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Minireview

Role of T-cells in Diabetic Pregnancy and Macrosomia

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A number of studies have recently addressed the correlationship between diabetic pregnancy/macrosomia and differentiation of T-cells into Th1 and Th2 subsets. Diabetic pregnancy has been found to be associated with a decreased Th1 phenotype and IL-4 mRNA expression. In macrosomic offspring, high expression of IL-2 and IFN-γ mRNA, but not of Th2 cytokines is observed, indicating that the Th1 phenotype is upregulated during macrosomia. T-cells of gestational diabetic rats and their macrosomic offspring seem to present a defect in signal transduction. Indeed, the recruitment of free intracellular calcium concentrations from intracellular pool in T-cells of these animals is altered. The phenotype of regulatory T-cells (T-Reg) is upregulated in diabetic pregnancy and their infants. T-cells in diabetic pregnancy and macrosomic obese offspring are *in vivo* activated. Adipokines and peroxisome proliferator-activated receptor-α (PPARα) also seem to modulate the pro-inflammatory cytokines in these pathologies. Hence, activation of the immune system might be considered as one of the regulatory pathways including metabolic abnormalities in these two pathologies.

Keywords: T-cells, Inflammation, Peroxisome proliferator-activated receptors, Diabetic pregnancy, Macrosomia

Introduction

Maternal diabetes during pregnancy is an important risk factor for foetal overnutrition and macrosomia[1-3]. Macrosomia has generally been defined as a birth weight greater than or equal to the 90th percentile birth weight for gestational age, *i.e.*, infants who weigh >4000 g at delivery, irrespective of gestational age or sex[4-6]. It has been reported to cause a number of prenatal complications such as foetal distress, shoulder dystocia and high incidence of caesarean delivery[5]. After birth, these infants are at increased risk for hypoglycemia, respiratory distress syndrome (RDS), hyperbilirubinemia and hypertrophic cardiomyopathy[5]. Besides, foetal macrosomia is a risk factor for maternal morbidity in type I, type II and gestational diabetic pregnancies[4,7-10].

It is noteworthy that several alterations in the metabolism of carbohydrate and lipid, observed in infants of diabetic mothers at birth also persist postnatally[11-15]. Maternal hypercholesterolaemia during pregnancy is associated with greatly increased fatty streak formation in human foetal arteries and accelerated progression of atherosclerosis during childhood[16]. A good correlation exists between maternal and foetal plasma cholesterol levels in 5–6-month-old human foetuses[17,18]. The role of *in utero programming* during diabetic pregnancy has been recently suggested[1]. *In utero programming* seems to create a kind of "metabolic memory" since the physiological anomalies of the gestational period are responsible at adulthood for the "onset" of the diseases like type II diabetes and obesity. It is possible that foetal hyperinsulinaemia may be an endogenous teratogen during critical periods of development, leading to permanent structural or functional organ changes and consequent *programming* of the "metabolic memory"[19]. Maternal hyperglycemia has been shown to lead to foetal hyperglycemia which stimulates foetal pancreatic islet cells to produce foetal hyperinsulinemia[20].

Insulin receptors have also been suggested to play a role in the increased insulin effects in infants. Evidences have been provided for the defective down-regulation of insulin receptors in hyperinsulinaemic foetuses, like increased insulin binding sites[21]. The insulin concentrations *in utero* may also affect the induction and activity of various hepatic enzymes associated with fat and carbohydrate metabolism[22]. The ability of foetal hyperinsulinemia to increase the availability of farnesylated p21-Ras may represent one of the mechanisms of the growth-promoting

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action of insulin during foetal development[23]. However, another study[24] has shown that the premature leptin surge in undernourished mice alters energy regulation by the hypothalamus and contributes to "developmental origins of obesity".

In this review, we will not describe all the physiological anomalies such as alterations in lipid and lipoproteins, and antioxidant status in macrosomic newborns and their diabetic mothers as a good account on this subject is available elsewhere[1,2]. Hence, we will try to shed light on the implication of T-cell functions in these pathologies. In the review, we will particularly focus on macrosomic offspring as far as the experimental studies are concerned. Sometimes, we will also mention the macrosomic and non-macrosomic offspring, born to diabetic dams.

