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Review Article

The Effect Gestational Diabetes has on DNA Methylation as Related to Fetal Development and the Outcomes of the Mother and Offspring

Michael P Sarras Jr[1*] and Alexey Leontovich[2]

[1]*Department of Cell Biology and Anatomy, Rosalind Franklin University of Medicine, Illinois, USA*

[2]*Division of Biomedical Statistics and Informatics, Mayo Clinic, Minnesota, USA*

Abstract

In the current review we will discuss the relationship of Gestational Diabetes (GDM) to DNA methylation and relate this epigenetic process to fetal development and the outcomes of offspring of mothers with GDM as well as the outcome of mothers who experience GDM. The article is organized into four sections that include: 1) DNA methylation in the placenta and placental cord, 2) Effects of gestational diabetes on DNA methylation patterns and particular genes and cell types in offspring, 3) Effects of gestational diabetes on the growth and weight of offspring, and 4) Potential epigenetic biomarkers for predicting gestational diabetes and the occurrence of T2DM following GDM. In summary, these studies indicate 1) A significant occurrence of DNA methylation in fetal placental tissues and cord blood, 2) The occurrence of specific genes known to be related to the on-set and continuance of diabetes in mothers with GDM and their offspring, 3) The occurrence in GDM of DNA methylation patterns affecting genes that control fetal growth and the weight of offspring, and 4) The potential identification of biomarkers that can be used to predict the on-set of GDM in mothers and the later on-set of T2DM in both GDM mothers and their offspring.

Keywords: Diabetes mellitus; DNA methylation; Epigenetics; Gestational diabetes

***Corresponding author:** Michael P Sarras Jr, Department of Cell Biology and Anatomy, Rosalind Franklin University of Medicine, Illinois, USA, Tel: +1 5204054739; E-mail: michael.sarras@rosalindfranklin.edu

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Abbreviations

GDM: Gestational Diabetes
DM: Diabetes Mellitus
T2DM: Type-2 Diabetes Mellitus

Introduction

A maternal form of Diabetes Mellitus (DM) is Gestational Diabetes (GDM) that affects approximately 6% of pregnant women in the United States [1] and can later lead to DM of both the affected mothers [2-4] and their offspring [4-8]. DM [9] in general often results in long term complications [10] stemming from metabolic dysregulation [11,12]. Clinical trials have established that once initiated, these complications persist and continue to progress unimpeded even when glycemic control is achieved through pharmaceutical intervention; a phenomenon termed, "Metabolic Memory" (MM) [13-16] The mechanism(s) of MM have been examined via both animal model approaches and *in vitro* based studies [17-23]. These studies indicate that the initial Hyperglycemia (HG) results in permanent aberrant gene expression in DM target tissues such as the general cardiovascular system, renal system, and retina; to name just a few. The ability to sustain these complications in the absence of HG invokes a role for the epigenome to perpetuate tissue dysfunction. While extensive epigenetic research has been conducted regarding histone modifications [24-27] and micro RNA mechanisms [28-34], less is known about the role of HG-induced persistent DNA methylation changes; although data from animal models and humans indicate that aberrant DNA methylation does occur in DM & GDM. Moreover, the HG environment induces changes in specific cells types, such as Endothelial Cells (EC) involving structural, metabolic, and functional alterations as in blood vessel formation [10,35-37]. This is of particular significance because impaired blood vessel formation is a common pathology associated with all organ and tissues systems affected in DM and GDM.

In the current review we will discuss the relationship of gestational diabetes to DNA methylation and relate this epigenetic process to fetal development and the outcomes of offspring of mothers with GDM as well as the outcome of mothers who experience GDM. The articles are organized into four sections that include: 1) DNA methylation in the placenta and placental cord, 2) Effects of gestational diabetes on DNA methylation patterns and particular genes and cell types in offspring, 3) Effects of gestational diabetes on the growth and weight of offspring, and 4) Identification of potential epigenetic biomarkers for predicting gestational diabetes and the occurrence of T2DM following GDM.

Discussion

DNA methylation in the placental cotyledon tissue, placental cord blood, and maternal blood of GDM mothers

