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Epigenetic modifications of placenta in women with gestational diabetes mellitus and their offspring

Yi Y *et al*. Epigenetic modifications of placenta in GDM

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Abstract

Gestational diabetes mellitus (GDM) is a pregnancy-related complication characterized by abnormal glucose metabolism in pregnant women and has an important impact on fetal development. As a bridge between the mother and the fetus, the placenta has nutrient transport functions, endocrine functions, *etc.*, and can regulate placental nutrient transport and fetal growth and development according to maternal metabolic status. Only by means of placental transmission can changes in maternal hyperglycemia affect the fetus. There are many reports on the placental pathophysiological changes associated with GDM, the impacts of GDM on the growth and development of offspring, and the prevalence of GDM in offspring after birth. Placental epigenetic changes in GDM are involved in the programming of fetal development and are involved in the pathogenesis of later chronic diseases. This paper summarizes the effects of changes in placental nutrient transport function and hormone secretion levels due to maternal hyperglycemia and hyperinsulinemia on the development of offspring as well as the participation of changes in placental epigenetic modifications due to maternal hyperglycemia in intrauterine fetal programming to promote a comprehensive understanding of the impacts of placental epigenetic modifications on the development of offspring from patients with GDM.

Key Words: Gestational diabetes mellitus; Placental functions; Epigenetics; Offspring development

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Core Tip: The minireview aims to investigate the effect of abnormal placental function on offspring development in pregnant women with gestational diabetes from the perspective of epigenetics.

INTRODUCTION

Gestational diabetes mellitus (GDM) is a common metabolic disorder during pregnancy and refers to an abnormal glucose tolerance that occurs or is first observed during pregnancy. Epidemiological evidence shows that in recent years, the prevalence of GDM has been on the rise worldwide. The international prevalence rate of GDM varies from 6.6% to 45.3%[1], dependenting on the region, population and diagnostic criteria and the total prevalence rate of GDM in China is 14.8%[2]. Like type 2 diabetes, GDM is characterized by relative insulin deficiency caused by changes in the function and mass of β cells and an increase in insulin resistance[3]. The offspring of patients with GDM are more prone to suffer from congenital developmental abnormalities[4,5] and complications such as macrosomia, hypoglycemia, hyperbilirubinemia, respiratory distress syndrome, and later obesity, metabolic disorders and cardiovascular abnormalities[6,7]. GDM has become a public health issue of global concern.

The placenta plays a crucial regulatory role in maintaining fetal growth and development throughout pregnancy, as it has multiple functions, such as nutrient transport and endocrine functions. Moreover, abnormal placental functions can also induce a variety of fetal diseases and complications, such as fetal overnutrition or growth restriction. Previous studies have shown that metabolic abnormalities in GDM patients could damage the structure, morphology and functions of the placenta and lead to pathological changes, affecting the energy conversion between the mother and the fetus, and affecting fetal development[8]. In recent years, an increasing number of studies have shown that the placenta is associated with diseases such as obesity in

offspring[9], cardiovascular diseases[10] and impaired neurodevelopment[11], implying the importance of the placenta during fetal development.

Studies have shown that pregnant women who are exposed to adverse conditions for a long time, such as smoking, alcohol abuse, lack of exercise, sleep deprivation, unhealthy dietary habits, and hormone use, may also experience changes in the epigenetic level of their placenta, leading to abnormal gene expression, which further results in alterations in placental function and metabolism[12] and an increase in the risk of GDM onset. GDM can also lead to epigenetic abnormalities in the placenta, such as changes in DNA methylation and miRNA expression, thereby affecting normal fetal development[13,14].

In this paper, with the placenta regarded as an important target organ through which GDM affects offspring development, the potential impacts of its functional and epigenetic changes on offspring development are reviewed, and the possible underlying mechanism is explored, providing a scientific basis for preventing abnormal development and ensuring the subsequent health of the offspring of patients with GDM.

IMPACTS OF GDM ON PLACENTAL TRANSPORT FUNCTION

The placenta is a transient multifunctional organ responsible for the transport of nutrients from the mother to the fetus. GDM can affect the nutrient transport function of the placenta, increase or decrease the amount of energy delivered to the fetus, and thus affect fetal weight[15] (Table 1).

Impacts on placental glucose transport

Glucose is the main energy source for the fetus and the placenta. The placental glucose transport function is affected by maternal glucose concentration, glucose transporters (GLUTs) and placental glucose metabolism[15] and is also regulated by insulin in early pregnancy[16]. For patients with GDM, the concentration of GLUT and glucose uptake in the basement membrane (BM) of the placenta increase, and the transport of maternal

glucose to the fetus increases, leading to macrosomia[17,18]. However, a decrease in or deficiency of placental GLUT leads to abnormal conditions, such as fetal hypoglycemia and weight loss[19], indicating that placental GLUTs are crucial for fetal growth and development.

In the full-term placenta of GDM patients, the expression levels of GLUT-1, GLUT-4, and GLUT-9 increase and are positively correlated with fetal birth weight[17]. For GDM patients treated with insulin, placental glucose uptake and transport increase, and the expression level of GLUT-4 in the placenta is positively correlated with birth weight and subscapular fat thickness[17]. Similar findings were observed in animal models, *e.g.*, in the placenta of mice with GDM induced by a high-fat diet, the AMPK-GLUT-3 axis was impaired, and the expression of GLUT-3 in the placental plasma membrane decreased, resulting in reduced glucose uptake by the placental trophoblast and excessive glucose input into the offspring, which led to the overgrowth of the offspring[20]. These research results indicate that an intrauterine hyperglycemic environment alters the expression of placental GLUTs and increases glucose transport between mothers and fetuses, thereby increasing offspring weight.

In addition, insulin can regulate glucose metabolism to promote fetal development in early pregnancy. Studies have shown that the phosphorylation of the insulin-like growth factor 1 receptor (IGF-1R) and increased expression of insulin receptor A (IR-A) in the placenta of GDM patients are associated with fetal overgrowth[21]. The ability of IGFBP to bind to the umbilical cord and placental stroma of patients with GDM is reduced, resulting in an increase in free IGF-1[22]; however, an increase in IGF-1 can activate insulin/IGF-1 signaling (Akt and Erk) in the placenta to increase placental GLUT-1 expression and fetal birth weight[23]. GLUT-4 in placental microvillous membranes (MVMs) increases placental glucose uptake under the regulation of insulin during early pregnancy, leading to an increase in glucose transfer to the fetus[16]. These results indicate that maternal hyperinsulinism regulates the activity and expression of placental GLUTs, which may accelerate fetal growth.

Impacts on placental amino acid transport

Placental amino acid transport is mediated by proteins expressed in maternal-circulation-oriented MVM and fetal-circulation-directed BM. The placenta has 15 amino acid transport systems, such as system A, which is responsible for supplying small neutral amino acids (a Na+-dependent transport protein), and system L, which is responsible for supplying essential large neutral amino acids (a broad Na+-independent transporter protein)[24]. The activation of placental IRs by maternal hyperinsulinism leads to the activation of mammalian target of rapamycin (mTOR)[9,25], which is a key regulatory factor for placental amino acid transport[26] and can promote cell proliferation and fetal growth. There are significant differences between maternal amino acid concentrations and amino acid concentrations in cord blood from GDM patients, even with well-controlled blood glucose[27], indicating that GDM alters placental amino acid transport or metabolism.

In the case of fetal overgrowth, the ability of the placenta to transport amino acids is significantly improved in GDM patients[28]. The signaling activities of IGF-I and mTOR in the placentas of GDM patients with well-controlled blood glucose increased and were positively correlated with birth weight. In particular, the upregulation of the system A amino acid transport protein in the placenta increased the probability of macrosomic babies occurring in women with GDM[25]. Through experiments on primary human trophoblasts (PHTs) and placental villous explants, maternal hyperinsulinism was shown to activate placental IR signaling (Erk and Akt) pathways and improve amino acid transport in system A[9]. In the placenta of GDM patients, the mTOR signaling pathway is activated, pro-oxidant/pro-inflammatory factors increase[29], and the proinflammatory cytokines TNF-α[30] and IL-6[31] can upregulate the amino acid transport of system A in PHT by activating the Erk/p38 MAPK and JAK/STAT signaling pathways, respectively. The activation of the Toll-like receptor 3 (TLR3) or TLR4 signaling pathway could lead to insulin resistance in primary trophoblast cells and significantly increase the expression of system A amino acids (SNAT1 and SNAT2) and the uptake of related amino acids[32]. Other studies have

shown that activation of the TLR4 signaling pathway is associated with increased uptake of system A amino acids stimulated by fatty acids (FAs) in PHT[33]. The L-system, another important placental amino acid transport system, is also involved in fetal weight programming. An increase in L-system-mediated leucine uptake in the placental MVM of a GDM patient with a baby large for gestational age (LGA) promoted placental leucine transport and facilitated the acceleration of fetal growth[28]. These results indicate that GDM increases the transport of amino acids in the placental system, leading to increased risks of fetal overgrowth and obesity.

Impacts on placental lipid transport

The essential FAs required for fetal growth mainly rely on maternal supply and placental transport. Placental FA transport relies mainly on the activity of lipid hydrolases in the syncytiotrophoblast MVM and FA uptake by various FA transport proteins [FA transporters (FATs), FA binding proteins (FABPs), and FA transport proteins (FATPs), *etc.*] in the plasma membrane[34-36].

