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# Impact and Mechanisms of Pancreatic Beta-Cell Mass Programming by Maternal Diabetes - Insight from Animal Model Studies

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## 1. Introduction

The incidence of type 2 diabetes mellitus (T2D) is growing worldwide. It is now established that interactions between the individual genetic makeup and environment contribute to the development of T2D. In this review, we first discuss the evidence for beta-cell dysfunction in IUED (*in utero* exposure to maternal diabetes), IUEO (*in utero* exposure to maternal overnutrition) and IUGR (*in utero* growth restriction) humans. We then evaluate relevant animal models of IUED, IUEO and IUGR focusing on the strengths and limits of each, in order to define critical periods and types of alterations that can lead to impaired beta-cell function. Finally, we discuss several potential mechanisms dissected in relevant animal models that begin to explain these outcomes.

## 2. Perinatal risk factors for diabetes in later life: Human studies

There are strong arguments showing that T2D is more prevalent among subjects that were exposed to maternal diabetes *in utero* (IUED). The role of maternal inheritance in T2D was first suggested by epidemiological studies. A higher susceptibility for diabetes is described in descendents from diabetic great grand mothers via the maternal line than via the paternal line (Dörner et al., 1984). A higher incidence of T2D and of gestational diabetes (GD) is seen in children of diabetic mothers as compared to those of diabetic fathers (Martin et al., 1985). A decreased prevalence of diabetes is seen in children from diabetic mothers, after starting a systematic treatment of diabetic pregnant women (Dörner et al., 1987). Especially interesting in this context are the studies on the Pima Indians, a population with an exceptionally high T2D incidence. The prevalence of impaired glucose tolerance, of T2D and of GD is much higher (7 fold increased) in children from mothers who had diabetes during pregnancy, than in children from mothers who developed diabetes only after their pregnancy. Moreover, paternal diabetes has a much smaller effect on the prevalence of diabetes in these offspring than maternal diabetes (Pettitt, 1996).

The maternal influence in the development of T2D was reported in a majority of studies (Alcolado et al., 2002). Although some studies did not find a maternal effect, none reported a

higher paternal transmission (Mitchell et al., 1993; Mc Carthy et al., 1996; Viswanathan et al., 1996; Frayling et al., 1999). The prospective Framingham Offspring Study in which all offspring and parents were formally tested for diabetes, demonstrated that the risk of impaired glucose tolerance or T2D was greater in offspring of mothers with early diabetes onset (before 50), suggesting the role of fetal environment (Meigs et al., 2000). However, the effects of fetal exposure to diabetes may be confounded by genetic factors. Mothers who had T2D before or during pregnancy have, by definition, early diabetes. Therefore, they may carry T2D susceptibility genes, which are transmitted to their offspring. To determine the role of the intrauterine diabetic environment per se, the prevalence of diabetes was compared in Pima nuclear families in which at least one sibling was born before and one after the mother was diagnosed with T2D. Offspring born after their mother displayed diabetes had a 4-fold higher risk of diabetes and a higher body mass index (BMI) than their full siblings born before their mother developed diabetes (Dabelea et al., 2000). These findings indicate that intrauterine exposure to a diabetic environment increases risk of obesity and T2D beyond that attributable to genetic factors, at least in Pima Indians. In Caucasians, offspring whose mothers had pregestational diabetes (type 1 or 2) or gestational diabetes had a higher frequency of impaired glucose tolerance (IGT). (Plagemann et al., 1997). Carriers of mutations in the MODY gene hepatocyte nuclear factor 1 alpha whose mothers had diabetes when they were *in utero*, were diagnosed with diabetes 8 years earlier than those who inherited the mutation from the father (Stride et al. 2002). To circumvent the confounding effect of genes linked to early onset T2D and transmitted by the pregnant T2D mother, the effect of fetal exposure to T1D was evaluated in adult offspring lacking T1D immunological markers. A 33% prevalence of IGT was reported in offspring of T1D mothers compared with none in offspring of T1D fathers (control group) (Sobngwi et al., 2003). Altogether, these findings suggest that fetal exposure to maternal diabetes is indeed associated with abnormal glucose homeostasis in offspring and may participate in the excess of maternal transmission in T2D.

There are some studies related to the metabolic defects associated with fetal exposure to maternal diabetes in human offspring. The typical feature of infants of diabetic mothers is fetal macrosomia and high birth weight. A correlation between high birth weight and later impairment of glucose tolerance therefore is expected. Among Pima Indians high birth weight increases the risk of developing diabetes in later life (Pettitt, 1996). In the population of Malta, with a high prevalence of type-2 diabetes, woman with high birth weight have an increased risk of developing gestational diabetes. Birth weight is significantly higher in mothers with a family history of diabetes from the maternal side than from the paternal side, and than in those with no family history of diabetes (Savona-Ventura & Chircop, 2002). The relation between large babies and later impaired glucose tolerance in these studies appears to be related to the macrosomia of babies from diabetic mothers.

Two studies reported that IGT in offspring exposed to intrauterine diabetic environment resulted from decreased insulin action based on finding of a high insulin-to-glucose ratio during oral glucose challenge (Plagemann et al., 1997; Silverman et al., 1995). However, fetal exposure to maternal T1D was not associated with reduced insulin sensitivity (minimal model) in young offspring (Hunter et al., 2004). Offspring of T2D mothers tended to have decreased insulin action, but were heavier compared with offspring of healthy mothers (Hunter et al., 2004). In adult Pima Indians with normal glucose tolerance and who had been exposed to an intrauterine diabetic environment, acute insulin response to iv glucose was

found reduced in those offspring whose mother was diabetic before pregnancy while it remained normal in those whose mother developed diabetes after pregnancy (Gautier et al., 2001). Body fat and insulin sensitivity (euglycemic hyperinsulinemic clamp) were similar in the two groups of subjects (Gautier et al., 2001). In the same study, acute insulin response was found reduced in offspring of parents (mother or father) with early onset of T2D (Gautier et al., 2001), suggesting that gene(s) linked to early onset diabetes is(are) associated with reduced insulin secretory response to glucose (Hanson et al., 1995). Offspring of T1D mothers had reduced insulin secretion, more pronounced in IGT subjects, but similar fat mass and insulin action compared with offspring of T1D fathers (Sobngwi et al., 2003). Also in non-diabetic offspring of mothers with young-onset T2D (diagnosed under age 50), beta-cell function (early insulin release after oral glucose) was found decreased as compared to that of offspring of fathers with young-onset T2D (Singh et al., 2006).