A number of articles have focused on DNA methylation in placental tissues and maternal blood of GDM mothers [6,38-44]. These articles subdivide into five groups to include: 1) Studies limited to

placental cotyledon tissue [6,38], 2) Studies limited to cord blood [39-41], 3) Studies comparing cord blood and placental cotyledon tissue [42], 4) Studies involving cord blood and maternal blood of GDM mothers [43], and 5) Studies limited to maternal blood of GDM mothers [44]. Group 1 studies indicated that mothers with GDM had significantly higher degree of placental DNA methylation than control groups. The results of Rong et al. 6) Extended these findings to observe that DNA methylation involved both hypermethylation and hypomethylation of DNA methylated regions and found that predominantly chromosomes 1, 2, and 11 were affected in this epigenetic process. These DNA methylated regions included both genome-wide methylation changes and promoter-specific methylation changes to the CpG dinucleotides that are known to be the predominate sites targeted in DNA methylation. These authors noted that specific gene analysis identified those classes of genes related to 1) Cell growth and death regulation, 2) Immune and inflammation response, 2) Nervous system development, and 3) Genes of the Wnt pathway that are involved in pancreatic beta cell function as also found by the studies of Petropoulos et al. [45]. Group 2 studies found that in the case of cord blood, DNA methylation changes were small (in the order of a few percentage points) when analyzed at the signal gene level but were associated with important gene classes such as those related to cardiovascular system function, diabetes, obesity, and stroke to name but a few. As with the group 1 studies, DNA methylation in cord blood involved both hypermethylation and hypomethylation. Group 3 studies compared cord blood DNA methylation patterns to that of placental cotyledon tissue and found some 1485 cord blood and 1708 placenta methylated sites in these groups. They found that specific gene classes affected in these two tissues included: Endocytosis, MAPK-signaling and extracellular triggers to intracellular metabolic processes to include the Wnt genes. The first two gene classes have been tied to placental function and fetal development while as discussed above, the Wnt genes have been tied to the control of insulin metabolism and therefore underlie the on-set and maintenance of diabetes. Group 4 included one study that focused on the top 200 loci (from 381,869 methylated sites of maternal blood and from 540,036 methylated sites of cord blood) with their corresponding genes within maternal blood of GDM mothers and cord blood and found that these regions had differentiated DNA methylated. Similar to the other groups (Groups 1-3) gene groups related to endocrine disorders, metabolic disorders, carbohydrate metabolism, and lipid metabolism were found to have differential DNA methylation. In agreement with the other groups, ties to Diabetes in the methylated regions affected were discussed. Group 5 contained one study that was unique in that it focused on women (N of 173) that had two consecutive pregnancies and who provided blood samples in both pregnancies. These women included women who did not experience GDM and women that developed GDM during their pregnancy. When normal and GDM women were compared, they found that the GDM group had significant DNA methylation patterns that involved both hypermethylation and hypomethylation. Novel genes were identified associated with DNA methylation that involved functions related to cellular morphology, organization, assembly, or compromise, and the cell cycle. Further analysis tied some of these genes to insulin resistance in T2D.

Summarizing the results of groups 1-5 one finds the common features of GDM to include: 1) Differential global DNA methylation, 2) Methylation sites observed to involve both hypermethylation and hypomethylation of CpG nucleotides, and 3) A broad array of gene classes that all appear to have some tie to diabetes. The effect of these genes on the later on-set of T2DM remains to be determined, but animal model studies indicate that once DNA methylation occurs it is not fully reversed [21,46-48].

As an extension of the above mentioned studies, a number of studies have focused on the effects of DNA methylation on particular genes as analyzed by DNA sequence analysis from the placenta, cord blood, and maternal blood or tissues [3,45,49-54] (Table 1). These studies have highlighted the importance of the following genes related to the potential on-set of DM (typically T2DM in the case of GDM) [3,45,49-54]: 1) MEST gene [49], 2) The NPR1, PANK1, SCAND1, GJA4, PYGO1 and CLN8 [50] genes, 3) DNA methyltransferases to include; DNMT1, DNMT3A, and DNMT3B [3], 4) GNAS and IGF2 [52], 5) Placental Lipoprotein Lipase (LPL) [51], 6) ZFP57,TBR1, DGKZ, AGPAT1 and MAPK10 [45], 7) The studies of Chen et al. [53], identified 29 genes and 10 intergenic regions with methylated regions in the blood of offspring of mothers with GDM, and 8) PGC-1 and PDX1 [54]. These genes showed either hypermethylation or hypomethylation as a consequence of the hyperglycemic environment created in mothers with GDM. However, whether these genes directly contribute to the on-set of DM in mothers with GDM or their offspring is unclear. As stated above however, animal model studies indicate that once DNA methylation occurs it is not fully reversed [21,46-48] thereby creating a link between this epigenetic event and the future on-set of diabetes.