The high expression levels of the placental proteins PI3K p110α, LXRα, FAS, and SCD1, which are related to lipid metabolism and lipoprotein lipase (LPL), in GDM may lead to the accumulation of placental triglycerides (TGs)[37].Although the uptake and transport of placental FAs are not affected by maternal hyperglycemia, hyperglycemia reduces the β-oxidation of the placenta and thus leads to an increase in the placental TG[38]. Experiments on human placental explants have shown that the activity of carnitine palmitoyltransferase is inhibited by hyperglycemia, such that β-oxidation is reduced and esterification pathways are increased, leading to the accumulation of placental TG[39]. Another animal experiment showed that maternal mice fed a high-fat/high-cholesterol diet (accompanied or not accompanied by GDM) had dysregulated placental lipid hydrolase activity, increased cholesteryl ester hydrolase activity, and decreased TG hydrolase activity; as such, excessive cholesterol was input into the offspring, resulting in an increase in liver lipids and the accumulation of placental TG, which may cause overgrowth[36]. These findings indicate that the oxidation of FAs is

reduced and that the expression of placental proteins and TG hydrolases becomes imbalanced, which causes the deposition of placental TG; moreover, although maternal TG does not pass through the placenta, it can be decomposed by placental LPL, TG hydrolases and other lipases and subsequently infiltrate the placenta. A series of factors are associated with fetal overgrowth.

It has been reported that the expression of FABP4 is increased and that the expression of LPL is decreased in the male placenta of a GDM patient with macrosomia. Additionally, the mRNA expression level of angiopoietin-like protein 3 (ANGPTL3) is increased, and the activity of LPL is inhibited by ANGPTL3, which leads to an increase in the storage of liver adipocytes; moreover, FABP4 increases the FA gradient to promote the delivery of placental lipids to the fetus[40]. Other studies have shown an increase in the deposition of TG and the expression of FA transport proteins (FAT, FABP3, and FABP4) in the placenta of GDM patients[35]. Treatment of GDM with insulin could significantly increase the phosphorylation of Akt and Erk in the placenta and the expression of placental lipid carriers (FAT, A-FABP, and endothelial lipase) and promote the transfer of placental lipids to the fetus[41]. Several studies have shown that the expression of FAT and TLR4 in the placenta of GDM patients significantly increases and is positively associated with neonatal weight[42]. The ANGPTL3-4-8 axis regulates lipid transport and protein expression and is related to fetal birth weight, body length and placental weight[43]. However, the dysregulated expression of this axis in the placenta of GDM patients has an impact on placental lipid transport and protein expression. These results indicate that an increase in the placental lipid transfer gradient and in the transport of proteins due to an intrauterine high-glucose environment leads to the accumulation of fetal lipids, which may lead to an elevated fetal obesity level and increased neonatal body fat mass in GDM patients.

Although macrosomia is common in the fetuses of GDM patients, growth retardation is a common manifestation in GDM animal models. The pregnancy of STZ-induced GDM rats is characterized by placental enlargement and varying degrees of growth retardation in the offspring[44]. The placental IR pathway is altered by hyperinsulinism

and activates the downstream endothelial carbon monoxide synthase to stimulate increased placental angiogenesis[45], thereby affecting placental nutrient metabolism. Animal and *in vitro* experiments have shown that amino acid transport proteins are downregulated in offspring with growth restriction, and the activity of placental mTORC1 is reduced in STZ-induced GDM rat models, resulting in a decrease in L-system amino acid transport proteins in the placenta, which is associated with intrauterine growth restriction and a reduced birth weight[46]. It has also been found in human and *in vitro* experiments that IL-15 is upregulated in the placenta of GDM patients and promotes trophoblast proliferation *in vitro* through the JAK/STAT signaling pathway, which is negatively correlated with neonatal weight[47].

EFFECTS ON THE HORMONE SECRETION FUNCTION OF THE PLACENTA

Animal experiments have shown that the dysregulation of hormones secreted by the placenta during pregnancy may alter insulin signaling and adversely affect fetal growth[11,48]. A number of studies have shown that the level of human placental lactogen (HPL) in GDM patients increases during the third trimester of pregnancy, and the expression levels of HPL in mothers and umbilical cord blood are closely related to placental weight and birth weight[49,50]. Placental enlargement in GDM patients may cause an increase in the levels of growth hormone (GH) and HPL, induce maternal insulin resistance and stimulate the generation of fetal IGF-1 and insulin, thereby resulting in fetal fat deposition and overgrowth[51]. HPL can also regulate fetal growth and development *via* a certain mechanism. A targeted reduction in placental HPL in sheep can lead to early intrauterine growth restriction and a significant decrease in the birth weight of the offspring in the later stage[52]. GH[53] and HPL[54] significantly increased in the placenta of LGA pregnancies, whereas the expression levels of HPL[55] and GH[53] were reduced in small for gestational age pregnancies. These results indicate that placental HPL and GH jointly regulate fetal growth and development in utero.

In addition, insulin/IGF and adipokines secreted by the placenta are also important for fetal growth and development. The expression of the IGF-1-IGFBP-1 axis is

dysregulated in the umbilical cord blood of GDM patients, and the opposite changes in IGF-1 and IGFBP-1 expression are observed. The increased bioavailability of IGF-1 caused by a reduction in IGFBP-1 leads to increased glucose uptake and utilization, increasing the risk of macrosomia[56]. Studies have shown a positive correlation between the risk of suffering from GDM and a higher level of IGF-1 in maternal blood[57,58]. Several studies have shown that the expression of IGFBP-1[59], IGFBP-2[58], IGFBP-3[60], and IGFBP-rP1[61] in the umbilical cord blood of GDM patients significantly decreases, leading to a reduction in the ability of IGFBP to bind to IGF-1 and IGF-2[60], whereby the level of free IGF-1 in umbilical cord blood[22] and the phosphorylation of IGF-1R in the placenta increase[21]. These changes improved the signaling activity of free IGF-1 and IGF-2 in umbilical cord blood. Moreover, several studies have shown that the fetal weight of GDM patients is significantly positively correlated with the expression of IGF-1[23,25,62] and IGF-2[63] in the placenta. Cellular experiments and clinical studies have also shown that GDM strengthens placental insulin/IGF-1 signaling, which activates downstream mammalian mTORC1 targets and increases placental nutrient transport[26], leading to fetal overgrowth, as its activation is positively correlated with birth weight[25,64]. These results indicate that changes in the insulin/IGF signaling axis may be an important mechanism for fetal birth weight gain in GDM patients. In addition, GDM patients with macrosomia have higher levels of umbilical cord leptin (LEP) and resistin[65] and lower levels of the maternal adiponectin gene (*ADIPOQ*)[23]. However, the expression levels of LEP and resistin in the umbilical cord were positively correlated with the body weight of large-for-date fetuses, whereas maternal ADIPOQ was inversely proportional to birth weight[65]. This may be because the phosphate site of IRS-1 was inhibited by low maternal ADIPOQ levels, which, together with insulin/IGF-1/mTOR signaling, regulated nutrients such as glucose, amino acids and lipids to stimulate fetal overgrowth[59,66]. These findings indicate that placental adipokines participate in insulin axis signaling to jointly regulate placental nutrient transport and fetal growth and development.

IMPACTS ON PLACENTAL DNA METHYLATION

It has been reported that the epigenetics of the placenta play key regulatory roles in placental development and function[67]. The impacts of GDM on the global methylation of the placenta and the methylation of imprinted genes and metabolic genes may result in impairments to the placenta and intrauterine fetal development and even an increased susceptibility of the offspring to diseases such as obesity and metabolic syndrome in the later stage (Figure 1).

Global methylation of the placenta and methylation of imprinted genes

A number of studies have shown that the methylation of a large number of genes in the placenta of GDM patients is associated with fetal weight. The differentially methylated position (DMP) of 11 genes in the placenta of GDM patients is associated with birth weight[68]. Among the differentially methylated genes in the placenta of GDM patients, 326 placental genes and 117 umbilical cord genes are also associated with neonatal weight[69].

Studies have shown that three CpG methylation sites in the DNA methylation region of the maternally expressed gene 3 (*MEG3*) gene on the maternal side of the placenta of GDM patients are significantly increased and are positively correlated with maternal blood glucose and fetal weight, whereas only one CpG position on the fetal side of the placenta is highly methylated and unrelated to fetal weight[70], indicating that maternal metabolic status alters the methylation level of the placenta and participates in fetal development. Some studies have shown that DNA methylation of the maternal imprinted gene MEST in the placenta of GDM patients significantly decreases and is related to GDM, possibly leading to the pathogenesis of GDM macrosomia. Researchers have also found that the methylation of MEST significantly decreases in the peripheral blood of adult obese individuals[71]. These results indicate that MEST is involved in the reprogramming of obesity in offspring and suggest the consequences of placental methylation on early exposure to an adverse intrauterine environment, including the tendency toward obesity in adult offspring. The hypermethylation of the imprinted

gene *DLK1* on the fetal and maternal sides of the placenta in GDM patients led to a significant decrease in its gene expression and was positively correlated with fetal weight and maternal two-hour oral glucose tolerance test (OGTT) blood glucose concentration[72], indicating that the methylation of DLK1 may be a potential mechanism for obesity and metabolic programming disorders in childhood and adulthood. Under the influence of a high-glucose environment, IGF-2 and H19, which are also pairs of imprinted genes, exhibit variable methylation levels, and the expression level of IGF-2 increases[73]; moreover, the expression of IGF-2 is directly proportional to the occurrence of macrosomia[63]. Studies have shown that changes in the methylation and expression levels of placental imprinted genes in STZ-induced GDM mice led to the hypomethylation and increased expression level of H19 and the hypermethylation and decreased expression level of peg3; and the methylation changes of the imprinted genes could be reversed by transferring prokaryotic embryos of diabetic female mice into normal pregnant uteruses[74]. The hypomethylation of the paternally expressed genes IGF1R and IGFBP-3 in the placenta and the high expression of these genes were negatively correlated with maternal blood glucose levels, and the increased expression of IGF1R mRNA was related to the birth weight of newborns, which may be involved in the pathogenesis of GDM macrosomia and increase the susceptibility of offspring to obesity[75]. These experiments indicate that alterations in the methylation of placental imprinted genes and their gene expression levels provide genetic information for fetal adipose tissue and metabolic programming and increase the susceptibility of offspring to metabolic diseases in the later stage.