Therefore human studies suggest that insulin secretion defect participates to the abnormal glucose tolerance observed in adult offspring exposed to maternal diabetes during fetal life. Importantly, they showed that insulin secretion may be reduced even in normal glucose-tolerant offspring. Nevertheless, in children and adolescent offspring, insulin resistance involvement was suggested and may be related, at least in part, to their higher body weight. Besides IUED populations, evidence continues to mount showing that T2D is also more prevalent among subjects that were intrauterine growth restricted (IUGR). The first study to link low birth weight to increased T2D risk was conducted in a group of men born in Hertfordshire, UK, who were 64 years old at the time of the study. Those men who had the lowest birth weight were 6 times more likely to currently have either impaired glucose tolerance or T2D than those men who were heaviest at birth (Hales et al., 1991). These findings have been reproduced in over 40 populations worldwide, including many ethnic groups. In some cohorts where there is a high prevalence of maternal obesity, there is also increased risk of diabetes at the high-birth weight end of the spectrum (U-shaped curve for diabetes risk distribution). This is thought to reflect the increased risk of diabetes in the macrosomic offspring of women with gestational diabetes (Nathanielsz et al., 2007). Some of the strongest evidence in support of the role for environment in underlying the relationship between fetal growth and T2D had come from the study of twins. Studies of adult twins in Denmark revealed that, in both monozygotic (identical) and dizygotic (nonidentical) twin pairs who were discordant for T2D, the diabetic twin had a significantly lower birth weight than the normoglycemic cotwin (Poulsen et al., 1997). If it is assumed that the monozygotic twins are genetically identical, then, the difference in birth weight must be related to the fetal environment. These studies thus provide strong evidence for the importance of a nongenetic intrauterine factor in the development of type 2 diabetes in later life. Assessing the impact of maternal nutrition on the health of offspring in humans is difficult. Investigations involving individuals conceived during conditions of famine have provided direct evidence of the effects exerted by maternal nutrition during gestation and lactation on the overall health of the adult offspring. The Dutch famine, which occurred in the western part of The Netherlands at the end of World War II, was a short period of famine lasting from December 1944 to May 1945. Prior to the onset of the famine, the affected area of The Netherlands consisted of a reasonably well-nourished population. The occurrence of this abrupt famine therefore granted researchers a unique opportunity to retrospectively study the effect of maternal nutrition on offspring's glucose tolerance. Compared with individuals born the year before the famine, those who were in utero during the famine had higher plasma glucose levels, 2 h after a standard oral glucose tolerance test (Ravelli et al., 1998).

However this association was not observed in the Leningrad Siege Study (Stanner et al., 1997). The inconsistent results might be due to differences in postnatal environmental life exposures. Although the Dutch population rapidly developed into a wealthy and rich population after the famine, the Leningrad people remained relatively poor. In a more recent study of a large sample of Chinese adults, a significant association was found between severe famine exposure during the fetal period and an increased risk of hyperglycemia in adulthood (Li et al., 2010). The association was stronger in subjects with a Western dietary pattern or higher economic status in adulthood. No consistent association was observed between famine exposure during childhood and hyperglycemia. These studies therefore provided direct evidence that poor maternal nutrition leads to increased susceptibility to T2D in the offspring.

The mechanisms that underlie the association between poor maternal nutrition and T2D are unclear. Several studies in children and adults have shown that non-diabetic and pre-diabetic subjects with low birth weight are insulin resistant and, thus, predisposed to develop T2D (Barker, 2004; Valdez et al., 1994; Bhargawa et al., 2004; Li et al., 2001; Boney et al., 2005; Clausen et al., 1997; Flanagan et al., 2000). Adults born small for gestational age showed a significantly higher percentage of body fat (Jaquet et al., 2000) and their insulin sensitivity adjusted for either BMI or total fat mass, was markedly decreased. In fact it was first thought that the adverse effect of IUGR on glucose homeostasis is mediated through programming of the fetal endocrine pancreas (Hales et al., 1991), since IUGR infants have reduced plasma concentrations of insulin (Economides et al., 1989) and beta-cell numbers (Van Assche et al., 1977). However, several studies found no impact of low birth weight on insulin secretion in humans (Barker, 2004; Clausen et al., 1997; Flanagan et al., 2000). To address this discrepancy and since insulin sensitivity per se has a profound impact on insulin secretion, Jensen et al. (2002) measured both insulin secretion and insulin sensitivity in well-matched Caucasian glucose-tolerant men either IUGR or controls. To eliminate the major confounders, such as 'diabetes genes', none of the participants had a family history of diabetes, hypertension and ischemic heart disease. There was no difference between the groups with regard to current weight, body mass index (BMI), body composition and lipid profile. When adjusted for insulin sensitivity, insulin secretion was found reduced by 30%. However insulin sensitivity was found normal in the IUGR subjects. The authors hypothesized that defects in insulin secretion might precede defects in insulin action and that when IUGR individuals accumulate body fat, they develop insulin resistance (Jensen et al., 2002). This is entirely consistent with the concept that despite insulin resistance being a crucial component of T2D in humans, the failure of beta-cell function and growth determines progression to the diabetic phenotype (Weir et al., 2001). Thus, decreased substrate availability to the IUGR fetus caused by uteroplacental insufficiency might have permanently impaired pancreatic beta-cell growth by neogenesis and proliferation processes which take place mostly during the fetal-neonatal period. This is consistent with the observation that pancreatic tissue taken from human fetuses with severe IUGR is characterized by a reduction in endocrine cell mass (Van Assche & Aerts, 1979). However this has not been confirmed since no difference was also found between IUGR and control human fetuses in insulin-positive area or islet organization during the last two months of pregnancy (Beringue et al., 2002).

