Along with a genetic association in the development of T2D, epigenetic regulation has been suggested as a significant contributor in altered gene expression. Recent studies have described DNA methylation changes in insulin-sensitive tissues involved in T2D pathogenesis, however epigenetic dynamics on early stages to metabolic alterations is still unclear.

We investigated potential DNA methylation signatures in 34 asymptomatic individuals from the GEMM family study. We compared differentially methylated CpG sites (DMC: B value>0 and delta Beta >|10%|; Infinium EPIC array) from subcutaneous adipose tissue (SCAT) in different groups of individuals according to BMI (kg/m^2) and HbA1c (%) levels as follow: Group A Control (C): n=9, 22.0±1.9 kg/m^2, 4.8±0.3%; Group B Overweight (OW) with normal HbA1c: n=6, 27.8±1.6 kg/m^2, 5±0.2%; Group C Obese (OB) with normal HbA1c: n=6, 34.6±4.2 kg/m^2, 5.2±0.2%; Group D Prediabetes (PD): n=7, 31.1±5.7 kg/m^2, 5.9±0.2% and Group E T2D: n=6, 30.6±7.3 kg/m^2, 7.2±0.9%.

We found 43 overlapping genes with shared pathways in all groups, mainly those related to metabolism and adipogenesis. We also documented particular altered methylated genes, in each group (OW: 386, OB:1005, PD:76 and T2D:189). Pathway enrichment analysis in OB and T2D was mainly related to glucose metabolism, while in OW and PD was NOTCH signaling. All groups displayed a consistent hypermethylation in *RARA*, *ESR1* and *NCOR2*, well known genes involved in lipid metabolism. Additionally, we describe for the first time, a progression toward hypomethylation in *ARHGAP15* and *MTAP*, related with an impaired metabolic status. Otherwise, analysis of overlapping CpG sites revealed a consistently hypermethylated state in OW (86.42%), OB (86.48%) and PD (51.72%), in contrast with the hypomethylation state (56.3%) observed in the T2D group, previously observed elsewhere (1).

In conclusion, comparison of methylation in SCAT obtained from OW, OB, PD and T2D individuals, display potential pathways and DMC signatures specific in each group. Common novel overlapping genes in global DNA methylation profiles of SCAT, were also observed.

Reference: (1) Barajas-Olmos et al., *BMC Med Genet*. 2018 Feb 21;19(1):1-8.

Nothing to Disclose: FE, FB, AM, EH, GEMM, ER, RB, LO.

Diabetes Mellitus and Glucose Metabolism

ISLETS, LIVERS, PLACENTA, AND VASCULATURE — THE MULTITISSUE IMPACT OF DIABETES

Association Between Placental Glucose Uptake and Protein O-Glcnacylation and Birth Outcomes in Obese Non-Diabetic Mothers

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Increased transport of nutrients such as glucose, across the placenta, has been linked to abnormal fetal growth and pregnancy complications in obese non-diabetic mothers (1); however, the underlying mechanisms are poorly understood. We hypothesized that in placenta, the metabolic and nutrient sensor O-GlcNAc transferase (OGT), highly sensitive to glucose flux through the hexosamine biosynthetic pathway (HBP), responds to maternal obesogenic environment by increasing O-GlcNAc post-translational modification of nucleocytoplasmic proteins in the placenta altering fetal growth trajectories. Tissue biopsies were isolated from placentas collected at term from 26 non-diabetic mothers alongside routine biochemistry and anthropometric data (maternal fasting glucose, glycated hemoglobin (HbA1c), early pregnancy body weight (BMI) and birth weight). OGT and glucose transporter 1 (GLUT1) protein expression as well as tissue levels of O-GlcNAcylation were determined by immunoblotting using specific antibodies. The BeWo choriocarcinoma cell line was also used as an *in vitro* model of trophoblast to test the effect of high glucose and GLUT1 silencing on the OGT activity by immunoblotting. Maternal BMI was positively correlated to birth weight centile (BWC) (p=0.0130, R^2=0.231), maternal fasting glucose (p=0.0177, R^2=0.221) and HbA1c levels (p= 0.0156, R^2=0.229) as well as placental OGT protein expression (p=0.0294, R^2=0.183). The latter was positively associated to the levels of protein O-GlcNAcylation (p=0.0023, R^2=0.326). Interestingly, GLUT1 protein levels were positively correlated to BWC (p=0.0056, R^2=0.279) and strongly correlated to protein O-GlcNAcylation (p<0.0001, R^2=0.507), suggesting an increase in the placental flux of glucose. In agreement with findings in placenta biopsies, in BeWo cells total protein O-GlcNAcylation levels were altered by cell exposure to different glucose levels (5 mM vs 15 mM, p<0.01). This was prevented by downregulating OGT or GLUT1 expression (p<0.001) using gene silencing. In addition, OGT protein levels were negatively associated to AMP-activated protein kinase (AMPK) activation (p=0.0005, R^2=0.402) in placenta biopsies identifying a novel cross-talk between two placental nutrient sensors, OGT and AMPK, previously shown in other tissues (2). Accordingly, the silencing of OGT promoted the activation of AMPK (p<0.01) and its downstream target acetyl-CoA carboxylase (ACC) (p<0.01) in BeWo cells, as demonstrated by increased phosphorylation of residues Thr172 and Ser79 for AMPK and ACC respectively. Such obesity-associated cross talk between metabolic and nutrient sensors might disrupt multiple cellular pathways involved in fetal development and growth.

***References**: (1) Acosta et al. Am J Obstet Gynecol. 2015 Feb;212(2):227. (2) Bullen et al. J Biol Chem. 2014 Apr 11;289(15):10592-606.*

Bone and Mineral Metabolism

BONE AND MINERAL CASE REPORTS II

Severe Hypercalcemia Following Hip Joint Implantation of Stimulan® Calcium Sulfate Antibiotic Beads

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