, and 2) nonspecific neonatal signs of mild-to-moderate neurological dysfunction and other complications within the hypoxic-ischaemia-related group (Zornberg *et al*., 2000).

Hypoxia is one of the most important external factors that influence susceptibility to schizophrenia. It has been hypothesised that hypoxia in the prenatal and perinatal period contributes to the neurodevelopmental alterations that later in life are involved in the onset of the complex dysfunctional state of schizophrenia (Schmidt-Kastner *et al*., 2005). There are currently two main, non-exclusive hypotheses for the development of schizophrenia, the neurodevelopmental hypothesis and the neurodegenerative hypothesis. Genetic and non-genetic mechanisms are thought to interact, in as yet not understood ways, to affect the developing brain, resulting in a predisposition to schizophrenia. Maternal infection with a wide variety of agents might potentially increase the risk for schizophrenia, suggesting that factors common to many infections may be mechanistically responsible (Boksa, 2008). A number of experimental studies reported that, in rodents, maternal infection during pregnancy can produce changes in central nervous system structure, function and behaviour in the offspring.

E. Developmental origin of immune system diseases

Although research on the early origins of immunity has received relatively little attention there is now considerable evidence that human immune function is, at least in part, conditioned by early environments. In particular, nutritional resources, growth rates, and pathogen exposures early in life have long-term effects on immune development and function that persist into adolescence and likely adulthood as well (Mcdade, 2005). Experimental results showed that intrauterine undernutrition in rats reduced leukocyte migration, downregulated endothelial expression of P-selectin and ICAM-1, as well as leukocyte expression of L-selectin, while reducing leukocyte counts. These data suggest that this phenomenon is involved in the increased predisposition to infections in undernourished subjects (Landgraf *et al*., 2005).

There are a number of potential mechanisms by which early infection may alter the developing immune system. These include functional alternatives of B cells and T cells and changes of the relative levels of pro and anti-inflammatory cytokines. Common mechanisms may be shared between autoimmune and allergic disease, whereby infections at critical periods of development produce permanent, and ultimately damaging, changes in immune functioning. These, in conjunction with specific genetic backgrounds and environmental factors may lead to disease (Edwards and Cooper 2006).

F. Developmental origin of asthma and other respiratory diseases

Foetal growth and duration of gestation are two of the major influences on lung development. An adverse environment in utero can affect foetal growth and influence lung function in mid adult life. Thus birth

weight appears to be a marker for adult lung function (Edwards *et al*., 2003). Negative effects on lung development can result from either: mother-related factors, including hypoxia, intoxications and other causes of intra-uterine stress, which leads to growth retardation; or child-related factors, such as foetal diseases (Greenough *et al*., 2004). Both epidemiological and animal studies point to the vulnerability of the developing lung and the immune system of infants or young children to air pollutants. Prenatal maternal exposure to air pollutants and exposure of children to environmental toxic substances result in decreased lung growth and increased rates of respiratory tract infections and childhood asthma. The severity of these problems is increasing with increased exposure (Wang and Pinkerton 2007). The effects of exposure to air pollutants in pregnancy indicate not only short-term immediate effects on foetal development but also long-term effects on the health of children (congenital abnormalities, childhood respiratory, cardiovascular and behavioural problems, and impaired immunological development). Findings from several studies suggest that foetal growth restriction is associated with increased respiratory morbidity and mortality during early childhood (Hoo *et al*., 2004). There is increasing evidence that prenatal, neonatal, and early childhood events affect the subsequent development of risk for asthma. The mechanism behind this relationship may be a compromised development of the lungs (Tantisira and Weiss, 2001).

G. Developmental origin of osteoporosis

Osteoporosis is a major cause of morbidity and mortality through its association with age-related fractures. Evidence is now accumulating from human studies that programming of bone growth might be an important contributor to the later risk of osteoporotic fractures (Javaid and Cooper 2002). Epidemiological studies demonstrated a relationship between birthweight, weight in infancy and adult bone mass. This appears to be mediated through modulation of the basal activity of the hypothalamic-pitutiary-adrenal and growth hormone/insulin-like growth factor I axes. The prenatal or perinatal environment can influence adult postnatal physiology. Animal models for the developmental origins of osteoporosis are confirming the observations made in humans. Although the environmental triggering is not yet fully understood, most manipulations have been dietary and include maternal undernutrition, low-protein diet, and high-fat diet. The maternal low protein diet affects litter size, growth trajectory in female offspring and bone biochemistry in the offspring. A maternal low protein diet has a deleterious effect on bone environment, with effects that persist into late adulthood (Langham *et al*., 2008a; Langham *et al*., 2008b).

The offspring of rats born to dams fed a low protein diet during pregnancy were found to have low density. The experimental animals also revealed widened epiphyseal growth plates, an observation compatible with the programming of cartilage and bone growth by maternal undernutrition in early life (Mehta *et al*., 2002). Fibroblast colony formation at 4 and 8 weeks revealed that maternal protein restriction downregulated the proliferation and differentiation of bone marrow stromal cells (Cooper *et al*., 2005).

CONCLUSION

Animal research shows that "*in utero* equilibrium" during early life, which is characterised high cell proliferation, organ development and the changing capabilities of foetal metabolism, is the vital factor for future quality of life. New knowledge of the mechanisms regulating foetal growth and development is expected to be beneficial for designing new therapeutic strategies to prevent and treat IUGR. Understanding of these mechanisms will have a broad impact on reproductive health and disease prevention. To obtain this information it is necessary to establish human markers which indicate the extent of environmentally-induced changes in the expression of the genome and could lead to early intervention and to the prevention of many diseases.

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