Gestational Exposure to PFOA and Development of Non-Alcoholic Fatty Liver Disease in the Offspring

Project Summary

Persistent fluorinated compounds (PFCs), including the most widely used compound perfluorooctanoic acid (PFOA), are a subgroup of persistent organic pollutants with oil and water repelling properties that are found in carpets, furniture, shoes, clothing (Gore-Tex), non-stick cookware (Teflon), and food packaging. Animals exposed to PFOA develop hepatomegaly, fatty liver, hepatic peroxisome proliferation, and immunotoxicity. Rodents exposed to PFCs *in utero* have altered hepatic cholesterol metabolism, increased hepatic *de novo* lipogenesis and increased susceptibility to fatty liver disease later in life but the underlying molecular mechanisms are not known. Epigenetic modifications, including DNA methylation provide a measurable mechanism that allows for the permanent propagation of gene activity states (including transcriptional activation and repression) from one generation of cells to the next. In addition, increasing evidence suggests that epigenetic modifications serve as a biological memory of an aberrant intrauterine environment. With the continued increase in the rates of obesity, diabetes, and non-alcoholic fatty liver disease (NAFLD) it is critical to examine the potential role of both *in utero* exposure to PFOA and epigenetic programming in the development of these diseases. Prior studies have found that nuclear receptors such as PPARα, FXR, LRXA, PXR and CAR are activated by PFOA and play critical roles in hepatic lipid metabolism. Additional studies report that DNA methylation and histone modifications may regulate activity of nuclear receptors. Therefore, we hypothesize that *in utero* exposure to PFOA triggers exaggerated lipotoxicity in the fetal liver driven by changes in fetal liver lipid metabolism. In addition, we hypothesize that gestational exposure to PFOA leads to permanent changes in expression of genes within the functional pathway of nuclear receptors which are driven by changes DNA methylation, ultimately leading to changes in hepatic metabolism and the development of NAFLD later in life. The specific aims include: 1) To determine the mechanisms by which the *in utero* exposure to PFOA leads to the development of hepatic steatosis in offspring; 2) Characterize changes in the DNA methylation profile of genes within the nuclear receptor functional pathway including FXR, LHXRA, PXR, CAR, FXR, and PPAR (α,δ,γ) in hepatocytes of PFOA exposed offspring. This proposal represents a collaborative project between the NIEHS P30 Centers at UPENN (Lead) and UCincinnati (Collaborative). PFOAs are a particular concern in both the Philadelphia and Cincinnati communities. This proposal will allow us to develop animal models to elucidate the underlying mechanisms responsible for PFOA's effects in the liver and provide the foundation for future translational studies in humans.