Maternal Pre-pregnancy BMI Associates With Sex-Specific Placental microRNA Patterns

Elizabeth Kennedy,[1] Karen Hermetz,[2] Amber Burt,[2] Dong Pei,[3] Devin Koestler,[3] Ke Hao,[4] Jia Chen,[4] Diane Gilbert-Diamond,[3] Usha Ramakrishnan,[2] Margaret Karagas,[5] and Carmen Marsit[2]

[1]Emory University; [2]Emory University, Rollins School of Public Health; [3]University of Kansas Medical Center; [4]Icahn School of Medicine at Mount Sinai; and [5]Dartmouth College

Objectives: Maternal obesity is communicated to the fetus through the placenta. Mouse studies have shown sex-specific responses to maternal obesity in both the placenta and offspring. Epigenetic mechanisms, like microRNAs, may mediate these changes, as they can modulate gene expression in response to environmental stimulus. Here we test the hypothesis that sex-specific responses to maternal pre-pregnancy BMI (ppBMI) are evident in placental microRNA abundances.

Methods: We used small-RNA sequencing to assay placental microRNAs from the New Hampshire Birth Cohort Study (NHBCS, n = 281) and the Rhode Island Child Health Study (RICHS, n = 187). MicroRNAs previously associated with ppBMI were regressed on the product of ppBMI and infant sex using negative binomial generalized linear models. Cohort-level results were combined using fixed effects meta-analysis.

Results: We found evidence of five microRNAs with sex-specific ppBMI associations (FDR < 0.05) in NHBCS and three microRNAs with consistent interaction effects across both cohorts (meta-analysis p-value < 0.05). In both cohorts, miR-9903, miR-122–5p and miR-548x-3p were downregulated in males, relative to females (51% in NHBCS and RICHS), with ppBMI. mRNA targets of miR-9903 are enriched among pathways related to glucose transport. Both miR-122–5p and miR-548x-3p are predicted to target estrogen receptor 1 transcript (*esr1*).

Conclusions: This study reveals that placental microRNAs are susceptible to maternal ppBMI, in an infant sex-specific manner. Our results support previous findings in mice and suggest that placental microRNAs may mediate the differential abundance of *esr1* in male and female placentae.

Funding Sources: NIEHS (R24ES028507, R01ES025145, P30ES019776), NIMHD R01MD011698 and NICHD 1K99HD104991-01.