Cell-mediated Immunity is altered in Diabetic Pregnancy and Macrosomia

As far as the activation of the immune system is concerned, not much is known on the subject since diabetic pregnancy and macrosomia are multifactorial pathologies. However, it has been shown that the abnormalities in humoral and cell-mediated immunity in type I diabetic (T1D) females may persist during pregnancy and hence may complicate immune-foetal interaction[25]. With regard to T-cell activation, only a few studies are available on the subject[25]. In fact, fully activated T-cells are detected in the cord blood of infants and mothers with type I diabetes, but not in infants from normal mothers[25]. In rat model, ConA-stimulated T-cell proliferation is significantly lower in diabetic pregnant rats and their macrosomic offspring as compared to control animals[26].

In human beings, from birth up to 15 years of age, the percentage of total T-cells is found to be higher in children of T1D mothers than in healthy mothers[27]. An increase in MHC class II positive lymphocytes has been observed in infants of T1D mothers compared to controls[28]. Moreover, the newborns of T1D mothers have shown a significant reduction in natural killer (NK) lymphocytes, indicating a deficit in natural immunity at birth[29]. They have also shown an increase in the number of $CD4^+$ T-cells[30]. Gestational diabetic mothers have shown higher numbers of total lymphocytes, $CD8^+$ cells, expressing TCR gamma/delta, and lower numbers of CD3 cells, expressing TCR alpha/beta than controls. Also, infants born to gestational diabetic women have shown higher $CD8^+$ gamma/delta cells than control babies[31]. Furthermore, production of IL-2 in the culture supernatants of mitogen-stimulated lymphocytes of these newborns is higher than that in controls[32]. However, the role of pancreatic and splenic T-helper (Th) subsets in the modulation of these pathologies has not yet been explored. On the basis of production of cytokines, Th cells can be classified into two principal populations — Th1 and Th2. Th1 cells support cell-mediated immunity and as a consequence promote inflammation, cytotoxicity and delayed-type hypersensitivity, whereas Th2 cells support humoral immunity and downregulate the inflammatory actions of Th1 cells[33]. Th1 cells secrete IL-2, IFN-γ and TNF-β, while Th2 cells secrete IL-4, IL-5, IL-6, IL-10 and IL-13[34].

Before, talking of the role of Th subets in diabetic pregnancy and their macrosomic offspring, we would like to mention that we have, in our laboratory, established a model by administrating streptozotocin (STZ) to Wistar female rats[35,36]. Indeed, maternal STZ administration before pregnancy affects fertility and impairs embryo development during the pre-implantation period[37]. We have induced diabetes by STZ injection on day 5 of gestation and hence, STZ exerted no effect on embryo development[38-40]. Pups from the streptozotocin-treated dams whose birth weights were 1.7 SD greater than the mean birth weight of the control pups, were considered macrosomic animals. The mean birth weight of the control pups was 5.73±0.28 g. Therefore, experimental pups with birth weight > 6.2 g were considered macrosomic animals and included in the study. The success rate in obtaining macrosomic pups was 75%. In order to avoid the interference of female reproductive hormones with immune system, only male macrosomic rats were included in the study. Indeed, reproductive hormones have been associated with prevalence, susceptibility and severity of autoimmune disease[41].

To our surprise, we noticed a decreased expression of IL-2 and IFN-γ mRNA both in the pancreas and spleen of diabetic pregnant rats[42] though the progression of type I diabetes has been demonstrated to be closely associated with high expression of mRNA of Th1 cytokines, particularly of IFN-γ[43]. Similarly, rats with diabetic pregnancy exhibited diminished concentrations of circulating IFN-γ, but increased IL-10 levels, as compared to control rats. Hence, low expression of Th1 phenotype in diabetic

pregnant rats may be due to the fact that, during pregnancy, Th1 cytokines are downregulated whereas Th2 cytokines are upregulated[44,45]. This upregulation of Th2 phenotype in the pregnancy is normalized after the delivery[44]. In fact, the shift from Th1 phenotype to Th2 during pregnancy has been shown to encourage vigorous production of antibodies which not only combat infections during pregnancy but also offer passive immunity to foetus[46]. The diminished Th1 cytokines and increased IL-10 may be implicated in maintaining the pregnancy in diabetic rats (Fig. 1). It is interesting to notice that the Th1 cytokines are upregulated in macrosomic offspring (Fig. 1).