Methylation of placental metabolic genes

Placental methylation can also affect fetal development by regulating the expression of metabolic genes. Studies have shown that placental LEP, which is capable of regulating insulin signaling and participating in insulin resistance, is associated with the pathogenesis of GDM. The average methylation level of LEP at 23 CpG sites in the placenta of GDM patients was greater than that in the placenta of healthy pregnancies,

and LEP, an adipokine for maintaining energy homeostasis, is capable of regulating fetal growth and placental nutrient exchange[76]. However, another study showed that the methylation level of LEP decreased in the placenta of GDM patients, and the DNA hypomethylation level of its gene locus (cg15758240) was negatively correlated with the expression level of LEP (a representative of neonatal obesity) in the fetus at birth and in early childhood obesity[77]. In addition, ADIPOQ and LPL are important metabolic genes in the placenta. The methylation level of ADIPOQ on the maternal side of the placenta is correlated with maternal two-hour OGTT blood glucose concentration, increased insulin resistance, and maternal ADIPOQ levels during pregnancy and after delivery, and higher adiponectin levels in umbilical cord blood are associated with fetal birth weight[78]. Adiponectin is the most abundant circulating hormone secreted by adipocytes and is regulated by the degree of insulin resistance. The methylation of adiponectin may lead to obesity, insulin resistance and glucose metabolic disturbance in offspring and increase the probability of suffering from type 2 diabetes in offspring. The methylation levels of the LPL proximal promoter and intronic CpG islands decreased in the placenta of GDM patients, wherein the hypomethylation levels of LPL at the CpG1 and CpG3 loci were negatively correlated with maternal blood glucose and high-density lipoprotein cholesterol (HDL-C), and the hypomethylation level of the LPL-CpG2 Locus was negatively correlated with the expression level of placental LPL mRNA and HDL-C in umbilical cord blood[79], indicating that the versatility of the methylation levels of LPL may be related to maternal and fetal metabolic profiles and involved in placental lipid transfer and intrauterine programming of fetal adipose tissue. Another experiment also showed that a low DNA methylation level at the 3.4 CpG site in the placenta of GDM patients was positively correlated with birth weight and mid-childhood fat mass[80]. In addition, the methylation level of LPL in the placenta was inversely proportional to its gene expression, and LPL in placental syncytiotrophoblasts was capable of hydrolyzing TG-rich lipoproteins into FAs to increase maternal-fetal lipid transfer gradients and promote placental lipid transfer to increase fetal weight. These energy metabolism genes participate in the regulation of

energy metabolism and insulin sensitivity, and adaptive changes may lead to sustained glucose metabolism disorders in both mothers and offspring.

Studies have shown that an increase in the nuclear receptor estrogen receptor a (ERa) protein and its mRNA level in extracellular trophoblasts on the maternal side of the placenta in GDM patients may be related to hypomethylation of the ERa promoter region[81]. Estrogen secreted by the placenta is an important regulator of fat metabolism and may participate in the programming of fetal fat metabolism in utero. The hypermethylation levels of IGFBP-1, IGFBP-2, IGFBP-6, and G6PD in the placenta of GDM patients were positively correlated with maternal fasting plasma glucose and one-hour blood glucose concentration after an OGTT. The methylation levels of IGFBP and G6PD were negatively correlated with their expression in the placenta. A decreased expression of IGFBP increases the availability of free IGF-1, contributing to the occurrence of macrosomia. Fetal birth weight was significantly negatively correlated with the expression of G6PD mRNA but was positively correlated with methylation[82]. The ATP-binding cassette transporter A1 (ABCA1) is a key regulator of placental lipid transfer. It has been reported that the hypermethylation level of ABCA1 on the maternal side of the placenta in pregnant women with impaired glucose tolerance is correlated with maternal HDL-C levels and two-hour OGTT blood glucose concentrations, and maternal blood glucose and HDL-C act together on the DNA methylation profile of ABCA1; moreover, the hypermethylation level of ABCA1 on the fetal side of the placenta is negatively correlated with TG levels in umbilical cord blood, and the hypomethylation level of ABCA1 in umbilical cord blood is negatively correlated with maternal two-hour OGTT blood glucose concentrations in the second trimester of pregnancy[83]. The difference in the methylation of ABCA1 between the placenta and the umbilical cord may be an adaptive response of the fetus to intrauterine hyperglycemia to compensate for the reduction in the placental transfer of maternal cholesterol, but it also leads to increased susceptibility to dyslipidemia, obesity, impaired endothelial function and cardiovascular diseases in the later stage. The melanocortin 4 receptor (*MC4R*) gene plays a crucial role in regulating metabolism by suppressing appetite and

participating in energy control. The methylation levels of the CpG-1 and CpG-2 Loci of the energy metabolism gene *MC4R* on the fetal side of the placenta in GDM patients decreased, whereas the methylation level of the CpG-1 locus of MC4R on the maternal side of the placenta increased in pregnant women with a smoking habit and was related to maternal one-hour and two-hour OGTT glucose concentrations and low-density lipoprotein cholesterol (LDL-C) levels[84]. The spatial difference in the methylation levels of energy metabolism genes between the fetal side and the maternal side of the placenta may be a certain environmental adaptation change to protect the metabolic health of the offspring and reveal the complexity of DNA methylation.

Peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α), a transcriptional coactivator, is a regulator that adjusts nutritional energy homeostasis and metabolism between the placenta and the fetus during pregnancy and participates in the metabolic programming of the fetus. Studies have shown that maternal two-hour OGTT glucose concentrations in the second trimester of pregnancy are positively correlated with DNA hypermethylation at the PGC-1α CpG locus in the placenta, and the degree of correlation increases with maternal weight and insulin resistance during pregnancy and is negatively correlated with the hypomethylation of PGC-1α DNA in the umbilical cord[85]. The difference in methylation between the placenta and the umbilical cord may be an adaptive mechanism to the intrauterine high-glucose environment. In the placenta of GDM patients, the methylation of the PGC-1α promoter increases, the expression of PGC-1α mRNA decreases, and the downregulation of PGC-1α in the placenta is negatively correlated with early fetal blood glucose[86]. The expression of PGC-1α and peroxisome proliferator-activated receptor γ in the placenta of GDM patients decreased and was negatively correlated with that in the offspring during young adulthood[87]. The methylation of PGC-1α may alter the methylation pattern of PGC-1α in fetal endocrine organs (such as islets) and the sensitivity of other tissues to insulin, resulting in an increase in blood glucose and an increased risk of diabetes in offspring. The hypomethylation and increased expression of GLUT-3 and resistin in the placenta of GDM patients led to excessive placental glucose transport to

the fetus and increased insulin resistance, thus giving rise to fetal glucose metabolism disorders and macrosomia[88].

In summary, changes in the methylation of placental metabolic genes may underlie the pathogenesis of obesity and other related metabolic diseases. These research data show that epigenetics provides valuable information for the programming of placental and fetal development and can guide future research directions, provide disease prediction information for clinical practice and facilitate the development of prevention and treatment measures.

Transgenerational effects of placental methylation

In the STZ-induced GDM model, intrauterine hyperglycemia may induce hypermethylation of the imprinted gene *Dlk1-DMR* and hypomethylation of IG-DMR and Gtl2-DMR in the placentas of the F1 and F2 generations and affect their gene expression levels, which may result in a reduction in the weight of the placentas of the F1 generation and can be transmitted to the F2 generation through a paternal line[89], indicating that the methylation of key genes in the placenta has potential transgenerational effects on offspring development.

IMPACT ON THE EXPRESSION OF PLACENTAL MIRNAS

The upregulation or downregulation of miRNAs in the placenta can regulate the proliferation and infiltration of placental trophoblasts and thus affect placental development and function. Inactivation of the placental miRNA mechanism has an impact on fetal weight and metabolism and may affect fetal growth and development[90].