Sources of Tissue		
Placental tissue, cord blood, and maternal blood or tissues with observed DNA methylation	Placental cord blood, placental cotyledon tissue, and mother's adipose tissue (from C-Section) as related to obesity and childhood weight	Peripheral blood of offspring and mothers
NPR1, PANK1, SCAND1, GJA4, PYGO1, CLN8, DNMT1, DNMT3A, and DNMT3B GNAS, IGF2, LPL, ZFP57,TBR1, DGKZ, AGPAT1, MAPK10, PGC-la and PDX1	POU2F1, PKHD1, NFE2, NHLH2, AGTR2, and LEP	COPSE, PIL3R5, HAAO, CCDC124, C5 or f34, methylated H3K27 and H3K4 (both histones), CTNND2, HNF4A, and RREB1
Endothelial cells derived from umbilical cord or cord blood with observed DNA methylation 1) Growth factors and proteins linked to insulin sensing (IGFBP3, IGFBP5, IRS1, SIRT1, mTOR); 2) Factors involved in ECM reorganization (TGFB2, FBN1, FBN2, COL1A1, COL3A1, DDR2, FN1, FST, FST13, CARD11, LIPG, ICAM1); 3) Non-insulin growth factors (FGF2, PDGFbR); 4) Cell cycle genes (CCND2, CDKN2B); and 5) Cell proliferation, survival, autophagy, and epithelial-to-mesenchyma I transition (PLAC8)		

Table 1: Genes that have been identified from tissues of gestational diabetes mothers that show DNA methylation pattern changes.

Effects of gestational diabetes on particular genes and particular cell types in the offspring of GDM mothers

As stated in the introduction Gestational diabetes can later lead to DM of the T2-form of both the affected mothers [2-4] and their offspring [4-8]. If T2DM does occur it often results in long term complications [10] affecting a broad spectrum of organs and tissues of the body because of the sustained metabolic dysregulation occurring in the disease [11,12]. A significant cell type targeted in the long term complications of the disease is the Endothelial Cell (EC) [10,35-37]. The hyperglycemic environment of GDM and DM induces changes in the EC involving structural, metabolic, and functional alterations as seen in the impairment of blood vessel formation [10,35-37]. Blood vessel formation is of particular importance because its impairment directly underlies many of the pathology's seen following the initial hyperglycemic episodes. A few studies have directly studied endothelial cells under the hyperglycemic conditions of GDM (Table 1). For example, Ambra et al. [55], have performed transcriptome analysis of Human Primary Endothelial Cells (HUVEC) from umbilical cords of gestational diabetic mothers and have identified candidate sites for an epigenetic modulation of specific gene expression in these cells. They reported that four categories of gene classes that were affected by the hyperglycemic GDM environment. These four categories included: 1) Growth factors and proteins linked to insulin sensing (IGFBP3, IGFBP5, IRS1, SIRT1, mTOR); 2) Factors involved in ECM reorganization (TGFB2, FBN1, FBN2, COL1A1, COL3A1, DDR2, FN1, FST, FSTL3, CARD11, LIPG, ICAM1); 3) Non-insulin growth factors (FGF2, PDGFbR); and 4) Cell cycle genes (CCND2, CDKN2B). They interconnect these four groups into a scheme that proposes that there is a functional interplay between the groups that involves:

Insulin Sensing ⟷ ECM Reorganization ⟷ Cell Cycle Control

The investigators do not propose mechanisms that explain the coordination of this interplay, but do indicate that their studies form a foundation for future studies to evaluate those mechanisms.

Blue et al. [56], have studied epigenetic altered function of endothelial colony-forming cells (endothelial progenitor cells) in GDM. They specifically studied the effects Placenta-Specific 8 gene (PLAC8) had on DNA methylation. PLAC8 is also known as onzin. PLAC8 was originally identified as a placental-enriched protein but later studies showed that PLAC8 was also expressed in epithelial cells, adipocytes, and hematopoietic cells [57-61]. Although the precise endogenous biochemical function of PLAC8 is unclear, more recent data indicates that it regulates adipocyte differentiation, the innate immune response, and cell proliferation/survival processes [57,60,61]. Additional studies demonstrated a role for PLAC8 in promoting tumorigenesis; possibly via mechanisms involving proliferation, survival, autophagy, and epithelial-to-mesenchymal transition [57-59,62]. For these studies, endothelial progenitor cells were obtained and cultured from isolated umbilical cord blood cells. Blue et al. [56], found that PLAC8 over expression functioned as a protective mechanism for endothelial colony-forming cells to avoid senescence. Given that hyperglycemia of GDM enhances endothelial colony-forming cells senescence and impairs vasculogenesis, their findings indicated an adaptive response of fetal endothelial colony-forming cells to circumvent the negative effects of a hyperglycemic environment. In addition, differential methylation was detected in endothelial colony-forming cells from GDM mothers in the first intron of an isoform of PLAC8. Moreover, the methylation of several individual CpG sites in these regions was seen to be negatively correlated with PLAC8 mRNA expression. This suggested a mechanistic link which the authors proposed was due to altered transcription factor binding. The authors conclude that their data indicates that neonatal endothelial progenitor cells of GDM mothers leads to altered gene expression and DNA methylation due to the hyperglycemic environment present during GDM. This would then open the possibility that altered epigenetic regulation had occurred. A cautionary note in regard to these studies concerns one aspect of the experimental protocol. Because the investigators cultured endothelial colony-forming cells for subsequent analysis, this opens the possibility that altered DNA methylation occurred due to *in vitro* culturing conditions; a process that in itself is suspected to induce DNA methylation.