To summarize, what are the more common factors that confer coincident risk of T2D and low birth weight? Although alterations in both insulin secretion and insulin action are



possible, a number of points support the hypothesis that early impairment in beta-cell development leads to fetal growth and predispose individuals to development of T2D later in life. Indeed, beta-cell mass deficit has been increasingly recognized as a central cause of T2D over the years (Meier, 2008). The importance of beta-cell mass for T2D risk has been further highlighted by the results of recent genome-wide scans that have linked the likelihood of developing T2D to genetic defects in insulin secretion (Saxena et al., 2007; Scott et al., 2007; Zeggini et al., 2007). Importantly, among these T2D loci, two of them (CDKAL1 and HHEX-IDE) which are associated with significant impairments in beta-cell function (Pascoe et al., 2008; Groenewoud et al., 2008), have been related to low birth weight (Freathy et al., 2009). In this case, the most likely explanation for the association between low birth weight and T2D risk seems to be a genetically determined defective development of beta-cells leading to insufficient insulin secretion. The intrauterine insulin deficiency may then impair fetal growth (Terauchi et al., 2000), while insufficient insulin secretion later in life may confer T2D risk.

### 3. Perinatal risk factors for diabetes in later life - Animal studies

Thank to abundant studies, mostly in rodents in which the foetal environment can be manipulated, a substantial body of data now addresses the mechanisms involved in the developmental programming of glucose intolerance and T2D.

#### 3.1 IUED models

In rat, maternal diabetes may be induced experimentally by streptozotocin (STZ) injection that selectively destroys beta-cells. Mild or severe diabetes ensue depending on the dose used. At birth, the progeny of mild diabetic mothers had normal weight or slight macrosomia and an enhanced percentage of pancreatic endocrine tissue due to hyperplasia and hypertrophy of the islet cells (Aerts et al., 1990 ; Reusens-Billen et al., 1984), leading to a higher beta-cell mass that was hyper-vascularized (Reusens & Remacle, 2001). The pancreatic insulin content and insulin secretion were raised in these fetuses (Kervran, et al., 1978). On the other hand, fetuses from severe diabetic dams were small at birth and had decreased pancreatic weight (Aerts et al., 1997). Their beta-cells were almost degranulated, leading to low pancreatic insulin content and low plasma insulin (Kervran, et al., 1978). Similar endocrine pancreas/beta-cell alterations with low beta-cell mass have been reported in fetuses from spontaneous diabetic BB rats (Verhaeghe et al., 1989) or spontaneous diabetic GK rats (Serradas et al., 1998; Miralles & Portha, 2001). The long-term consequences have been evaluated in the progeny of these models. Impaired glucose tolerance was observed in the offspring of mild STZ diabetic rats due to lower insulin secretion in response to glucose, while insulin resistance was reported in the offspring of the severe STZ diabetic mothers (Aerts & Van Assche, 2006; Han et al., 2007; Grill et al., 1991). Glucose tolerance was also impaired in offspring of normal mothers receiving glucose infusion during late gestation, and it was associated to decreased glucose-induced insulin secretion (Ktorza et al., 1990; Aerts et al., 1990; Oh et al., 1988; Gauguier et al., 1991).

The greatest difficulty in most animal models of diabetic pregnancy has been the attainment of a stable degree of mild hyperglycemia during gestation. Though useful, most techniques used to achieve models of diabetes in pregnancy have some drawbacks. Maternal glucose infusions limited to the last trimester of pregnancy result in hyperglycemia and

hyperinsulinemia, and do not mimic the relative insulin deficiency of gestational diabetes (Bihoreau et al., 1986). The multiple lipid and protein abnormalities associated with diabetes may be as important in the induction of fetal abnormalities as hyperglycemia, but they are not replicated by the maternal glucose infusion model. A concern of studies using STZ during pregnancy is the possibility that the toxin might cross the placenta and be directly harmful to the fetal pancreas and other fetal tissues, and thus make any analysis of the long-term effects of hyperglycemia *in utero* difficult (Ryan et al., 1995). The problem may be circumvented by giving STZ to female neonates who will later become pregnant: this will result in moderate gestational hyperglycemia (Triadou et al., 1982). Finally it must be recognized that none of the previously mentioned models will serve directly as a model of human gestational diabetes.

An ideal animal model to test the isolated impact of diabetic pregnancy would enter the pregnancy in a euglycemic state, become exposed to hyperglycaemic during whole pregnancy and return postpartum to normoglycemic environment. Such a model also would allow study of the long-term effects of diabetes independent of any genetic influence. It was recently proposed that the pregnant GK rat being transferred normal Wistar (W) rat embryo represents a more relevant paradigm in such a perspective (Gill-Randall et al., 2004). Using the GK/Par rat we have transferred W rat oocytes to diabetic GK/Par females and at their birth the W neonates were suckled by non-diabetic W foster mothers. Under these unique conditions, we have found that maternal diabetes negatively imprints the growth of a genetically normal (Wistar) beta-cell mass in a way as the insult is still present later at adult age as a decreased beta-cell population (Chavey et al., 2008; Portha et al., 2009).

### 3.2 IUGR models

Not only maternal diabetes but also intrauterine undernutrition induced by several means such as protein or calorie restriction, or alteration in the availability of the nutrients by placental insufficiency alter early islet development and provoke lasting consequences in rodents.

Global restrictions (to 40-50% of normal intake) in the last week of rat pregnancy results in low birth weight offspring with decreased beta-cell mass. Although these animals can regain their body and pancreatic weights upon normal postnatal feeding, they still demonstrate a reduced beta-cell mass and insulin content in adulthood (Garofano et al., 1997; Bertin et al., 2002). Extending this level of nutrient restriction during suckling results in a permanent reduction of beta-cell mass (Martin et al., 1997; Garofano et al., 1998) and subsequent age-dependent loss of glucose tolerance in the offspring (Garofano et al., 1999). Underfeeding the rat mothers during the first two trimesters of gestation exerts no adverse effect upon insulin secretion and insulin action in the adult male offspring (Portha et al., 1995).