An experiment with HTR-8/SVneo and BeWo cells reported that high glucose concentrations inhibited cell viability and reduced the expression levels of placental miR-132, which could promote trophoblast cell proliferation and infiltration[91]. In addition, some studies have reported that placental trophoblast proliferation is related to macrosomia. Human and *in vitro* placental experiments have shown that placental

weight is closely related to macrosomia in GDM patients, possibly because Erk1/2 signaling is activated by hyperglycemia and promotes trophoblast cell proliferation[92]. Another study also confirmed that the macrosomia of GDM patients is associated with placental trophoblast proliferation[93]. The expression levels of miR-130b-3p, miR-29a-3p, and miR-let-7a-5p in the placenta of GDM patients decreased with increasing birth weight[94]. MiR-508-3p was upregulated in GDM patients, and EGFR/PI13K/Akt signaling was activated by the targeted reduction in PIKfyve, a negative regulator of EGFR (epidermal growth factor receptor), leading to the occurrence of macrosomia[95]. These findings indicate that the placenta alters key miRNAs involved in fetal development to adapt to a maternal intrauterine hyperglyceemic environment and plays an important role in fetal development.

miRNAs also participate in placental glucose and lipid metabolism. It has been reported that miR-21 is downregulated in the placenta of GDM patients, whereas the expression of PPARα[96], a nuclear receptor involved in lipid and glucose homeostasis, is increased. miR-9 and miR-22 are downregulated in the placenta of GDM patients and upregulate the expression of GLUT1 and HK2, leading to increased glucose uptake in primary syncytiotrophoblasts and HTR8/SVneo cells[97]. The downregulation of miR-29b in the placenta of GDM patients promoted trophoblast activity in the placenta and increased glucose uptake by increasing the expression of hypoxia-inducible factor 3 subunit α (HIF3A)[98]. However, the expression levels of miR-98[99] and miR-199a[100] were significantly increased in the placentas of GDM patients, and these genes indirectly regulated glucose uptake by targeting the Mecp2-Trpc3 pathway. It has been reported that the expression level of miRNA7 in the placenta of GDM patients increases, and the placental insulin signaling pathway and glucose metabolism are regulated by means of targeted downregulation of IRS1 and IRS2[14]. These results indicate that miRNAs participate in glucose metabolism and insulin signaling alterations in the placentas of GDM patients and may be involved in the pathogenesis of GDM and lead to metabolic disorders in offspring. Therefore, the NRS-2002 can also be used as a useful marker for the diagnosis of GDM.

In conclusion, placental epigenetic modifications play an important regulatory role in the programming of fetal development in patients with GDM and are related to maternal metabolism. Multiple placental epigenetic modifications affect fetal development by regulating placental function, gene expression, fetal weight and fetal metabolism. Understanding the relationship between placental epigenetic changes and fetal development is highly important for revealing the molecular mechanism of fetal development and identifying related diseases. In the future, by means of interfering with placental epigenetic abnormalities, new treatments can be explored to improve fetal development and prevent the occurrence of related diseases.

DEFICIENCIES AND PROSPECTS

An intrauterine high-glucose environment alters placental function, epigenetics and gene expression; participates in fetal intrauterine programming; has an important impact on offspring development; and increases the prevalence of obesity, cardiovascular disease and metabolic syndrome in adult offspring. The understanding of the impacts of the placenta on fetal development is insufficient at present, and there is still a long way to go. First, there is a theoretical relationship between placental function and epigenetic abnormalities in GDM patients and fetal development, and there is some supporting evidence to prove their correlation with fetal development. The placenta receives signals from both maternal nutritional reserves and fetal development needs, but the mechanism of integration and the exact nature of these signals and their regulation and influence on a high-glucose environment are still unclear.In the future, further probing of the molecular mechanism and etiology of placental epigenetic changes and their effects on the development of offspring can be performed by means of a molecular pathological epidemiology (MPE)[101] technique, which links potential risk factors with the molecular pathology of diseases and contributes to precision prevention and precision medicine[102], providing a theoretical and scientific basis for early warning, prevention and treatment of GDM. In addition, MPE research can explore the association between GDM and later chronic diseases and

other diseases[103], providing new strategies for combined prevention and individualized treatment of diseases. Second, the current research has focused mainly on static analysis of placental function and epigenetics and has lacked observations of dynamic changes. However, the process of fetal development is dynamic, and our study can provide information only on changes at certain time points. To better understand the temporal relationship between placental function and epigenetics and fetal development, long-term follow-up observations are needed to obtain additional comprehensive information. In addition, although the animal models used in the experiments are similar to those used in humans, there are still some differences that prevent direct application of the results to the human placenta. However, further validation combined with human placenta studies is needed.

GDM has a profound impact on the development and subsequent health of offspring. As an intermediary organ between the mother and the fetus, the placenta plays a crucial role, and further investigations of the relationship between MPE changes in the placenta and abnormal fetal development are needed to understand the specific mechanism involved in the development of the placenta in offspring and to determine the causal relationship between the placenta and fetal development. Only in this way can we have a deeper understanding of the pathophysiological process of abnormal development in offspring and associate this process with external factors and the development of chronic diseases in the later stage to improve the outcomes of pregnant women with GDM and their offspring.

CONCLUSION

REFERENCES

1 **Brown FM**, Wyckoff J. Application of One-Step IADPSG Versus Two-Step Diagnostic Criteria for Gestational Diabetes in the Real World: Impact on Health Services, Clinical Care, and Outcomes. *Curr Diab Rep* 2017; **17**: 85 [PMID: 28799123 DOI: 10.1007/s11892-017-0922-z]

2 **Gao C**, Sun X, Lu L, Liu F, Yuan J. Prevalence of gestational diabetes mellitus in mainland China: A systematic review and meta-analysis. *J Diabetes Investig* 2019; **10**: 154-162 [PMID: 29683557 DOI: 10.1111/jdi.12854]

3 **Weir GC**, Gaglia J, Bonner-Weir S. Inadequate β-cell mass is essential for the pathogenesis of type 2 diabetes. *Lancet Diabetes Endocrinol* 2020; **8**: 249-256 [PMID: 32006519 DOI: 10.1016/S2213-8587(20)30022-X]

4 **Wu Y**, Liu B, Sun Y, Du Y, Santillan MK, Santillan DA, Snetselaar LG, Bao W. Association of Maternal Prepregnancy Diabetes and Gestational Diabetes Mellitus With Congenital Anomalies of the Newborn. *Diabetes Care* 2020; **43**: 2983-2990 [PMID: 33087319 DOI: 10.2337/dc20-0261]

5 **Zhang TN**, Huang XM, Zhao XY, Wang W, Wen R, Gao SY. Risks of specific congenital anomalies in offspring of women with diabetes: A systematic review and meta-analysis of population-based studies including over 80 million births. *PLoS Med* 2022; **19**: e1003900 [PMID: 35104296 DOI: 10.1371/journal.pmed.1003900]

6 **American Diabetes Association**. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2020. *Diabetes Care* 2020; **43**: S14-S31 [PMID: 31862745 DOI: 10.2337/dc20-S002]

7 **Yu Y**, Arah OA, Liew Z, Cnattingius S, Olsen J, Sørensen HT, Qin G, Li J. Maternal diabetes during pregnancy and early onset of cardiovascular disease in offspring: population based cohort study with 40 years of follow-up. *BMJ* 2019; **367**: l6398 [PMID: 31801789 DOI: 10.1136/bmj.l6398]

8 **Musa E**, Salazar-Petres E, Arowolo A, Levitt N, Matjila M, Sferruzzi-Perri AN. Obesity and gestational diabetes independently and collectively induce specific effects on placental structure, inflammation and endocrine function in a cohort of South African women. *J Physiol* 2023; **601**: 1287-1306 [PMID: 36849131 DOI: 10.1113/JP284139]

9 **Castillo-Castrejon M**, Jansson T, Powell TL. No evidence of attenuation of placental insulin-stimulated Akt phosphorylation and amino acid transport in maternal obesity and gestational diabetes mellitus. *Am J Physiol Endocrinol Metab* 2019; **317**: E1037-E1049 [PMID: 31573844 DOI: 10.1152/ajpendo.00196.2019]

10 **Shi R**, Zhao L, Cai W, Wei M, Zhou X, Yang G, Yuan L. Maternal exosomes in diabetes contribute to the cardiac development deficiency. *Biochem Biophys Res Commun* 2017; **483**: 602-608 [PMID: 27998767 DOI: 10.1016/j.bbrc.2016.12.097]

11 **Lopez-Tello J**, Sferruzzi-Perri AN. Characterization of placental endocrine function and fetal brain development in a mouse model of small for gestational age. *Front Endocrinol (Lausanne)* 2023; **14**: 1116770 [PMID: 36843585 DOI: 10.3389/fendo.2023.1116770]

12 **Everson TM**, Vives-Usano M, Seyve E, Cardenas A, Lacasaña M, Craig JM, Lesseur C, Baker ER, Fernandez-Jimenez N, Heude B, Perron P, Gónzalez-Alzaga B, Halliday J, Deyssenroth MA, Karagas MR, Íñiguez C, Bouchard L, Carmona-Sáez P, Loke YJ, Hao K, Belmonte T, Charles MA, Martorell-Marugán J, Muggli E, Chen J, Fernández MF, Tost J, Gómez-Martín A, London SJ, Sunyer J, Marsit CJ, Lepeule J, Hivert MF, Bustamante M. Placental DNA methylation signatures of maternal smoking during pregnancy and potential impacts on fetal growth. *Nat Commun* 2021; **12**: 5095 [PMID: 34429407 DOI: 10.1038/s41467-021-24558-y]

13 **Meyrueix LP**, Gharaibeh R, Xue J, Brouwer C, Jones C, Adair L, Norris SA, Ideraabdullah F. Gestational diabetes mellitus placentas exhibit epimutations at placental development genes. *Epigenetics* 2022; **17**: 2157-2177 [PMID: 35993304 DOI: 10.1080/15592294.2022.2111751]

