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Review

Maternal diabetes, programming of beta-cell disorders and intergenerational risk of type 2 diabetes

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Abstract

A substantial body of evidence suggests that an abnormal intra-uterine milieu elicited by maternal metabolic disturbances as diverse as malnutrition, placental insufficiency, diabetes and obesity may be able to programme susceptibility of the foetus to later develop chronic degenerative diseases such as obesity, hypertension, cardiovascular diseases and type 2 diabetes (T2D). As insulin-producing cells have been placed centre stage in the development of T2D, this review examines developmental programming of the beta-cell mass (BCM) in various rodent models of maternal protein restriction, calorie restriction, overnutrition and diabetes. The main message is that whatever the initial maternal insult (F0 generation) and whether alone or in combination, it gives rise to the same programmed BCM outcome in the daughter generation (F1). The altered BCM phenotype in F1 females prohibits normal BCM adaptation during pregnancy and, thus, diabetes (gestational diabetes) ensues. This gestational diabetes is then passed from one generation (F1) to the next (F2, F3 and so on). This review highlights a number of studies that have identified epigenetic mechanisms that may contribute to altered BCM development and beta-cell failure, as observed in diabetes. In addition to their role in instilling the programmed defect, these non-genomic mechanisms may also be involved in its intergenerational transmission.

Keywords: Type 2 diabetes; Diabetes risk; Insulin secretion; Maternal diabetes; Beta-cell mass; Epigenomics

1. Developmental origin of type 2 diabetes: Human studies

Type 2 diabetes (T2D) is a complex polygenic disease that often manifests years before its eventual clinical diagnosis [1]. The disease develops due to failure to adequately increase beta-cell function and mass to meet the demands of prevailing insulin resistance [2]. The contribution of beta-cell failure to the pathophysiology of T2D is supported by islet pathology, which reveals a beta-cell deficit of approximately 50% and 65% in people with impaired fasting glucose and T2D, respectively [3]. Consistent with these observations, most of the genes linked with T2D via genome-wide association scans have been shown to influence aspects of beta-cell biology, such as regulation of beta-cell secretory function, and the development and growth of the beta-cell mass (BCM) [4].

It has also long been recognized that nutrient availability during foetal and early postnatal life is an important determinant of adult health [5]. There are strong arguments that T2D is more prevalent among subjects who experienced foetal exposure to maternal diabetes (FEMD), and the role of maternal inheritance in T2D has been reported in a majority of epidemiological studies [6,7]. To determine the role of the intra-uterine diabetic environment per se, the prevalence of diabetes was compared in Pima nuclear families in which at least one sibling was born before and another was born after the mother was diagnosed with T2D. Offspring born after their mother presented with diabetes had a fourfold higher risk of diabetes and a higher body mass index (BMI) score than their full siblings born before

Abbreviations: T2D, type 2 diabetes; IGT, impaired glucose tolerance; F1, first-generation animals procreated by parent (F0) females subjected to metabolic disturbances during pregnancy; F2, second-generation animals procreated by F1 females exposed to intra-uterine metabolic disturbances; BCM, beta-cell mass; FEMD, foetal exposure to maternal diabetes; FEMO, foetal exposure to maternal obesity; UPI, uteroplacental insufficiency; FCR, foetal caloric restriction; FPR, foetal protein restriction.

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their mother developed diabetes [8]. These findings indicate that intra-uterine exposure to a diabetic environment increases the risk of obesity and T2D beyond that attributable to genetic factors, at least in Pima Indians. To circumvent the confounding effect of genes linked to early-onset T2D and transmitted by the pregnant T2D mother, the effect of foetal exposure to type 1 diabetes (T1D) was evaluated in adult offspring lacking T1D immunological markers. A 33% prevalence of impaired glucose tolerance (IGT) was reported in the offspring of T1D mothers compared with none in those with T1D fathers (control group) [9]. Altogether, these findings suggest that foetal exposure to maternal diabetes is indeed associated with abnormal glucose homoeostasis in offspring and may be involved in maternal T2D transmission.