The maternal protein restriction (5-8% as compared to 20% in normal diet) model has been one of the most extensively studied models of IUGR. The low-protein-fed mothers give birth to growth-restricted offspring (Snoeck et al., 1990; Dahri et al., 1991; Langley-Evans et al., 1998; Desai et al., 1996; Fernandez-Twinn et al., 2005), and when suckled by their mothers maintained on the same low-protein diet, they remain permanently growth restricted, despite being weaned on a normal diet (Desai et al., 1996). Reduced placental weight and endocrine and metabolic abnormalities are also observed (Dahri et al., 1991; Fernandez-Twinn et al., 2003; Ozanne et al., 1998). Despite young offspring of low-protein-fed dams demonstrating improved glucose tolerance (Ozanne et al., 1998; Shepherd et al., 1997), the

male offspring undergo an age-dependent loss in glucose tolerance, such that by 17 months of age they develop T2D and insulin resistance (Petry et al., 2001). Female offspring only develop hyperinsulinemia and impaired glucose tolerance at a much later age (21 months) (Fernandez-Twinn et al., 2005). Studies in this model have also demonstrated reductions in beta-cell mass (Snoeck et al., 1990), skeletal muscle mass (Desai et al., 1996), central adipose deposit weights (Shepherd et al., 1997; Ozanne et al., 2000) and insulin signalling defects in muscle, adipocytes and liver (Ozanne et al., 1996; Ozanne et al., 2000; Ozanne et al., 2005). This IUGR model has also been associated with the development of hypertension with the kidney and the renin-angiotensin system as playing a role (Langley-Evans et al., 2003). Administration of either dexamethasone or carbenoxolone (to inhibit 11 beta-hydroxysteroid dehydrogenase type 2) to normal pregnant rats also causes fetal growth retardation and the adult offspring are hypertensive and hyperglycemic, with hyperactive hypothalamic-pituitary-adrenal axis (Seckl, 2004). Fetal growth retardation may also result from experimental uteroplacental insufficiency (UPI). Fetal UPI rats have decreased levels of glucose, insulin, IGF1, amino acids and oxygen (Ogata et al., 1986; Simmons et al., 1992; Unterman et al., 1990). UPI offspring develop diabetes in later life (Simmons et al. 2001; Boloker et al., 2002) with a phenotype that is similar to that observed in T2D humans with alterations in insulin secretion and action and a failure of beta-cell function and growth (Holemans et al. 2003; Stoffers et al., 2003).

### 3.3 IUEO models

There are several reports on the consequences of a high fat diet (during gestation only or both gestation and lactation) on the adult progeny. High fat diet consumption by female rats malprograms the male offspring for glucose intolerance and increased body weight in adulthood (Srinivasan et al., 2006). Some of the observed consequences include reduced whole body insulin sensitivity, impaired insulin secretion and changes in the structure of pancreas (Guo & Jen, 1995; Taylor et al., 2005), defective mesenteric artery endothelial function (Khan et al., 2005), hypertension (Khan et al., 2003; Langley-Evans et al., 1996), alterations in renal functions (Armitage et al., 2005), increased body adiposity (Guo & Jen, 1995; Khan et al., 2005), deranged blood lipid profile (Guo & Jen, 1995; Karnik et al., 1989; Khan et al., 2003), hyperleptinemia (Taylor et al., 2005), and proatherogenic lesions (Palinski et al., 2001). There are not many reports on fetal islet adaptations due to a high fat dietary modification in the dam. Cerf et al. (2005) demonstrated that feeding female rats with a high fat diet throughout gestation resulted in significant decreases in beta-cell volume and number resulting in hyperglycemia in 1-day-old newborn rat pups without changes in serum insulin concentrations. However, the report of fetal hyperinsulinemia in the high fat term rat fetus (Srinivasan et al., 2006) is not consistent with this finding.

Also male mice whose mothers consumed a high fat diet were heavier, glucose intolerant and insulin resistant, and produced second-generation offspring who were insulin resistant, although not obese (Dunn & Bale, 2009). Whether this is a consequence of paternal *in utero* exposure or their adult sequelae of obesity and diabetes, is unclear. It was recently reported that chronic high fat diet consumption in father rats induced increased body weight, adiposity, impaired glucose tolerance and insulin sensitivity in their offspring (Ng et al., 2010). Relative to controls, their female offspring had an early onset of impaired insulin secretion and glucose tolerance that worsened with time, and normal adiposity. Among the differentially expressed islet genes, hypomethylation of the *Il13ra2* gene was demonstrated.



This is a proof of concept that paternal high-fat-diet exposure programs beta-cell dysfunction in rat F1 female offspring. This is the first report in mammals of non-genetic, intergenerational transmission of metabolic sequelae of a high fat diet from father to offspring (Ng et al., 2010).

Among the many types of maternal metabolic stress used to produce IUGR, hypercholesterolemia combined to high fat diet was recently added since feeding LDL receptor null (LDLR<sup>-/-</sup>) mice a high fat resulted in litters with significant growth retardation. The LDLR<sup>-/-</sup> high fat diet offspring developed significantly larger atherosclerotic lesions by 90 days compared with chow diet offspring (Bhasin et al., 2009). Importantly, maternal hypoaminoacidemia proved to be an important antecedent in this hypercholesterolemic IUGR mouse (Bhasin et al., 2009) as in a protein-deficient IUGR mouse model (Bhasin et al., 2009) and a IUED rat model (Aerts et al., 1989). An important between these mechanisms may contribute to adult glucose intolerance onset, obesity, and atherosclerosis. In this study beta-cell mass was not investigated.

To sum-up, it turns to be manifest that despite differences in the type, timing, and duration of intrauterine insult, most animal models of IUED, IUEO or IUGR have outcomes of impaired glucose tolerance or T2D, similar to IUED, IUEO or IUGR humans.