14 **Bhushan R**, Rani A, Gupta D, Ali A, Dubey PK. MicroRNA-7 Regulates Insulin Signaling Pathway by Targeting IRS1, IRS2, and RAF1 Genes in Gestational Diabetes Mellitus. *Microrna* 2022; **11**: 57-72 [PMID: 35422233 DOI: 10.2174/2211536611666220413100636]

15 **Castillo-Castrejon M**, Powell TL. Placental Nutrient Transport in Gestational Diabetic Pregnancies. *Front Endocrinol (Lausanne)* 2017; **8**: 306 [PMID: 29163373 DOI: 10.3389/fendo.2017.00306]

16 **Ericsson A**, Hamark B, Powell TL, Jansson T. Glucose transporter isoform 4 is expressed in the syncytiotrophoblast of first trimester human placenta. *Hum Reprod* 2005; **20**: 521-530 [PMID: 15528266 DOI: 10.1093/humrep/deh596]

17 **Stanirowski PJ**, Szukiewicz D, Pyzlak M, Abdalla N, Sawicki W, Cendrowski K. Analysis of correlations between the placental expression of glucose transporters GLUT-1, GLUT-4 and GLUT-9 and selected maternal and fetal parameters in pregnancies complicated by diabetes mellitus. *J Matern Fetal Neonatal Med* 2019; **32**: 650-659 [PMID: 28969476 DOI: 10.1080/14767058.2017.1387897]

18 **Gaither K**, Quraishi AN, Illsley NP. Diabetes alters the expression and activity of the human placental GLUT1 glucose transporter. *J Clin Endocrinol Metab* 1999; **84**: 695-701 [PMID: 10022440 DOI: 10.1210/jc.84.2.695]

19 **Lynch CS**, Kennedy VC, Tanner AR, Ali A, Winger QA, Rozance PJ, Anthony RV. Impact of Placental SLC2A3 Deficiency during the First-Half of Gestation. *Int J Mol Sci* 2022; **23** [PMID: 36293384 DOI: 10.3390/ijms232012530]

20 **Zhang L**, Yu X, Wu Y, Fu H, Xu P, Zheng Y, Wen L, Yang X, Zhang F, Hu M, Wang H, Liu X, Qiao J, Peng C, Gao R, Saffery R, Fu Y, Qi H, Tong C, Kilby MD, Baker PN. Gestational Diabetes Mellitus-Associated Hyperglycemia Impairs Glucose Transporter 3 Trafficking in Trophoblasts Through the Downregulation of AMP-Activated Protein Kinase. *Front Cell Dev Biol* 2021; **9**: 722024 [PMID: 34796169 DOI: 10.3389/fcell.2021.722024]

21 **Tumminia A**, Scalisi NM, Milluzzo A, Ettore G, Vigneri R, Sciacca L. Maternal Diabetes Impairs Insulin and IGF-1 Receptor Expression and Signaling in Human Placenta. *Front Endocrinol (Lausanne)* 2021; **12**: 621680 [PMID: 33776919 DOI: 10.3389/fendo.2021.621680]

22 **Borges MH**, Pullockaran J, Catalano PM, Baumann MU, Zamudio S, Illsley NP. Human placental GLUT1 glucose transporter expression and the fetal insulin-like growth factor axis in pregnancies complicated by diabetes. *Biochim Biophys Acta Mol Basis Dis* 2019; **1865**: 2411-2419 [PMID: 31175930 DOI: 10.1016/j.bbadis.2019.06.002]

23 **Balachandiran M**, Bobby Z, Dorairajan G, Gladwin V, Vinayagam V, Packirisamy RM. Decreased maternal serum adiponectin and increased insulin-like growth factor-1 levels along with increased placental glucose transporter-1 expression in gestational

diabetes mellitus: Possible role in fetal overgrowth. *Placenta* 2021; **104**: 71-80 [PMID: 33285436 DOI: 10.1016/j.placenta.2020.11.008]

24 **Vaughan OR**, Rosario FJ, Powell TL, Jansson T. Regulation of Placental Amino Acid Transport and Fetal Growth. *Prog Mol Biol Transl Sci* 2017; **145**: 217-251 [PMID: 28110752 DOI: 10.1016/bs.pmbts.2016.12.008]

25 **Shang M**, Wen Z. Increased placental IGF-1/mTOR activity in macrosomia born to women with gestational diabetes. *Diabetes Res Clin Pract* 2018; **146**: 211-219 [PMID: 30389621 DOI: 10.1016/j.diabres.2018.10.017]

26 **Rosario FJ**, Kanai Y, Powell TL, Jansson T. Mammalian target of rapamycin signalling modulates amino acid uptake by regulating transporter cell surface abundance in primary human trophoblast cells. *J Physiol* 2013; **591**: 609-625 [PMID: 23165769 DOI: 10.1113/jphysiol.2012.238014]

27 **Cetin I**, de Santis MS, Taricco E, Radaelli T, Teng C, Ronzoni S, Spada E, Milani S, Pardi G. Maternal and fetal amino acid concentrations in normal pregnancies and in pregnancies with gestational diabetes mellitus. *Am J Obstet Gynecol* 2005; **192**: 610-617 [PMID: 15696011 DOI: 10.1016/j.ajog.2004.08.011]

28 **Jansson T**, Ekstrand Y, Björn C, Wennergren M, Powell TL. Alterations in the activity of placental amino acid transporters in pregnancies complicated by diabetes. *Diabetes* 2002; **51**: 2214-2219 [PMID: 12086952 DOI: 10.2337/diabetes.51.7.2214]

29 **Capobianco E**, Fornes D, Linenberg I, Powell TL, Jansson T, Jawerbaum A. A novel rat model of gestational diabetes induced by intrauterine programming is associated with alterations in placental signaling and fetal overgrowth. *Mol Cell Endocrinol* 2016; **422**: 221-232 [PMID: 26747729 DOI: 10.1016/j.mce.2015.12.020]

30 **Aye IL**, Jansson T, Powell TL. TNF-α stimulates System A amino acid transport in primary human trophoblast cells mediated by p38 MAPK signaling. *Physiol Rep* 2015; **3** [PMID: 26508738 DOI: 10.14814/phy2.12594]

31 **Jones HN**, Jansson T, Powell TL. IL-6 stimulates system A amino acid transporter activity in trophoblast cells through STAT3 and increased expression of SNAT2. *Am J*

Physiol Cell Physiol 2009; **297**: C1228-C1235 [PMID: 19741197 DOI: 10.1152/ajpcell.00195.2009]

32 **Liong S**, Lappas M. Lipopolysaccharide and double stranded viral RNA mediate insulin resistance and increase system a amino acid transport in human trophoblast cells in vitro. *Placenta* 2017; **51**: 18-27 [PMID: 28292465 DOI: 10.1016/j.placenta.2017.01.124]

33 **Lager S**, Gaccioli F, Ramirez VI, Jones HN, Jansson T, Powell TL. Oleic acid stimulates system A amino acid transport in primary human trophoblast cells mediated by toll-like receptor 4. *J Lipid Res* 2013; **54**: 725-733 [PMID: 23275648 DOI: 10.1194/jlr.M033050]

34 **Magnusson AL**, Waterman IJ, Wennergren M, Jansson T, Powell TL. Triglyceride hydrolase activities and expression of fatty acid binding proteins in the human placenta in pregnancies complicated by intrauterine growth restriction and diabetes. *J Clin Endocrinol Metab* 2004; **89**: 4607-4614 [PMID: 15356070 DOI: 10.1210/jc.2003-032234]

35 **Mishra JS**, Zhao H, Hattis S, Kumar S. Elevated Glucose and Insulin Levels Decrease DHA Transfer across Human Trophoblasts via SIRT1-Dependent Mechanism. *Nutrients* 2020; **12** [PMID: 32365792 DOI: 10.3390/nu12051271]

36 **Kuentzel KB**, Bradić I, Mihalič ZN, Korbelius M, Rainer S, Pirchheim A, Kargl J, Kratky D. Dysregulation of Placental Lipid Hydrolysis by High-Fat/High-Cholesterol Feeding and Gestational Diabetes Mellitus in Mice. *Int J Mol Sci* 2022; **23** [PMID: 36293139 DOI: 10.3390/ijms232012286]

37 **Balachandiran M**, Bobby Z, Dorairajan G, Jacob SE, Gladwin V, Vinayagam V, Packirisamy RM. Placental Accumulation of Triacylglycerols in Gestational Diabetes Mellitus and Its Association with Altered Fetal Growth are Related to the Differential Expressions of Proteins of Lipid Metabolism. *Exp Clin Endocrinol Diabetes* 2021; **129**: 803-812 [PMID: 31968385 DOI: 10.1055/a-1017-3182]

38 **Hulme CH**, Nicolaou A, Murphy SA, Heazell AEP, Myers JE, Westwood M. The effect of high glucose on lipid metabolism in the human placenta. *Sci Rep* 2019; **9**: 14114 [PMID: 31575970 DOI: 10.1038/s41598-019-50626-x]

39 **Visiedo F**, Bugatto F, Sánchez V, Cózar-Castellano I, Bartha JL, Perdomo G. High glucose levels reduce fatty acid oxidation and increase triglyceride accumulation in human placenta. *Am J Physiol Endocrinol Metab* 2013; **305**: E205-E212 [PMID: 23673156 DOI: 10.1152/ajpendo.00032.2013]

40 **Yang H**, He B, Yallampalli C, Gao H. Fetal macrosomia in a Hispanic/Latinx predominant cohort and altered expressions of genes related to placental lipid transport and metabolism. *Int J Obes (Lond)* 2020; **44**: 1743-1752 [PMID: 32494035 DOI: 10.1038/s41366-020-0610-y]