Effects of gestational diabetes on the growth and weight of offspring

A number of studies have focused on the effects of GDM-induced DNA methylation on fetal growth and newborn weigh [8,63-68] (Table 1). The majority of these studies have analyzed placental cord blood [8,63-65] while two studied both cord blood and placental cotyledon tissue [66,67]. These studies shared the finding that restricted fetal growth and offspring weight correlated with changed DNA methylation patterns in genes associated with growth control such as POU2F1, PKHD1, NFE2, NHLH2, and AGTR2 [8]. Complementing these studies were the findings of Lesseur et al., who found in analysis of placental cotyledon tissue significant changes in the DNA methylation pattern of the Leptin gene [66]. Leptin is important to energy homeostasis and functions as a satiety signal. During pregnancy, leptin is produced by the placenta and has pleiotropic functions that include regulation of growth and nutrient exchange [69]. Finally, Deng et al. [68], analyzed adipose tissue of control and GDM women obtained during C-section births. They found that genes related to obesity control in adipose tissue were significantly methylated. They concluded that fetuses of GDM mothers had a higher potential for childhood obesity than those of non-GDM mothers.

Potential epigenetic biomarkers for predicting gestational diabetes and the occurrence of T2DM following GDM

Recent studies have attempted to identify epigenetic biomarkers that can be used to predict the on-set of T2DM following the occurrence of GDM [70-72] (Table 1). The studies of Wu et al. [70], stand out because they identified maternal DNA methylation changes prior to the diagnosis of GDM; thereby pointing to specific genes (COPS8, PIL3R5, HAAO, CCDC124, and C5 or f34) that may be used as biomarkers for the on-set of GDM prior to its clinical diagnosis. Studying the epigenetic process of histone methylation, as opposed to DNA methylation, Michalczyk et al. [71], studied the blood of GDM versus non-GDM mothers and determined that methylated H3K27 was significantly lower at 8-10 and 20 weeks postpartum in women with GDM who developed T2DM, compared with nondiabetic women. Likewise methylated H3K4 was significantly lower at 8-10 weeks postpartum in women with GDM who later developed T2DM compared with women who had GDM who did later develop the disease. They concluded that because the percentage of methylated H3K27 and H3K4 varied with diabetic state; it was a potential predictive biomarker for the identification of women who will later development T2DM after experiencing GDM. Finally, the studies of

Kim et al. [72], focused on DNA methylation analysis in sibling pairs who were either exposed to *in utero* GDM or were not exposed to *in utero* GDM. Analysis of their data indicated that several suggestive epigenetic markers could be identified. For example, one CpG site, cg04988367, which was located 39 kb downstream of Catenin Delta 2 (CTNND2) showed a significant difference. An additional 11 CpG sites also had significant methylation differences. This later group included cg08407434 which was positioned at the intron of Hepatocyte Nuclear Factor 4A (HNF4A). This gene is known to be related to maturity on-set diabetes of the young. Another CpG marker, cg18255813, was located at intron of Ras Responsive Element Binding protein 1 (RREB1), which was reported to be associated with visceral fat mass and glycemic traits.

All of these studies suggest that GDM related biomarkers exist, but extensive studies must be completed to firmly establish any one of them as true biomarkers for GDM.

Summary and Conclusion

The literature clearly established that DNA methylation is induced by gestational diabetes as analyzed in placental cotyledon tissue and cord blood. The DNA methylation patterns affect both exons and introns and are observed as both hypermethylation and hypomethylation of CpG dinucleotides. The genes affected by this epigenetic process include a broad spectrum of functional groups involved in such pathways as metabolic processes related to insulin control and subsequent diabetic dysregulation, growth control, and childhood obesity. Finally, recent studies have begun to identify potential biomarkers for the prediction of those women who may develop GDM and the later on-set of T2D in GDM mothers and their offspring.

In regard to the effect of DNA methylation on gene/protein function we propose that these epigenetic changes affect regulatory regions upstream of genes that cause these genes to either up or down regulate depending on whether hypermethylation or hypomethylation has occurred. This would result in dysfunction of tissues/organs in the long term metabolic memory state because of these alterations in gene expression patterns.

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Conflict of Interest

The authors have no conflict of interests or commercial interests as related to the information provided in this review.

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