In adult Pima Indians with normal glucose tolerance and exposure to a diabetic intra-uterine environment, their acute insulin response to intravenous glucose was reduced in those offspring with mothers who had been diabetic before pregnancy, whereas it remained normal in those whose mothers had developed diabetes after pregnancy [10]. Body fat and insulin sensitivity (as determined by hyperinsulinaemic–euglycaemic clamp) were similar in the two groups of offspring [10]. In the same study, the acute insulin response was reduced in the offspring with parents (either mother or father) who had early-onset T2D [10], suggesting that the gene(s) linked to early-onset diabetes is(are) associated with reduced insulin secretory response to glucose [11]. The offspring of T1D mothers had reduced insulin secretion that was more pronounced in IGT subjects, but similar fat mass and insulin activity compared with the offspring of T1D fathers [9]. Also, in the non-diabetic offspring of mothers with young-onset T2D (diagnosed at age < 50 years), beta-cell function (early insulin release after oral glucose) was decreased compared with the offspring of fathers with young-onset T2D [12]. Thus, human studies suggest that a defect of insulin secretion is involved in the abnormal glucose tolerance observed in adult offspring exposed to maternal diabetes as foetuses. More important, they found that insulin secretion might be reduced even in normal glucose-tolerant offspring. Nevertheless, in such children and adolescents, insulin resistance may be involved and may be related, at least in part, to heavier body weight.

In addition to these findings in FEMD populations, prenatal nutrient insufficiency resulting in low birth weights has also been associated with increased risks for obesity, cardiovascular disease and T2D [13–15]. The association between low birth weight and development of T2D was first reported in classical studies by Hales et al. [15], who demonstrated a several-fold increase in the incidence of glucose intolerance and T2D in adult men who were born small compared with those born with normal birth weight. Since then, these seminal observations have been consistently replicated by numerous investigators worldwide [16]. Nevertheless, although the epidemiological evidence linking low birth weight with increased susceptibility to T2D is strong [16], the molecular and physiological mechanisms underlying this association are still under investigation [17]. It has long been appreciated that low birth weight is linked to adult insulin resistance, which can contribute to the increased risk of developing T2D [18]. However, the susceptibility to T2D of low-birth-weight individuals has also been hypothesized as attributable to inadequate BCM formation [15]. The foetal period is critical for endocrine pancreatic development in rodents and in humans [19], and the clinical data show that children and adults with low birth weights have impaired beta-cell function compared with their normal-birth-weight counterparts [20,21]. Indeed, one report concluded that human foetuses with severe growth retardation have a reduction in pancreatic endocrine cell mass on autopsy [22]. However, as it is not possible to measure BCM in vivo, this hypothesis cannot be tested directly in humans.

For this reason, the present review has focused on the strengths and limitations of FEMD models to determine the critical periods and types of alterations that might lead to impaired beta-cell quantity and function. Also discussed are the potential mechanisms derived from relevant animal models to explain this outcome, with a particular focus on the role of epigenetic markers.

2. Developmental origin of type 2 diabetes: FEMD models

In rat and mouse models, maternal diabetes can be induced experimentally by injecting streptozotocin (STZ) to selectively destroy beta-cells. Mild or severe diabetes ensues, depending on the dose. At birth, the progeny of mildly diabetic mothers had normal weight or slight macrosomia and an enhanced percentage of pancreatic endocrine tissue due to hyperplasia and hypertrophy of islet cells [23,24], leading to an increased BCM that was also hypervascularised [25]. Pancreatic insulin content and insulin secretion were also raised in these foetuses [26]. In contrast, foetuses from severely diabetic dams were small at birth and had decreased pancreatic weights [27], and their beta-cells were almost degranulated, leading to low pancreatic insulin content and low plasma insulin [26]. Similar beta-cell alterations with decreased BCM have been reported in foetuses from both spontaneously diabetic BB rats [28] (T1D model) and spontaneously diabetic GK rats (T2D model) [29,30]. On evaluating the long-term consequences for the progeny in these models, IGT was observed in the offspring of mildly STZ-induced diabetic rats due to lower insulin secretion in response to glucose, while insulin resistance was reported in the offspring of severely STZ-diabetic mothers [31–33]. Glucose tolerance was also impaired in the offspring of normal mothers receiving glucose infusions during late gestation, and was associated with decreased glucose-induced insulin secretion [23,34–36].

The biggest challenge in most animal models of diabetic pregnancy is to attain a stable degree of mild hyperglycaemia during gestation. Most of the techniques used to achieve models of diabetes in pregnancy, although useful, have drawbacks. Maternal glucose infusions limited to the last trimester of pregnancy result in hyperglycaemia and hyperinsulinaemia, and fail to mimic the relative insulin deficiency of gestational diabetes [37]. Also, the multiple lipid and protein abnormalities associated with diabetes may be as important to the induction of foetal abnormalities as hyperglycaemia, yet these are not replicated by the maternal