Both the diabetic pregnant and macrosomic animals are associated with hyperglycaemia. The difference in Th1 phenotype may be due to different physiological status of animals in two pathologies. Low Th1 profile in diabetic pregnant rats, associated with successful pregnancy may be contributed by elevated levels of reproductive hormones like hCG, whose administration is known to diminish the production of Th1 cytokines[47]. The upregulated Th1 profile in macrosomic animals may be due to their "diabetogenic status", associated with hyperglycaemia and hyperinsulinaemia[48]. A study conducted on Tunisian women with gestational diabetes and their macrosomic babies corroborate these observations[49]. In accordance with the experimental findings, the circulating levels of IL-10 are found increased in these diabetic mothers. While comparing the ratios of Th1/Th2 cytokines, an increase in Th1 phenotype in macrosomic babies is observed[49].

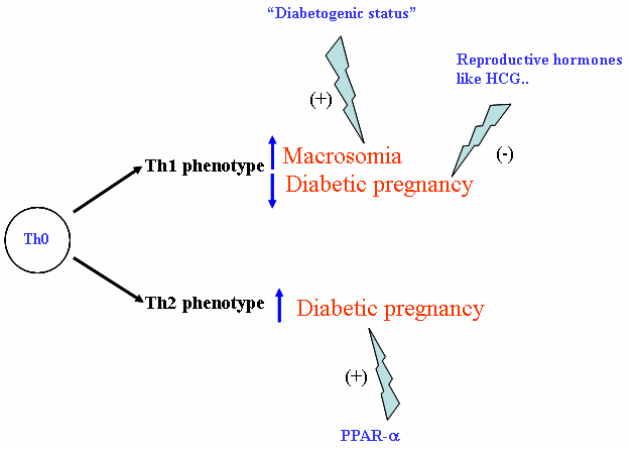

Fig. 1—Th0 cells are differentiated into Th2 phenotype in diabetic pregnancy with concomitant downregulation of Th1 phenotype caused by steroid hormones like hCG. PPARα will be implicated in the upregulation of Th2 differentiation. Macrosomia is associated with an accelerated differentiation of Th0 cells into Th1 phenotype, induced by their diabetogenic status (insulin resistance, hyperglycemia, etc.). (+), Stimulatory effect; (-), inhibitory effect

T-Cells present a defect in Cell Signalling in Diabetic Pregnancy and Macrosomia

During T cell activation, an increase in intracellular free calcium concentrations, $[Ca^{2+}]i$, is one of the earliest events which is triggered as a result of the hydrolysis of phosphatidyl-inositol-diphosphate catalyzed by the phospholipase C (PLC). Hence, PLC gives rise to inositol trisphosphate which mobilizes calcium from endoplasmic pool and diacylglycerol which activates the protein kinase C. According to the capacitative model of calcium entry, first calcium is released via T-cell receptor (TCR) activation from the endoplasmic reticulum and then it is extruded into the extracellular medium. In turn, the cells refill their intracellular emptied pool by opening calcium channels[50]. Ionomycin at 50 nM opens calcium channels and thapsigargin (TG) recruits calcium which belongs to endoplasmic reticulum (ER) pool. Interestingly, the ionomycin-induced increase in $[Ca^{2+}]i$ in T-cells of diabetic mothers and macrosomic offspring is greater than in control rats[26]. In 0% calcium buffer, TG induces increase in $[Ca^{2+}]i$ exclusively from ER pool and no influx occurs in the absence of calcium from the extracellular medium[51]. Hence, both in 100% and 0% calcium media, TG-induced increase in $[Ca^{2+}]i$ in T-cells is higher in diabetic pregnant and macrosomic rats than control animals[26], demonstrating that T-cell calcium signalling is altered during gestational diabetes and macrosomia.

