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Disrupted GSK-3β/β-catenin signaling induces greater adipogenesis in mesenchymal stem cells derived from babies of obese women: The Healthy Start BabyBUMP Project

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Background: Maternal obesity increases risk for obesity and metabolic disease in the offspring, however the molecular mechanisms in human infants remain poorly understood. We hypothesized that mesenchymal stem cells (MSCs) from infants born to obese mothers would demonstrate greater potential for adipogenesis and less potential for myogenesis, which would correspond to differences in β-catenin content, a regulator of MSC commitment. **Methods:** MSCs were cultured from umbilical cord of infants born to normal weight (pre-pregnancy [pp]BMI 21.1±0.3 kg/m2, n=15; NW-MSCs) and obese (ppBMI=34.6±1.0 kg/m2, n=14;Ob-MSCs) mothers. Measurements were made in undifferentiated cells and following 21 days of either adipogenesis or myogenesis. **Results:** Upon differentiation, Ob-MSCs exhibit evidence of greater adipogenesis (+30% Oil Red O stain [ORO], +50% PPARγ protein; P<0.05) compared with NW-MSCs, though no differences in markers of myogenesis were observed. In undifferentiated cells, total β-catenin protein content was 10% lower and phosphoThr41/Ser45 β-catenin was 25% higher (P<0.05) in Ob-MSCs vs. NW-MSCs (P<0.05). Coupled with 25% lower inhibitory phosphorylation of GSK-3β in Ob-MSCs (P<0.05), these data suggest greater β-catenin degradation in Ob-MSCs. Adipogenesis and myogenesis were reciprocally correlated with β-catenin measures. Lastly, ORO in adipogenic differentiating cells was positively correlated with infant percent fat mass at birth (r=0.475, P<0.05). **Conclusions:** These results suggest that lower β-catenin in MSCs of infants exposed to maternal obesity may have important consequences for MSC lineage commitment, fetal fat accrual, and offspring obesity risk.

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Elucidating the Effects of Maternal Obesity on Human Oocytes via Single Cell Transcriptome Analysis

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Background: Maternal obesity has been linked to developmental programming of offspring metabolism, resulting in greater fat deposition and increased risk of obesity. However, the precise mechanisms underlying this programming remain unclear. **Methods:** Using single cell transcriptomic analyses, we investigated the impact of maternal obesity on human oocytes at various maturation stages [germinal vesicle (GV); metaphase I (MI); and metaphase II (MII)] from 11 overweight/obese (OW) women and 13 normal weight (NW) women undergoing fertility treatments. Assessments were also carried out in corresponding follicular fluid (FF) samples. **Results:** OW women had significantly higher BMI, fat mass, and serum HOMA-IR compared to NW women (p<0.01). Leptin and C-reactive protein were increased in both serum and FF from OW compared to NW women (p<0.05). GV (N=5 OW; N=5 NW), MI (N=6 OW; N=8 NW), and MII oocytes (N=3 OW; N=4 NW) were analyzed using RNA sequencing. Analysis using DeSeq (min 2-fold and FDR adjusted p-value of 0.05) revealed 192 genes in GV, 711 genes in MI, and 338 genes in MII oocytes that were differentially expressed in OW compared to NW women. Functional annotation and pathway analysis (WebGestalt) indicated that compared to those from NW women, oocytes from OW women had increased expression of pro-inflammatory genes including chemokines CXCL2 and CXCL3; interleukins IL-8, IL-16 and IL-34; and immunity-related GTPase family, M (IRGM). In addition, gene expression of pyruvate dehydrogenase kinase isozyme 1 (PDK1), phosphoinositide-3-kinase interacting protein 1 (PIK3IP1) and regulatory associated protein of mTOR (RPTOR) were decreased in oocytes from OW compared to NW women. **Conclusions:** These results suggest that maternal obesity alters the oocyte transcriptome prior to fertilization by up-regulating pro-inflammatory genes and down- regulating the PI3K-AKT pathway. These findings further suggest that the pre-conception period may be an important window of opportunity for lifestyle interventions.