#### **4. Various early life stressors, the same target: The developing beta-cell mass**

As abundantly illustrated in animal models, many early life stressors such as maternal hyperglycaemia, undernutrition, overnutrition, hypercholesterolemia, corticosteroid therapy, uteroplacental insufficiency, or hypoxia, trigger a beta-cell mass adaptive response in the fetus.

##### **4.1 Critical windows for beta-cell adaptive response to early life stressors**

The development of the endocrine pancreas starts from a pool of common precursor cells that become progressively committed to the endocrine lineage under the control of a hierarchical network of transcription factors. During late fetal and early postnatal life, the beta cell mass is determined by the recruitment of undifferentiated precursors, as well as the replication and apoptosis rates of the beta cells. Obviously, any disturbance of the environment of the endocrine cells at a specific developmental time-point, as it occurs in a perturbed intra-uterine milieu, may modify the balance of controlling factors, thereby contributing to an adaptive beta-cell growth response which is metabolically appropriate on the short term. However this adaptive response may turn to be detrimental if maintained on the long term, as it may foster beta-cell failure and diabetes later in life. We are largely ignorant of when programming may be initiated during development.

##### **4.1.1 Pre-implantation**

An early onset for programming was indicated, as maternal low protein diet during only the preimplantation period of rat development (0-4 days after mating), before return to control diet for the remainder of the gestation, induced blastocyst abnormalities and programming of postnatal growth rate and hypertension (Kwong et al., 2000). More specifically it was shown that preimplantation embryos collected from dams after 0-4 days of maternal low

protein diet displayed significantly reduced cell numbers, within the inner cell mass and trophectoderm lineages, apparently induced by a slower rate of cellular proliferation. The low protein diet significantly reduced insulin and essential amino acid levels, and increased glucose levels within maternal serum by day 4 of development. These data indicate that the mildly hyperglycemic and amino acid-depleted maternal environment generated by undernutrition may act as an early mechanism of programming and initiate conditions of 'metabolic stress', restricting early embryonic proliferation and the generation of appropriately sized stem-cell lineages. In chemically or genetically obtained rat diabetes models in which maternal serum insulin depletion and hyperglycemia are induced, proliferation of inner cell mass or total cell numbers within blastocysts is inhibited (Lea et al., 1996; Pampfer et al., 1997). Therefore the preimplantation embryo is particularly sensitive to metabolic modifications that may have programming consequences (Reik et al., 1993; Dean et al., 1998), and one possibility is that the preimplantation embryo itself is programmed.

#### **4.1.2 Post-implantation**

Embryo transfer experiments may also help to dissociate the impact of the maternal environment into early (pre-implantation) versus late gestation (postimplantation). We recently found that embryos (blastocysts) from a nondiabetic Wistar strain, placed into a diabetic GK/Par uterus, develop a reduced beta-cell mass which remains low on the long term (Chavey et al., 2008). Data with rat models of prenatal undernutrition (Dumortier et al., 2007) also illustrate that low-energy and low-protein diets that reduce the development of the beta-cell mass in both cases, act at different critical time-windows. The beta-cell mass is deficient in the low-energy pancreas because this diet reduces neogenesis, probably because of high glucocorticoid levels, rather than by impairing vascularisation and proliferation. Early gestation is thus a very sensitive period in this model. By contrast, pancreatic alterations take place at a later fetal stage in the low-protein model and the beta-cell mass is deficient in this case because this diet reduces beta-cell vascularisation and proliferation without altering beta-cell differentiation (Dumortier et al., 2007).

#### **4.1.3 Postnatal versus prenatal**

Further support for the crucial impact of prenatal nutritional environment is the recent report that prenatal nutrient restriction in both male and female rats led to an inappropriate postnatal beta-cell mass formation attributed to a decrease in the rate of beta-cell replication and beta-cell neogenesis (Matveyenko et al., 2010). In contrast, male and female rats exposed to postnatal nutrient restriction alone (with normal prenatal nutrient exposure) were characterized by decreased pancreatic and body weights, but a weight-adjusted beta-cell mass higher than control animals (Matveyenko et al., 2010). Another illustration is offered by observations in normal rat pups reared artificially on a high carbohydrate milk formula (Patel & Srinivasan, 2002): such alteration of nutrition during the suckling period only, induced persistent adaptation of energy metabolism in adulthood (obesity, glucose intolerance, impaired insulin secretion).

#### **4.2 Molecular mechanisms mediating the perinatal beta-cell adaptive response**

Molecular mechanisms responsible for impaired beta-cell mass formation after IUGR have come under investigation. First, it has been proposed that IUGR can result in a reduction of

the embryonic beta-cell progenitor pool, leading to inappropriate postnatal beta-cell formation. Stanger et al. (2007) demonstrated that selective genetic reduction in the size of Pdx1+ pancreatic progenitors during the fetal period results in impaired beta-cell formation during the postnatal period with consequent development of glucose intolerance during adulthood. Consistent with this, maternal food restriction leads to significant reduction in Pdx1+ and Ngn3+ (Neurogenin 3) pancreatic precursors during embryonic development in rats, decreased postnatal beta-cell formation, and inability to expand beta-cell mass in response to pregnancy (Garofano et al., 1998; Blondeau et al., 2002). Another mechanism proposed to explain reduced beta-cell formation after IUGR is related to prenatal glucocorticoid exposure. Maternal undernutrition significantly increased both fetal and maternal corticosterone concentrations in rats (Blondeau et al., 2001). Subsequently, maternal and/or fetal overexposure to glucocorticoids (via administration of dexamethasone) impairs both fetal and postnatal beta-cell formation in rodents and nonhuman primates (Blondeau et al., 2002; Bréant et al., 2006; De Vries et al., 2007; Gesina et al., 2004). Blondeau et al. (2001) have shown that fetal corticosterone concentrations are inversely correlated with fetal insulin content and postnatal beta-cell formation in rats. Evidence suggests that glucocorticoids can exert a direct effect on the developing fetal pancreas via transcriptional modulation of transcription factors involved in beta-cell formation and differentiation (Bréant et al., 2006). Glucocorticoid receptors are present in the pancreas during embryonic development of rodents and humans (Bréant et al., 2006) and glucocorticoids can bind to the Pdx1 promoter and thus suppress fetal endocrine cell differentiation (Bréant et al., 2006). Glucocorticoid treatment has been shown to significantly reduce fetal expression of key endocrine transcription factors such as Pdx1 and Pax6 but simultaneously increase expression of transcription factors that regulate development of the exocrine pancreas (Gesina et al., 2006).