41 **Ruiz-Palacios M**, Prieto-Sánchez MT, Ruiz-Alcaraz AJ, Blanco-Carnero JE, Sanchez-Campillo M, Parrilla JJ, Larqué E. Insulin Treatment May Alter Fatty Acid Carriers in Placentas from Gestational Diabetes Subjects. *Int J Mol Sci* 2017; **18** [PMID: 28587267 DOI: 10.3390/ijms18061203]

42 **Zhou J**, Bai J, Guo Y, Fu L, Xing J. Higher Levels of Triglyceride, Fatty Acid Translocase, and Toll-Like Receptor 4 and Lower Level of HDL-C in Pregnant Women with GDM and Their Close Correlation with Neonatal Weight. *Gynecol Obstet Invest* 2021; **86**: 48-54 [PMID: 33486480 DOI: 10.1159/000510032]

43 **Klid S**, Maymó-Masip E, Algaba-Chueca F, Ballesteros M, Inglès-Puig M, Guarque A, Madeira A, Jareño C, Vendrell J, Fernández-Veledo S, Megía A. The ANGPTL3-4-8 Axis in Normal Gestation and in Gestational Diabetes, and Its Potential Involvement in Fetal Growth. *Int J Mol Sci* 2023; **24** [PMID: 36768809 DOI: 10.3390/ijms24032486]

44 **Korgun ET**, Acar N, Sati L, Kipmen-Korgun D, Ozen A, Unek G, Ustunel I, Demir R. Expression of glucocorticoid receptor and glucose transporter-1 during placental development in the diabetic rat. *Folia Histochem Cytobiol* 2011; **49**: 325-334 [PMID: 21744335 DOI: 10.5603/FHC.2011.0045]

45 **Lassance L**, Miedl H, Absenger M, Diaz-Perez F, Lang U, Desoye G, Hiden U. Hyperinsulinemia stimulates angiogenesis of human fetoplacental endothelial cells: a possible role of insulin in placental hypervascularization in diabetes mellitus. *J Clin Endocrinol Metab* 2013; **98**: E1438-E1447 [PMID: 23824413 DOI: 10.1210/jc.2013-1210]

46 **Xu J**, Wang J, Cao Y, Jia X, Huang Y, Cai M, Lu C, Zhu H. Downregulation of Placental Amino Acid Transporter Expression and mTORC1 Signaling Activity Contributes to Fetal Growth Retardation in Diabetic Rats. *Int J Mol Sci* 2020; **21** [PMID: 32156054 DOI: 10.3390/ijms21051849]

47 **Li J**, Li Y, Zhou X, Wei L, Zhang J, Zhu S, Zhang H, Gao X, Sharifu LM, Wang S, Xi L, Feng L. Upregulation of IL-15 in the placenta alters trophoblasts behavior contributing to gestational diabetes mellitus. *Cell Biosci* 2021; **11**: 33 [PMID: 33557944 DOI: 10.1186/s13578-021-00533-4]

48 **McIntyre HD**. Discovery, Knowledge, and Action-Diabetes in Pregnancy Across the Translational Spectrum: The 2016 Norbert Freinkel Award Lecture. *Diabetes Care* 2018; **41**: 227-232 [PMID: 29358466 DOI: 10.2337/dci17-0056]

49 **Houghton DJ**, Shackleton P, Obiekwe BC, Chard T. Relationship of maternal and fetal levels of human placental lactogen to the weight and sex of the fetus. *Placenta* 1984; **5**: 455-458 [PMID: 6522356 DOI: 10.1016/S0143-4004(84)80026-0]

50 **Knopp RH**, Bergelin RO, Wahl PW, Walden CE. Relationships of infant birth size to maternal lipoproteins, apoproteins, fuels, hormones, clinical chemistries, and body weight at 36 weeks gestation. *Diabetes* 1985; **34 Suppl 2**: 71-77 [PMID: 3922827 DOI: 10.2337/diab.34.2.S71]

51 **Newbern D**, Freemark M. Placental hormones and the control of maternal metabolism and fetal growth. *Curr Opin Endocrinol Diabetes Obes* 2011; **18**: 409-416 [PMID: 21986512 DOI: 10.1097/MED.0b013e32834c800d]

52 **Jeckel KM**, Boyarko AC, Bouma GJ, Winger QA, Anthony RV. Chorionic somatomammotropin impacts early fetal growth and placental gene expression. *J Endocrinol* 2018; **237**: 301-310 [PMID: 29661800 DOI: 10.1530/JOE-18-0093]

53 **Männik J**, Vaas P, Rull K, Teesalu P, Rebane T, Laan M. Differential expression profile of growth hormone/chorionic somatomammotropin genes in placenta of small- and large-for-gestational-age newborns. *J Clin Endocrinol Metab* 2010; **95**: 2433-2442 [PMID: 20233782 DOI: 10.1210/jc.2010-0023]

54 **Liao S**, Vickers MH, Taylor RS, Fraser M, McCowan LME, Baker PN, Perry JK. Maternal serum placental growth hormone, insulin-like growth factors and their binding proteins at 20 weeks' gestation in pregnancies complicated by gestational diabetes mellitus. *Hormones (Athens)* 2017; **16**: 282-290 [PMID: 29278514 DOI: 10.1007/BF03401522]

55 **Markestad T**, Bergsjø P, Aakvaag A, Lie RT, Jacobsen G, Hoffman HJ, Bakketeig LS. Prediction of fetal growth based on maternal serum concentrations of human chorionic gonadotropin, human placental lactogen and estriol. *Acta Obstet Gynecol Scand Suppl* 1997; **165**: 50-55 [PMID: 9219457]

56 **Lindsay RS**, Westgate JA, Beattie J, Pattison NS, Gamble G, Mildenhall LF, Breier BH, Johnstone FD. Inverse changes in fetal insulin-like growth factor (IGF)-1 and IGF binding protein-1 in association with higher birth weight in maternal diabetes. *Clin Endocrinol (Oxf)* 2007; **66**: 322-328 [PMID: 17302863 DOI: 10.1111/j.1365-2265.2006.02719.x]

57 **Wang XR**, Wang WJ, Yu X, Hua X, Ouyang F, Luo ZC. Insulin-Like Growth Factor Axis Biomarkers and Gestational Diabetes Mellitus: A Systematic Review and Meta-Analysis. *Front Endocrinol (Lausanne)* 2019; **10**: 444 [PMID: 31354622 DOI: 10.3389/fendo.2019.00444]

58 **Zhu Y**, Mendola P, Albert PS, Bao W, Hinkle SN, Tsai MY, Zhang C. Insulin-Like Growth Factor Axis and Gestational Diabetes Mellitus: A Longitudinal Study in a Multiracial Cohort. *Diabetes* 2016; **65**: 3495-3504 [PMID: 27468747 DOI: 10.2337/db16-0514]

59 **Jansson N**, Nilsfelt A, Gellerstedt M, Wennergren M, Rossander-Hulthén L, Powell TL, Jansson T. Maternal hormones linking maternal body mass index and dietary intake to birth weight. *Am J Clin Nutr* 2008; **87**: 1743-1749 [PMID: 18541564 DOI: 10.1093/ajcn/87.6.1743]

60 **Gęca T**, Kwaśniewska A. The Influence of Gestational Diabetes Mellitus upon the Selected Parameters of the Maternal and Fetal System of Insulin-Like Growth Factors

(IGF-1, IGF-2, IGFBP1-3)-A Review and a Clinical Study. *J Clin Med* 2020; **9** [PMID: 33053704 DOI: 10.3390/jcm9103256]

61 **Lappas M**. Insulin-like growth factor-binding protein 1 and 7 concentrations are lower in obese pregnant women, women with gestational diabetes and their fetuses. *J Perinatol* 2015; **35**: 32-38 [PMID: 25078866 DOI: 10.1038/jp.2014.144]

62 **Luo ZC**, Nuyt AM, Delvin E, Audibert F, Girard I, Shatenstein B, Cloutier A, Cousineau J, Djemli A, Deal C, Levy E, Wu Y, Julien P, Fraser WD. Maternal and fetal IGF-I and IGF-II levels, fetal growth, and gestational diabetes. *J Clin Endocrinol Metab* 2012; **97**: 1720-1728 [PMID: 22419731 DOI: 10.1210/jc.2011-3296]

63 **Zhang Q**, Qin S, Huai J, Yang H, Wei Y. Overexpression of IGF2 affects mouse weight and glycolipid metabolism and IGF2 is positively related to macrosomia. *Front Endocrinol (Lausanne)* 2023; **14**: 1030453 [PMID: 37152930 DOI: 10.3389/fendo.2023.1030453]

64 **Rosario FJ**, Powell TL, Jansson T. Activation of placental insulin and mTOR signaling in a mouse model of maternal obesity associated with fetal overgrowth. *Am J Physiol Regul Integr Comp Physiol* 2016; **310**: R87-R93 [PMID: 26491103 DOI: 10.1152/ajpregu.00356.2015]

65 **Shang M**, Dong X, Hou L. Correlation of adipokines and markers of oxidative stress in women with gestational diabetes mellitus and their newborns. *J Obstet Gynaecol Res* 2018; **44**: 637-646 [PMID: 29399931 DOI: 10.1111/jog.13586]