T-Regulatory (T-Reg) Cells are Upregulated in Diabetic Pregnancy

The self-reactive T cells are deleted during their development in the thymus via a process known as central tolerance. However, because this negative selection is incomplete, self-reactive T cells that have escaped from this clonal deletion are supposed to be controlled in the periphery by T-regulatory (T-Reg) cells. These cells suppress activation and expansion of self-reactive escapees[52]. Thus, T-Reg cells control the delicate balance between immunity and tolerance, explaining their important role in autoimmune diseases, cancer, transplantation tolerance, and even allergy. However, their implication in gestational diabetes and macrosomia is not well known. It is

important to mention that these cells constitutively express $CD4^+CD25^+$, a transcription factor called Foxp3 and CTLA-4. The frequency of $CD4^+CD25^+$ T-cells is significantly increased in children born to T1D mothers than in those born to normal women[53]. Besides, $CD4^+CD25^+$ T-cells of children born to T1D mothers exhibit a more pronounced memory phenotype with increased CCR4 expression and down-regulation of CD62L, suggesting an early activation of the foetal immune system as a consequence of maternal immune status. In Kuwaiti women, higher number of $CD4^+CD25^+$, $CD4^+$HLA-DR and $CD4^+CD45RO^+$ T-cells have been observed in gestational diabetic subjects than in the control pregnant ladies[54,55].

PPARα Modulates T-cell Activation in Diabetic Pregnancy

Peroxisome proliferator-activated receptors (PPARs) are ligand-activated transcriptional factors that regulate a large number of genes by transcriptional activation and repression[56]. The three isotypes PPARα, β(δ) and γ have been identified in lower vertebrates and mammals[57]. They exhibit different tissue distribution as well as different ligand specificities and functions[58]. PPARα is highly expressed in the liver and brown adipose tissue and regulates lipid homeostasis. It is activated by natural ligands, such as fatty acids as well as the lipid-lowering fibrates, which are used clinically for the treatment of hypertriglyceridaemia[59]. It plays an important role in the regulation of chronic diseases such as diabetes, obesity and atherosclerosis**.** PARα has been identified in lymphocytes and its expression wanes soon after lymphocyte activation[60]. Indeed, PPARα ligands have been shown to regulate inflammatory responses, as they can inhibit IL-2 production and T-cell proliferation[60]. PPARα ligands have also been shown to increase IL-4 expression[60]. Most of these results argue for an immunosuppressive effect of PPARα, which may promote Th2 immunity necessary for a successful pregnancy[61].

Recently, we conducted a study on wild-type and PPARα-null mice to assess the implication of PPARα in the modulation of T-cell differentiation in murine diabetic pregnancy and their offspring[62]. We found that 50% of PPARα-null mice with diabetic pregnancy aborted, while the abortion rate was only 8.3% in wild-type diabetic dams. Similarly, a high rate of mortality (nearly 79%) was observed in the neonates of diabetic PPARα-null animals. Th1/Th2 balance was shifted to a pregnancy protecting Th2 phenotype in wild-type diabetic dams and to a noxious Th1 immunity in PPARα-null diabetic pregnant mice[62]. It is also interesting to mention that mouse model differs from the rat, as the offspring of the former were not macrosomic, though they were showing the signs of insulin resistance, *e.g.*, hyper-insulinemia and hyperglycaemia. Interestingly, offspring born to diabetic PPARα-null dams were hypoinsulinemic and hyperglycaemic. Nonetheless, PPARα seems implicated in the prevention of maternal abortion, neonatal survival and T-cell differentiation during diabetic pregnancy in mice.

Adipokines Modulate Cytokines in Diabetic Pregnancy and Macrosomia

Adipocytes secrete a number of molecules, including adiponectin, leptin and resistin, that modulate peripheral insulin sensitivity[63]. During insulin resistant state, adipocytes secrete monocyte chemotactic protein-1 **(**MCP-1), which favours the infiltration of macrophages that consequently produce

