# Mechanisms by Which Gestational Exposure to Endocrine Disrupting Chemicals Causes Metabolic Dysfunction

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**Abstract**

Endocrine disrupting chemical (EDC) are ubiquitous in the environment and gestational exposure increases risk of metabolic diseases in the offspring. Animal models have identified mitochondrial dysfunction as a key contributor to pathology. Mitochondria are signaling organelles that can package their components in an extracellular vesicle (EV). EVs are signaling molecules that have the capability of delivering cargo to recipient cells thereby metabolic changes and are implicated in diabetes and obesity. I hypothesize that gestational EDC exposure alters maternal circulating EV numbers and cargo that have direct adverse effects on the developing offspring pancreas leading to the development of T2D in adulthood. In this proposal, I will determine the effect of gestational EDC exposure on offspring islet function. The mixture includes phenols, phthalates and other non-persistent EDCs that are commonly present in humans. In a preliminary study, I observed that gestationally EDC-exposed males were born small and experienced catch-up growth. Males also had smaller islets and pancreatic inflammation. In Aim 1, I will test the hypothesis that gestational exposure to EDCs alters circulating EV populations. In a preliminary study, I determined that circulating EVs from EDC exposed dams were increased compared to controls. I will characterize EV size and cargo (particularly mitochondrial components, RNA and protein). In Aim 2, I will expose control fetal islets to EVs isolated from maternal blood gestationally exposed to control and EDC mixture in vitro. Using high-resolution microscopy, I observed robust uptake of EVs into ß-cells. Islets will be assessed for proliferation, death, insulin secretion, mitochondrial function, and bioenergetics. Dr. Zhiping Wang will assist this project by performing bioinformatic analysis of EV transcriptome. Dr. Clementina Mesaros will support this project by measuring EDCs in plasma. The research proposed in this application will support my transition to independence and serve as preliminary data for NIH grant applications.