66 **Dumolt JH**, Powell TL, Jansson T. Placental Function and the Development of Fetal Overgrowth and Fetal Growth Restriction. *Obstet Gynecol Clin North Am* 2021; **48**: 247-266 [PMID: 33972064 DOI: 10.1016/j.ogc.2021.02.001]

67 **Vaiman D**. Genes, epigenetics and miRNA regulation in the placenta. *Placenta* 2017; **52**: 127-133 [PMID: 28043658 DOI: 10.1016/j.placenta.2016.12.026]

68 **Wang WJ**, Huang R, Zheng T, Du Q, Yang MN, Xu YJ, Liu X, Tao MY, He H, Fang F, Li F, Fan JG, Zhang J, Briollais L, Ouyang F, Luo ZC. Genome-Wide Placental Gene Methylations in Gestational Diabetes Mellitus, Fetal Growth and Metabolic Health

Biomarkers in Cord Blood. *Front Endocrinol (Lausanne)* 2022; **13**: 875180 [PMID: 35721735 DOI: 10.3389/fendo.2022.875180]

69 **Ruchat SM**, Houde AA, Voisin G, St-Pierre J, Perron P, Baillargeon JP, Gaudet D, Hivert MF, Brisson D, Bouchard L. Gestational diabetes mellitus epigenetically affects genes predominantly involved in metabolic diseases. *Epigenetics* 2013; **8**: 935-943 [PMID: 23975224 DOI: 10.4161/epi.25578]

70 **Chen C**, Jiang Y, Yan T, Chen Y, Yang M, Lv M, Xi F, Lu J, Zhao B, Luo Q. Placental maternally expressed gene 3 differentially methylated region methylation profile is associated with maternal glucose concentration and newborn birthweight. *J Diabetes Investig* 2021; **12**: 1074-1082 [PMID: 33090678 DOI: 10.1111/jdi.13432]

71 **El Hajj N**, Pliushch G, Schneider E, Dittrich M, Müller T, Korenkov M, Aretz M, Zechner U, Lehnen H, Haaf T. Metabolic programming of MEST DNA methylation by intrauterine exposure to gestational diabetes mellitus. *Diabetes* 2013; **62**: 1320-1328 [PMID: 23209187 DOI: 10.2337/db12-0289]

72 **Zhao BH**, Jiang Y, Zhu H, Xi FF, Chen Y, Xu YT, Liu F, Wang YY, Hu WS, Lv WG, Luo Q. Placental Delta-Like 1 Gene DNA Methylation Levels Are Related to Mothers' Blood Glucose Concentration. *J Diabetes Res* 2019; **2019**: 9521510 [PMID: 31886292 DOI: 10.1155/2019/9521510]

73 **Su R**, Wang C, Feng H, Lin L, Liu X, Wei Y, Yang H. Alteration in Expression and Methylation of IGF2/H19 in Placenta and Umbilical Cord Blood Are Associated with Macrosomia Exposed to Intrauterine Hyperglycemia. *PLoS One* 2016; **11**: e0148399 [PMID: 26840070 DOI: 10.1371/journal.pone.0148399]

74 **Ge ZJ**, Liang QX, Luo SM, Wei YC, Han ZM, Schatten H, Sun QY, Zhang CL. Diabetic uterus environment may play a key role in alterations of DNA methylation of several imprinted genes at mid-gestation in mice. *Reprod Biol Endocrinol* 2013; **11**: 119 [PMID: 24378208 DOI: 10.1186/1477-7827-11-119]

75 **Desgagné V**, Hivert MF, St-Pierre J, Guay SP, Baillargeon JP, Perron P, Gaudet D, Brisson D, Bouchard L. Epigenetic dysregulation of the IGF system in placenta of

newborns exposed to maternal impaired glucose tolerance. *Epigenomics* 2014; **6**: 193-207 [PMID: 24811788 DOI: 10.2217/epi.14.3]

76 **Lesseur C**, Armstrong DA, Paquette AG, Li Z, Padbury JF, Marsit CJ. Maternal obesity and gestational diabetes are associated with placental leptin DNA methylation. *Am J Obstet Gynecol* 2014; **211**: 654.e1-654.e9 [PMID: 24954653 DOI: 10.1016/j.ajog.2014.06.037]

77 **Gagné-Ouellet V**, Breton E, Thibeault K, Fortin CA, Cardenas A, Guérin R, Perron P, Hivert MF, Bouchard L. Mediation Analysis Supports a Causal Relationship between Maternal Hyperglycemia and Placental DNA Methylation Variations at the Leptin Gene Locus and Cord Blood Leptin Levels. *Int J Mol Sci* 2020; **21** [PMID: 31947745 DOI: 10.3390/ijms21010329]

78 **Bouchard L**, Hivert MF, Guay SP, St-Pierre J, Perron P, Brisson D. Placental adiponectin gene DNA methylation levels are associated with mothers' blood glucose concentration. *Diabetes* 2012; **61**: 1272-1280 [PMID: 22396200 DOI: 10.2337/db11-1160]

79 **Houde AA**, St-Pierre J, Hivert MF, Baillargeon JP, Perron P, Gaudet D, Brisson D, Bouchard L. Placental lipoprotein lipase DNA methylation levels are associated with gestational diabetes mellitus and maternal and cord blood lipid profiles. *J Dev Orig Health Dis* 2014; **5**: 132-141 [PMID: 24847699 DOI: 10.1017/S2040174414000038]

80 **Gagné-Ouellet V**, Houde AA, Guay SP, Perron P, Gaudet D, Guérin R, Jean-Patrice B, Hivert MF, Brisson D, Bouchard L. Placental lipoprotein lipase DNA methylation alterations are associated with gestational diabetes and body composition at 5 years of age. *Epigenetics* 2017; **12**: 616-625 [PMID: 28486003 DOI: 10.1080/15592294.2017.1322254]

81 **Knabl J**, Hiden U, Hüttenbrenner R, Riedel C, Hutter S, Kirn V, Günthner-Biller M, Desoye G, Kainer F, Jeschke U. GDM Alters Expression of Placental Estrogen Receptor α in a Cell Type and Gender-Specific Manner. *Reprod Sci* 2015; **22**: 1488-1495 [PMID: 25947892 DOI: 10.1177/1933719115585147]

82 **Steyn A**, Crowther NJ, Norris SA, Rabionet R, Estivill X, Ramsay M. Epigenetic modification of the pentose phosphate pathway and the IGF-axis in women with

gestational diabetes mellitus. *Epigenomics* 2019; **11**: 1371-1385 [PMID: 31583916 DOI: 10.2217/epi-2018-0206]

83 **Houde AA**, Guay SP, Desgagné V, Hivert MF, Baillargeon JP, St-Pierre J, Perron P, Gaudet D, Brisson D, Bouchard L. Adaptations of placental and cord blood ABCA1 DNA methylation profile to maternal metabolic status. *Epigenetics* 2013; **8**: 1289-1302 [PMID: 24113149 DOI: 10.4161/epi.26554]

84 **Franzago M**, Porreca A, D'Ardes M, Di Nicola M, Di Tizio L, Liberati M, Stuppia L, Vitacolonna E. The Obesogenic Environment: Epigenetic Modifications in Placental Melanocortin 4 Receptor Gene Connected to Gestational Diabetes and Smoking. *Front Nutr* 2022; **9**: 879526 [PMID: 35571924 DOI: 10.3389/fnut.2022.879526]

85 **Xie X**, Gao H, Zeng W, Chen S, Feng L, Deng D, Qiao FY, Liao L, McCormick K, Ning Q, Luo X. Placental DNA methylation of peroxisome-proliferator-activated receptor-γ co-activator-1α promoter is associated with maternal gestational glucose level. *Clin Sci (Lond)* 2015; **129**: 385-394 [PMID: 25875376 DOI: 10.1042/CS20140688]

86 **Wang L**, Fan H, Zhou L, Wu Y, Lu H, Luo J. Altered expression of PGC-1α and PDX1 and their methylation status are associated with fetal glucose metabolism in gestational diabetes mellitus. *Biochem Biophys Res Commun* 2018; **501**: 300-306 [PMID: 29730292 DOI: 10.1016/j.bbrc.2018.05.010]

87 **Zhao Q**, Yang D, Gao L, Zhao M, He X, Zhu M, Tian C, Liu G, Li L, Hu C. Downregulation of peroxisome proliferator-activated receptor gamma in the placenta correlates to hyperglycemia in offspring at young adulthood after exposure to gestational diabetes mellitus. *J Diabetes Investig* 2019; **10**: 499-512 [PMID: 30187673 DOI: 10.1111/jdi.12928]

88 **Rong C**, Cui X, Chen J, Qian Y, Jia R, Hu Y. DNA methylation profiles in placenta and its association with gestational diabetes mellitus. *Exp Clin Endocrinol Diabetes* 2015; **123**: 282-288 [PMID: 25962407 DOI: 10.1055/s-0034-1398666]

89 **Jiang Y**, Yu YC, Ding GL, Gao Q, Chen F, Luo Q. Intrauterine hyperglycemia induces intergenerational Dlk1-Gtl2 methylation changes in mouse placenta. *Oncotarget* 2018; **9**: 22398-22405 [PMID: 29854287 DOI: 10.18632/oncotarget.23976]