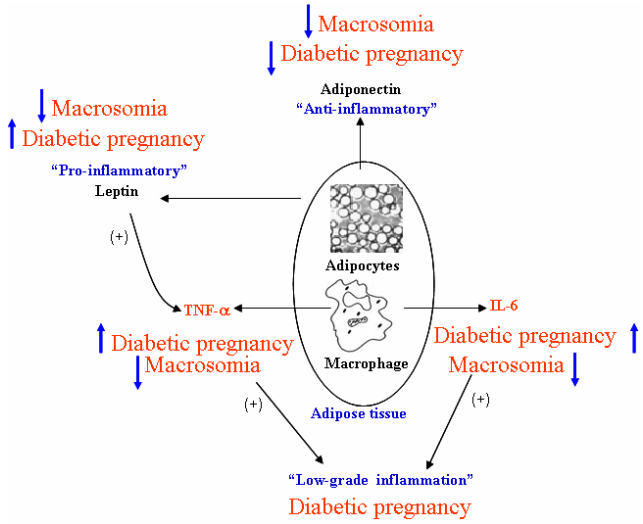

Fig. 2—Low adiponectin levels are associated with the pathogenesis of gestational diabetes mellitus (GDM) and macrosomia [It has been proposed that during insulin-resistant state, macrophages infiltrate adipose tissues and consequently secrete IL-6 and TNF-α. Macrosomia is marked by low levels of leptin, IL-6, and TNF-α. Low leptin levels in these macrosomic babies may contribute to weight gain. The diabetic pregnancy is associated with high concentrations of these agents which might induce "low grade inflammation" responsible for the complications. Leptin will also contribute to inflammation as this agent has been shown to induce increases in TNF-α. (+), Stimulatory effect]

IL-6 and TNF-α in high quantities[64]. From the immunological point of view, adiponectin exhibits anti-inflammatory properties[63] and leptin exerts pro-inflammatory actions and favours the differentiation of Th0 cells to Th1 phenotype[65].

Since adipocytokines may play an important role in the early defects of type 2 diabetes[66], women with gestational diabetes represent an ideal population model to study this inter-relationships[67]. Recent studies have suggested a role for TNF-α, a pro-inflammatory cytokine in this pathology[68-70]. Leptin is also produced by the placenta and involved in weight regulation and lipid metabolism. Contradictory results have been reported on its secretion in gestational diabetes. Elevated leptin levels have been observed in gestational diabetic women in one study[71], while in another study, no such change is observed[72]. However, in another study[73], leptin level has been found reduced in gestational diabetes. The low circulating levels of adiponectin are associated with the pathogenesis of gestational diabetes mellitus and macrosomia[67]. In women with gestational diabetes[49], the adiponectin levels are decreased, whereas the concentrations of inflammatory cytokines including leptin, IL-6 and TNF-α are increased. Adiponectin levels are also decreased in human pregnancies complicated with diabetes mellitus as compared to non-diabetic pregnancies[74]. Leptin, being pro-inflammatory might contribute to the inflammatory state during diabetic pregnancy (Fig. 2). It is important to note that concentrations of TNF-α, IL-6, adiponectin and leptin are decreased in macrosomic infants as compared to control babies. Low leptin levels in the macrosomic babies may contribute to weight gain, as leptin-deficient rodents[75] and humans[76] have been shown to develop marked obesity.

Conclusion

A perusal of above-mentioned studies suggests that T-cells in diabetic pregnancy and macrosomic offspring are *in vivo* activated and are differentiated to Th2 phenotype in diabetic pregnancy and to a Th1 phenotype in macrosomia. The Th2 cells in diabetic pregnancy exert a pregnancy-protecting effect, though the inflammatory state is caused by high concentrations of pro-inflammatory cytokines like IL-6, TNF-α and leptin, and by downregulation of adiponectin, an anti-inflammatory agent. Furthermore, high concentrations of IL-6, TNF-α and leptin also contribute to insulin resistance in this pathology. It is noteworthy that the inflammatory state in macrosomia is contributed by upregulation of Th1 cytokines, but not by IL-6, TNF-α and leptin, as their secretion is downregultaed in this pathology. The phenotype of regulatory T-cells (T-Reg) is upregulated in diabetic pregnancy and their infants. The *in vivo* stimulants, implicated in the modulation of T-cell dichotomy and defective T-cell signalling remain to be ascertained in future. Furthermore, it has to be determined how metabolic modulators like insulin and lipids influence activation of T-cells in these pathologies.

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