The UPI model of IUGR (due to bilateral uterine artery ligation) is also characterized by a permanent decrease in islet Pdx1 mRNA expression. This decrease has recently been shown to be due to progressive epigenetic silencing of the Pdx1 gene locus secondary to proximal promoter methylation (Stoffers et al., 2003; Park et al., 2008) and it may be responsible for the decreased rate of beta-cell replication and inappropriate postnatal beta-cell mass development (Stoffers et al., 2003; Kulkarni et al., 2004).

It has also been demonstrated that the UPI or the low protein IUGR offspring experience increased oxidative stress and impaired mitochondrial function (Simmons et al., 2005). The mitochondrial dysfunction was not limited to just the beta-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 T2D (Peterside et al., 2003; Selak et al., 2003). Also exposure to a Western-style diet before and during pregnancy (an IUEO model) alters the redox state as early as preimplantation development, leading to mild oxidative stress associated with inflammation. The finding that administration of antioxidants to the dam reverses oxidative stress and completely prevents the development of glucose intolerance and increased adiposity in the adult offspring suggests that oxidative stress plays an important role in the development of adiposity in this case (Sen & Simmons, 2010).

Some studies in the low protein IUGR model 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 (Chen et al., 2007). While DNA is being targeted throughout by ROS, there are particular regions that are known to be more sensitive to ROS-mediated damage, for example telomeres. Telomeres comprise GC-rich repeats 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. Investigations using a low protein IUGR model have indeed reported a decrease in longevity in the offspring (Jennings et al., 1999; Chen et al., 2009) accompanied by reduction in mitochondrial antioxidant defences (Tarry-Adkins et al., 2009) and telomere length in islets (Tarry-Adkins et al., 2009).

Pancreatic islet development has been shown to be influenced by a number of growth factors including the insulin-like growth factors, IGF-I and IGF-II whose expression *in utero* is regulated by nutrient and hormone concentrations. IUGR modify expression of both IGF genes in a variety of fetal tissues. In a low protein IUGR rat model with a decreased beta-cell mass and beta-cell replication and an increased rate of beta-cell apoptosis, gene expression for IGF-II but not IGF-I was found reduced in the fetal pancreas and this was (Petrik et al., 1999). In a different IUGR model with more severe global food restriction which induced hyperinsulinemia and an increase in beta-cell mass in their fetuses (Alvarez et al., 1997), the fetal phenotype was associated with an increase in pancreatic IGF-I expression, islet IGF-1R (Martin et al., 2005) and IRS-2 (Fernandez et al., 2007). In the fetal GK/Par rat exposed to mild hyperglycemia during gestation (a model of IUED), data from our group suggest that the beta-cell deficit (reduced by more than 50%) starts as early as fetal age 16 days E16 and reflects decreased beta-cell proliferation, a limitation of beta-cell neogenesis from precursors and increased apoptosis of both beta-cells and their precursors (Calderari et al., 2007). Notably, Pdx1 and Ngn3 expression were decreased on E18 but normally expressed on E13 (Calderari et al., 2007). Defective signalling through the IGF2/IGF1-R pathway may represent the primary instrumental anomaly since IGF2 and IGF1-R protein expressions are already decreased within the GK/Par pancreatic rudiment at E13, at a time when beta-cell mass (first wave of beta cell expansion) is in fact normal (Miralles & Portha, 2001). Low levels of pancreatic IGF2, associated with beta-cell mass deficiency, are maintained thereafter within the fetal pancreas (Serradas et al., 2002). Crossbreeding protocols between non-diabetic W and diabetic GK rats showed that in late gestation (E18), pancreatic IGF2 protein expression was as low in GKmother/GKfather and Wmother/GKfather crosses than in GKmother/GK father crosses (Serradas et al., 2002). These findings rather support the hypothesis that the pancreatic IGF2 anomaly in the GK diabetic model is linked to a genetic determinism. This view is also consistent with the results of genetic analyses that linked a locus containing the gene encoding IGF2 to diabetes in the GK rat (Gauguier et al., 1996). The *Igf2* gene is subjected to paternal genomic imprinting. However, because the *Igf2* expression is similarly affected in fetuses, regardless of whether the father is W or GK (Serradas et al., 2002), we cannot conclude to a simple change of *Igf2* gene imprinting in the GK rat.

Finally, studies have demonstrated that the maintenance of methylated histone H3 Lys4 by Set7/9 a member of the SET methyltransferase family, is crucial to Pdx1 activity in beta-cell lines (Chakrabarti et al., 2003; Francis et al., 2005; Deering et al., 2009). This led to the hypothesis that Set7/9 may represent a novel chromatin-modifying protein that functions in part through its recruitment to target genes by cell-specific transcription factors such as Pdx1. Since, a role of histone methyl transferases, particularly set7, has also been demonstrated in the sustained deleterious effects of chronic hyperglycemia on human



microvascular endothelial cells (Siebel et al., 2010), such an epigenetic change could potentially be involved in the deleterious effect of high glucose upon the fetal pancreas in the IUED models.

### **5. Various early life stressors, one ultimate programming agent: Perinatal hyperglycemia**

As abundantly illustrated in animal models, early life stressors such as maternal undernutrition, overnutrition, hypercholesterolemia, corticosteroid therapy, uteroplacental insufficiency, or hypoxia, program metabolic adaptations that favor survival initially, but are ultimately detrimental to adult health. Interestingly, a crucial commonality exists between these models with quite different etiologies: in most of the cases, the altered maternal/fetal metabolism appears to be associated with a diabetogenic effect in the adult offspring either male or female, resulting in a permanent deficiency of the endocrine pancreatic function (F1). In females, the combination of a latent diabetogenic tendency (low insulin response) and the metabolic stress of pregnancy promotes gestational diabetes. F1 gestational diabetes per se is an inducing factor for impaired glucose tolerance and gestational diabetes again in the next female generation (F2).