90 **Carreras-Badosa G**, Bonmatí A, Ortega FJ, Mercader JM, Guindo-Martínez M, Torrents D, Prats-Puig A, Martinez-Calcerrada JM, de Zegher F, Ibáñez L, Fernandez-Real JM, Lopez-Bermejo A, Bassols J. Dysregulation of Placental miRNA in Maternal Obesity Is Associated With Pre- and Postnatal Growth. *J Clin Endocrinol Metab* 2017; **102**: 2584-2594 [PMID: 28368446 DOI: 10.1210/jc.2017-00089]

91 **Zhou X**, Xiang C, Zheng X. miR-132 serves as a diagnostic biomarker in gestational diabetes mellitus and its regulatory effect on trophoblast cell viability. *Diagn Pathol* 2019; **14**: 119 [PMID: 31653266 DOI: 10.1186/s13000-019-0899-9]

92 **Zheng Y**, Huang M, Lu X, Xu J, Han Y, Ji J, Han Y. Association of hyperglycaemia with the placenta of GDM-induced macrosomia with normal pre-pregnancy BMI and the proliferation of trophoblast cells. *J Obstet Gynaecol* 2022; **42**: 1759-1768 [PMID: 35260025 DOI: 10.1080/01443615.2022.2036969]

93 **Guiyu S**, Quan N, Ruochen W, Dan W, Bingnan C, Yuanyua L, Yue B, Feng J, Chong Q, Leilei W. LncRNA-SNX17 Promotes HTR-8/SVneo Proliferation and Invasion Through miR-517a/IGF-1 in the Placenta of Diabetic Macrosomia. *Reprod Sci* 2022; **29**: 596-605 [PMID: 34270000 DOI: 10.1007/s43032-021-00687-z]

94 **Shah KB**, Chernausek SD, Teague AM, Bard DE, Tryggestad JB. Maternal diabetes alters microRNA expression in fetal exosomes, human umbilical vein endothelial cells and placenta. *Pediatr Res* 2021; **89**: 1157-1163 [PMID: 32663836 DOI: 10.1038/s41390-020-1060-x]

95 **Li J**, Song L, Zhou L, Wu J, Sheng C, Chen H, Liu Y, Gao S, Huang W. A MicroRNA Signature in Gestational Diabetes Mellitus Associated with Risk of Macrosomia. *Cell Physiol Biochem* 2015; **37**: 243-252 [PMID: 26302821 DOI: 10.1159/000430349]

96 **Guan CY**, Tian S, Cao JL, Wang XQ, Ma X, Xia HF. Down-Regulated miR-21 in Gestational Diabetes Mellitus Placenta Induces PPAR-α to Inhibit Cell Proliferation and Infiltration. *Diabetes Metab Syndr Obes* 2020; **13**: 3009-3034 [PMID: 32943895 DOI: 10.2147/DMSO.S253920]

97 **Song TR**, Su GD, Chi YL, Wu T, Xu Y, Chen CC. Dysregulated miRNAs contribute to altered placental glucose metabolism in patients with gestational diabetes via targeting

GLUT1 and HK2. *Placenta* 2021; **105**: 14-22 [PMID: 33517149 DOI: 10.1016/j.placenta.2021.01.015]

98 **Sun DG**, Tian S, Zhang L, Hu Y, Guan CY, Ma X, Xia HF. The miRNA-29b Is Downregulated in Placenta During Gestational Diabetes Mellitus and May Alter Placenta Development by Regulating Trophoblast Migration and Invasion Through a HIF3A-Dependent Mechanism. *Front Endocrinol (Lausanne)* 2020; **11**: 169 [PMID: 32296392 DOI: 10.3389/fendo.2020.00169]

99 **Cao JL**, Zhang L, Li J, Tian S, Lv XD, Wang XQ, Su X, Li Y, Hu Y, Ma X, Xia HF. Up-regulation of miR-98 and unraveling regulatory mechanisms in gestational diabetes mellitus. *Sci Rep* 2016; **6**: 32268 [PMID: 27573367 DOI: 10.1038/srep32268]

100 **Guan CY**, Cao JL, Zhang L, Wang XQ, Ma X, Xia HF. miR-199a Is Upregulated in GDM Targeting the MeCP2-Trpc3 Pathway. *Front Endocrinol (Lausanne)* 2022; **13**: 917386 [PMID: 35909537 DOI: 10.3389/fendo.2022.917386]

101 **Ogino S**, Lochhead P, Chan AT, Nishihara R, Cho E, Wolpin BM, Meyerhardt JA, Meissner A, Schernhammer ES, Fuchs CS, Giovannucci E. Molecular pathological epidemiology of epigenetics: emerging integrative science to analyze environment, host, and disease. *Mod Pathol* 2013; **26**: 465-484 [PMID: 23307060 DOI: 10.1038/modpathol.2012.214]

102 **Ogino S**, Nowak JA, Hamada T, Milner DA Jr, Nishihara R. Insights into Pathogenic Interactions Among Environment, Host, and Tumor at the Crossroads of Molecular Pathology and Epidemiology. *Annu Rev Pathol* 2019; **14**: 83-103 [PMID: 30125150 DOI: 10.1146/annurev-pathmechdis-012418-012818]

103 **Gao C**. Molecular pathological epidemiology in diabetes mellitus and risk of hepatocellular carcinoma. *World J Hepatol* 2016; **8**: 1119-1127 [PMID: 27721917 DOI: 10.4254/wjh.v8.i27.1119]

Figure 1 Role of placenta epigenetic modification in offspring development of gestational diabetes mellitus. MEG3: Maternally expressed gene 3; IGF-1R: Insulin-like growth factor 1 receptor; LEP: Umbilical cord leptin; HIF3A: Hypoxia-inducible factor 3 subunit α; PGC-1α: Proliferator-activated receptor-γ coactivator-1α; GLUT: Glucose transporters.

Table 1 Relationship between placental transport function and fetal weight in gestational diabetes mellitus

Nutrient	Transporter	GDM model		Cell lines	Mechanism of action	Localization	Result	Ref.
		Gestational age	Animal species					
Glucose	GLUT1	37+ wk gestation	-	-	-	P↑; BM↑	FBW (+); AFM (+), SSFM (+)	[17,18]
		Full-term placenta	-	-	p-Akt and Erk↑	P↑	FBW↑	[23]
	GLUT4	37+ wk gestation	-	-	-	P↑	SSFM (+); FBW (+)	[17]
	GLUT9	37+ wk gestation	-	-	-	P↑	FBW (*)	[17]

	GLUT3	-	db/+mice & HFD-induced C57B L/6J mice	-	AMPK↓	PM↓	FBW↑	[20]
Amino acids	System A	-	-	Insulin stimulates PHT cell and PVE	p-Akt and Erk↑	PHT↑	FBW↑	[9]
		-	-	TNF-α stimulation PHT cell	Erk; p38MAPK	PHT↑	FBW↑	[30]
		-	-	IL-6 treat PCT	JAK/STAT	PCT↑	FBW↑	[31]
		-	-	LPS and poly (I:C) treat PCT	TLR3 and TLR4↑	PCT↑	FBW↑	[32]
	SNAT 1	37-41^{+6} wk gestation	-	-	IGF-I and mTOR↑	P↑	FBW (+)	[25]

	-	-	TNF-α stimulation PHT cell	Erk; p38MAPK	PHT↑	FBW↑	[30]
	-	-	LPS and poly (I:C) treat PCT	TLR3 and TLR4↑	PCT↑	FBW↑	[32]
SNAT2	-	-	TNF-α stimulation PHT cell	Erk; p38MAPK	PHT↑	FBW↑	[30]
	-	-	IL-6 treat PCT	JAK/STAT	PCT↑	FBW↑	[31]
	-	-	LPS and poly (I:C) treat PCT	TLR3 and TLR4↑	PCT↑	FBW↑	[32]
SNAT3	-	-	IL-6 treat PCT	JAK/STAT	PCT↑	FBW↑	[31]
System L	-	-	MVM and	-	MVM↑	FBW↑	[28]

				BMs from GDM				
		-	STZ-induced SD rats	-	mTORC1↓	P↓	FBW↓	[46]
Lipids	TG	-	-	Hight glucose and insulin treat PHT	-	PHT↑	FBW↑	[35]
		-	HF/HCD induced C57BL/6J mice	-	CEH↑, TGH↓	P↑	FBW↑	[36]
		37-42 wk gestation	-	Hight glucose treat PE	β-oxidation↓	P↑	FBW↑	[38]
	EL	Full-term placenta	-	-	p-Akt and Erk↑	P↑	FBW↑	[41]
	FAT	-	-	Hight glucose and	-	PHT↑	FBW↑	[35]

				insulin treat PHT				
	Full-term placenta	-	-	p-Akt and Erk↑		P↑	FBW↑, FBW (+)	[41,42]
FABP4 A-FABP L-FABP	Full-term placenta	-	-	p-Akt and Erk↑		PHT↑, P↑	FBW↑	[34,40,41]
FABP3, FABP4	-	-	Hight glucose and insulin treat PHT	-		PHT↑	FBW↑	[35]
FATP-1	Full-term placenta	-	-	p-Akt and Erk↑		P↑	FBW↑	[41]

P: Placenta; FBW: Fetal baby weight; SSFM: Subscapular fat mass; AFM: Abdominal; PM: Plasma membrane; BM: Basement membrane; PHT: Primary human trophoblast; PVE: Placental villous explants; PE: Placental explants; PTC: Primary trophoblast cells; CEH: Cholesterol ester hydrolase; MVMs: Microvillous plasma membranes; +: Positive correlation; *: Correlation; FATPs: Fatty acids transport proteins.

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