Impact of Maternal Diabetes on microRNA Expression in Fetal Tissue

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Introduction

- Maternal health, nutrition, obesity, and metabolic disease including diabetes mellitus (DM) alter offspring metabolic memory and lead to numerous ill effects, including obesity, insulin resistance, DM, cardiovascular disease (CVD), and metabolic syndrome.
- Fetal epigenetic changes have been implicated as an important mechanism underlying the regulation and reprogramming of metabolic memory that confers high risk of metabolic and cardiovascular disease to DM exposed offspring.
- One of the epigenetic mechanisms proposed to alter metabolic programming are microRNAs (miRNAs), which are small noncoding RNAs that regulate gene expression by repressing mRNA translation.

Methods

- A nonbiased sequencing approach was used to examine the impact of DM exposure in utero on miRNA abundance in human umbilical vein endothelial cells (HUVEC) from 6 infants born to mothers with diabetes and 6 infants born to mothers with normal glycemia matched for infant sex, ethnicity, and gestational age.
- To predict the genes targeted by the most abundant miRNAs, two computational target prediction algorithms, TargetScan and Miranda 3.3a, were used to identify miRNA binding sites.
- The data predicted by both algorithms were combined and the overlaps were calculated. The gene ontology (GO) terms and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways of these most abundant miRNAs and their mRNA targets were also annotated. RT-PCR was then used to quantify the changes in miRNA expression.

microRNA Sequencing Results

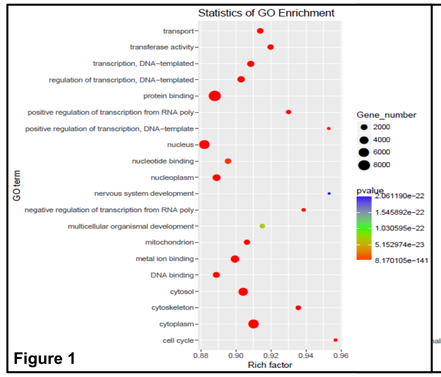

Figure 1

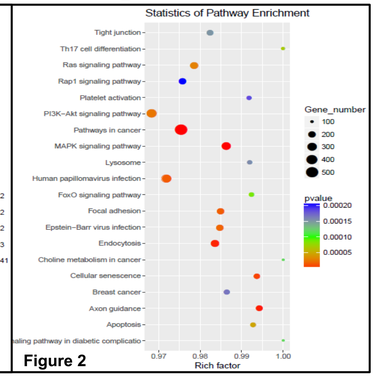

Figure 2

- The Rich Factor (x-axis) is the ratio of differentially expressed genes to all genes in the pathway. The Y-axis are the individual pathways; the dots are color-coded for p-values and the size corresponds to the number of genes.
- **Figure 1:** GO target enrichment analysis suggested the targets of the most abundant miRNAs were involved in transport, protein binding, mitochondria, DNA transcription, and cell cycle.
- **Figure 2:** The KEGG analysis found the most significantly enriched pathways were PI3K-Akt, AGE-RAGE signaling in diabetic complications, apoptosis, FoxO signaling, MAPK signaling, and cell senescence.

Distribution of microRNAs in Control vs. Diabetes Exposed HUVECs

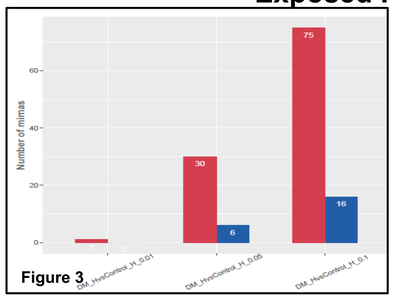

Figure 3

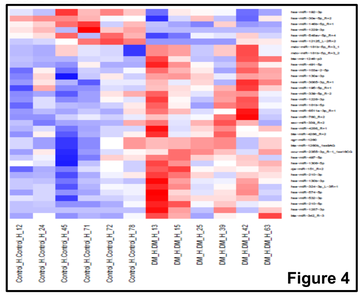

Figure 4

- **Figure 3:** The red bar shows the number of miRNAs that are increased while the blue bar shows the number of microRNAs that are decreased in control vs. DM-exposed HUVECs.
- **Figure 4:** The first 6 columns are controls while the next 6 are samples from DM exposed HUVECs. The Y-axis lists the microRNAs. As you can appreciate, for the most part, microRNAs in the HUVECs of DM-exposed infants had a relative increase or are upregulated as indicated by the warmer/red shade of the boxes.

microRNA Expression in HUVEC

	miR-146b		miR-30e		miR-210	
	Control	DM	Control	DM	Control	DM
N	39	23	39	23	39	23
Average	1	0.75	1	1.04	1	1.28
SD	0.46	0.43	0.28	0.52	0.46	0.77
SEM	0.07	0.09	0.04	0.11	0.07	0.16
MW U, p	0.03		0.73		0.13	

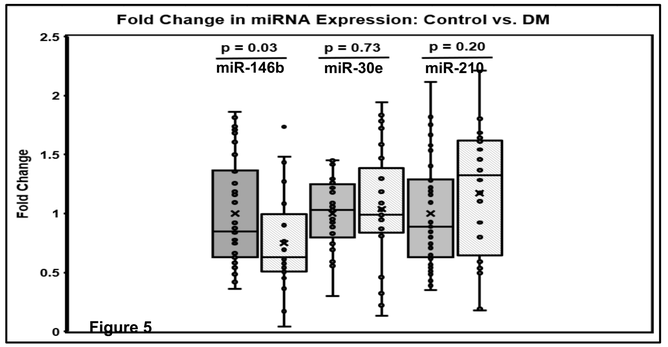

Figure 5

- Figure 5: Only microRNA 146b was noted to have an average of a 25% statistically significant (p = 0.03) decrease in HUVECs from DM-exposed infants.

Discussion

- The decrease in miR-146b in HUVECs exposed to DM is particularly noteworthy. MicroRNA-146b has been shown to be an anti-inflammatory molecule that targets IRAK1 and TRAF6, both of which modulate the NF-kB inflammatory pathway and affect the progression of CVD.
- MiRNA-146b is also reduced in hypercholesterolemia and has been found to be protective to cardiomyocytes under chronic hypoxia.
- Sortilin, a predicted target of miR-146b, is also associated with CVD.
- Thus, miR-146b may play a role in the development of excess CVD risk noted after in utero DM exposure.
- Ongoing experiments will address the effect of specific conditions of the diabetic milieu that contribute to altered miR-146b expression in DM.

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