Finally, the relevant message is that programming of the endocrine pancreas ultimately originates from hyperglycemia experienced during the fetal and/or early postnatal life, whatever the etiology of maternal hyperglycemia is primary (in F0 diabetic mothers) or secondary (in F1 diabetic mothers issued from F0 mothers exposed to undernutrition, UPI, or high glucocorticoid).

### **6. Transgenerational inheritance of beta-cell mass programming**

While a large number of animal studies have shown the effects of undernutrition during foetal/perinatal development on the glucose metabolism of offspring (F1) in adulthood, several studies have shown that glucose metabolism is also altered in the offspring (F2) as well as grand offspring (F3) of fetally malnourished F1 females, even when the F1 and F2 females have been well nourished since weaning (Aerts & Van Assche, 2006; Benyshek et al., 2006). With a aim to dissect the relative parental contributions that lead to F2 offspring outcomes in these models of maternal (F0) undernutrition, it was recently reported that F1 males exhibit moderate hyperglycemia and IGT with aging and impaired glucose-stimulated insulin secretion and that all F2 offspring of F1 males or F1 females develop glucose intolerance (Jimenez-Chillaron et al., 2005). Therefore, intergenerational progression of glucose intolerance can derive from both the maternal and paternal lines. This is an experimental proof that transgenerational transmission of IGT may also occur through the paternal lineage, besides the more widely accepted maternal and grand maternal inheritance of diabetes (Zambrano et al., 2005; Drake et al., 2005; Blondeau et al., 2002; Benyshek et al., 2006).

Conceptually, transgenerational inheritance of disease risk may be mediated by nongenomic mechanisms, including either 1) epigenetic mechanisms (Ozanne & Constancia, 2007; Pinney & Simmons, 2009; Drake & Liu, 2009; Waterland & Michels, 2007) or 2) other broader indirect mechanisms associated with parental physiology (Gluckman et al., 2007). First, alterations in nutrition during development can alter epigenetic marks, thus regulating gene expression through DNA methylation and/or histone modifications. Interestingly, such epigenetic modifications may progress with aging during postnatal life, in association with

metabolic phenotypes, as recently observed at the Pdx1 and GLUT4 loci in UPI rats (Park et al., 2008; Raychaudhuri et al., 2008). If these epigenetic changes occur in the germ line, they can be inherited through meiosis (Chong et al., 2007), thus providing a plausible explanation for intergenerational effects, transmitted via either maternal or paternal lines. In addition, other indirect biological processes may influence phenotypes in subsequent generations. For example, physical constraints may alter birth size through the maternal lineage: since uterine size is reduced in girls that are born small and remain short, this may influence fetal growth and reduce weight in their progeny (Gluckman et al., 2007).

Furthermore, maternal metabolism may also influence cross-generational phenotypes (Aerts & Van Assche, 2006). Maternal undernutrition during pregnancy (F0) increases risk for developing diabetes and obesity in her offspring (F1). When these high-risk adult F1 females become pregnant, the metabolic stress of pregnancy may result in hyperglycemia and/or overt gestational diabetes that may, in turn, contribute to defective beta-cell mass and increased diabetes risk in F2 offspring (Aerts & Van Assche, 2006). By this mechanism gestational diabetes may pass from one generation to the next one. In these last examples, intergenerational transmission of phenotypes would occur exclusively through the maternal lineage, as opposed to the epigenetic mechanisms mentioned above. Such a scenario is relevant to the GK/Par rat, since the GK/Par mothers are mildly hyperglycemic through their gestation and during the suckling period. It offers a rationale to elucidate several clues: 1/ the initiation of pancreas programming in the F1 offspring of the first founders (F0), since the GK line is issued from intercrosses between Wistar females and males with borderline IGT but otherwise normal basal blood glucose level (Goto et al., 1975); 2/ the progression of the IGT phenotype until a stable mild diabetic phenotype was reached among the generations (n=35) (Goto et al., 1975); 3/ the lack of attenuation of the diabetic GK phenotype overtime (along more than 20 years and 80 generations), since offspring of GK female/W male crosses were more hyperglycemic than those of W female/GK male crosses (Gauguier et al., 1994).

## **7. Epigenetic mechanisms mediating the diabetes risk associated with beta-cell mass programming**

Several lines of evidence indicate that epigenetic modification may be a key unifying mechanism mediating risk associated with a perturbed intrauterine environment. First, disruption of physiologic responses and functional capacity as observed in multiple tissues in of IUED or IUGR animals and humans, including muscle, adipose, pancreas, liver, and CNS may be related to histone modification and DNA methylation thereby altering related gene expression (Waterland & Michels, 2007).

The preimplantation embryo is particularly sensitive to epigenetic modifications that might permanently alter the phenotype in the adult (Reik et al., 1993; Doherty et al., 2000). For example, in the agouti mouse model, folate supplementation of the maternal diet at conception increases DNA methylation of the agouti gene and increases longevity of the offspring (Cooney et al., 2002). Maternal protein restriction has been shown to alter the methylation status of the promoters of the glucocorticoid receptor (Lillicrop et al., 2005), PPAR $\alpha$  (Lillicrop et al., 2008), and the angiotensin receptor (Bogdarina et al., 2007) with parallel changes in gene expression. More recent studies have shown that histone modifications can also be influenced by the early environment. Alterations in histone modifications have also been implicated in mediating the effect of caloric restriction during

