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Maternal Obesity During Pregnancy: Impacts on pancreatic proteome of offspring

Maternal obesity, resulting from an excess- of nutrition during pregnancy, can impair development of the pancreas in the offspring and result in an increased incidence of diabetes.. Proteomic analysis of the cellular processes, signaling pathways, and molecular mechanisms underlying these changes could offer insight about these conditions. We hypothesize that maternal obesity during pregnancy leads to reduced expression of proteins associated with β-cell function and increased expression of proteins associated with cellular apoptosis. C57BL/6J (N= 6) female mice were fed either a high fat diet (HFD; n= 3; TD.07011 Pellet Envigo, Somerset, NJ) or a control diet (CON; n=3) for fourteen weeks prior to breeding and for the duration of pregnancy and lactation. All pups from both treatment groups were weaned at 4 wks of age and maintained on a CON diet regardless of maternal treatment. The pups were euthanized at 8 wks of age. Proteomics analysis of the pancreatic tissue from the pups was performed via ultra-performance liquid chromatography-tandem mass spectrometry Q Exactive HF mass spectrometer; ThermoFisher Scientific, Waltham, MA;University of Connecticut Proteomics and Metabolomics Facility, Storrs, CT).The number and identity of differentially expressed proteins were determined using the average precursor intensity in Scaffold v5.3.2 ($P \leq 0.05$; Proteome Software, Inc; Portland OR). A total of 2329 proteins were identified in each of the treatment comparisons for CON vs HFD male and CON vs HFD female offspring. A subset of 165 differentially expressed (DE) proteins were parsed from these groups (CON vs HFD male: 145; CON vs HFD female: 20; $P \leq 0.05$) for further evaluation. In the male offspring, 14 DE proteins were up-regulated, whereas 131 were down-regulated in HFD and CON males, respectively. In contrast, of the 20 DE proteins identified in female offspring, 13 were up-regulated and 7 were down-regulated in HFD and CON females, respectively.

Following further assessment of the above-described DE proteins, four were identified as common in both the male and female offspring (Mgat2: Alpha-1,6-mannosyl-glycoprotein 2-beta-N acetylglucosaminyltransferase; Lama2: Laminin subunit alpha-2; Isyna1:Inositol-3-phosphate synthase 1 , and Got2: Glutamic-oxaloacetic transaminase 2;. Among these, expression of Mgat2, Isyna1, and Got2 decreased in HFD males but increased in HFD females compared to their respective CON offspring. Conversely, expression of Lama2 increased in both males and females. Additionally, in male HFD offspring, there was reduced expression of proteins involved in the regulation of cellular apoptosis. Several of these proteins are needed to inhibit apoptosis (Ppib: Peptidyl-prolyl cis-trans isomerase B; Mcts1:Malignant T-cell-amplified sequence 1) while others induce apoptosis (Hrg: Histidine-rich glycoprotein; Hspa1:Heat shock 70 kDa protein 1; and Mecr: Enoyl-[acyl-carrier-protein] reductase, mitochondria). Proteins implicated in mitochondrial function and insulin secretion, such as

mitochondrial fission 1 protein (F1S1), vesicle-fusing ATPase (NSF), and malate dehydrogenase, mitochondrial (Mdh2), exhibited reduced expression patterns in male HFD offspring.Pathway analyses indicated that the greatest proportions of DE proteins were associated with metabolic pathways. Notably, a total of 6 DE proteins in HFD vs CON males involved multiple neurodegenerative pathways. The results support our proposed hypothesis, and suggest that excess nutrition during pregnancy impacts pancreatic regulatory mechanisms in the offspring.