the second half of pregnancy on the programmed reduction of GLUT4 expression in the offspring (Raychaudhuri et al., 2008). In the case of the UPI rat model and the pancreatic tissue, Simmons and colleagues have reported a progressive reduction in expression of Pdx1, a key transcription factor regulating pancreatic development and function (Stoffers et al., 2003). Pdx1 expression is reduced by 50% in UPI fetuses and by 80% in adult UPI offspring. Notably, these changes precede the onset of beta-cell dysfunction, suggesting a primary pathogenic role. Since the Pdx1 promoter is a target for epigenetic modification, as it contains a conserved CpG islands and is associated with high levels of histone acetylation. Interestingly, binding of both acetylated histone H3/H4 and the transcription factor USF1 was found abolished in UPI fetuses (Park et al., 2008). While there was methylation at multiple CpGs in UPI adult offspring, no methylation was detected in UPI neonates, indicating that methylation was unlikely to explain Pdx1 repression early in life. Together, these data indicate that progressive silencing of gene expression is largely initiated by early epigenetic changes and is maintained thereafter even in the absence of further experimental insults during postnatal life. UPI also increases histone acetylation of the PPARalpha coactivator PGC-1 and carnitine-palmitoyltransferase I (CPT1) promoters in newborn and young rats, and these changes are associated with increased PGC-1 and CPT1 mRNAs (Fu et al., 2004). Finally, there is now little doubt that epigenetic regulation of gene expression also occurs in humans as a response to early nutritional insult: a recent study has revealed that individuals who were exposed to famine *in utero* during the Dutch Hunger Winter had altered methylation of the Igf2 gene in white blood cells in adulthood (Heijmans et al., 2008).

## 8. Implications for human health

Although the focus of most studies in the metabolic programming field has been on delineating the effects of reduced maternal nutrition, there is now a growing interest in the role of maternal overnutrition in the programming of diabetes risk. The worldwide prevalence of obesity continues to increase, in association with an increase in the risk of metabolic T2D. Indeed, a recent study estimated that the number of people worldwide with diabetes would increase from 171 million in 2000 to 366 million by 2030 if the prevalence of obesity remained constant (Wild et al., 2004), which has major implications for public health strategies worldwide (WHO, 2000). This global trend to increasing obesity is reflected in the increasing numbers of women who are obese during pregnancy (Kanagalingam et al., 2005). Given that the offspring of obese mothers have an increased risk of developing obesity and T2D themselves (Boney et al., 2005; Catalano, 2003; Catalano et al., 2009), the potential impact of the intergenerational consequences of maternal obesity is of great concern for public health policy makers.

Moreover, maternal hyperglycemia per se increases the probability of adolescent obesity and future T2D. To what extent maternal hyperglycemia is fuelling the global rise in obesity and T2D is unknown, but its contribution is highly significant. The exact degree of hyperglycemia that has this effect and the exact timing in pregnancy at which hyperglycemia is impressionable on fetal programming is unknown. The need to identify and treat all women with gestational diabetes is very much dependent on us knowing this. Meanwhile, achieving rigorous glycemic control in women with diabetic pregnancy has to remain a major therapeutic goal.

Several interventions (dietary or pharmacological) to reduce the long-term sequelae of early life programming effects have been used in animal models. For example, the administration of folic acid with a low protein diet during pregnancy prevents the altered phenotype and epigenotype in rat offspring (Lillycrop et al., 2005), and administration of a diet rich in methyl donors prevents the transgenerational increase in obesity in agouti yellow mice (Waterland et al., 2008). Importantly, the timing of such interventions can be crucial. Examples include neonatal leptin treatment which reverses the programming effects of prenatal undernutrition (Vickers et al., 2005). In the UPI rat model, epigenetic silencing of the Pdx1 gene can be reversed during a critical developmental window in the neonatal period, using trichostatin A which inhibit HDACs (Park et al., 2008). In the same model, exposure to Exendin-4 in the neonatal period reversed the detrimental fetal programming of the beta-cell mass and prevented the development of diabetes in adulthood: this was closely related to restoration of pdx1 expression and beta-cell proliferation rate (Stoffers Diabetes 2003). A GLP-1 or Exendin-4 treatment limited to the neonatal pre-diabetic period was also shown to delay the installation and limit the severity of T2D in the GK/Par model (Tourrel et al., 2002). In such context, it is important to note that GLP1-derived drugs that are currently used to treat patients with T2D may target chromatin remodelling. Treating beta-cells from the INS1 cell line or dispersed mouse islet cells with GLP-1 increased global acetylation of histone H3 and increased its phosphorylation in a concentration-dependent manner (Kim et al., 2009). Such histone modifications increased association with the transcription factor phospho- CREB and with cAMP-response CREB coactivator 2. Taken as a whole, these data may provoke optimism - that there may be a window for potential postnatal therapeutic interventions to prevent/modify the “programmed” diabetes risk.

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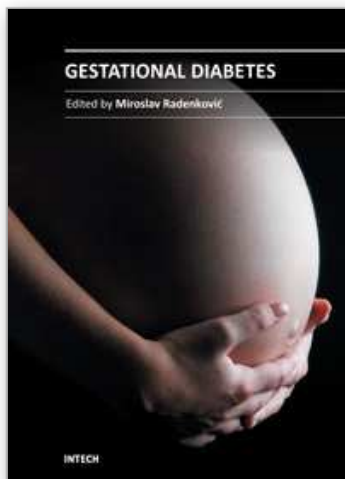
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Gestational diabetes mellitus is defined as hyperglycemia with onset or first recognition during pregnancy. The incidence of gestational diabetes is still increasing and this pathological condition has strong association with adverse pregnancy outcomes. Since gestational diabetes can have long-term pathological consequences for both mother and the child, it is important that it is promptly recognized and adequately managed. Treatment of gestational diabetes is aimed to maintain euglycemia and it should involve regular glucose monitoring, dietary modifications, life style changes, appropriate physical activity, and when necessary, pharmacotherapy. Adequate glycemic control throughout the pregnancy can notably reduce the occurrence of specific adverse perinatal and maternal outcomes. In a long-term prospect, in order to prevent development of diabetes later in life, as well to avoid associated complications, an adequate education on lifestyle modifications should start in pregnancy and continue postpartum.

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