Comparative genomics, epigenomics, and nutrition in perinatal health: Keys to understanding the molecular basis of the developmental origins of adult disease

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Our lab is dedicated to studying the effects of the *in utero* milieu, especially with regards to maternal high fat diet, on epigenetic changes in the fetus which could help to potentially elucidate the mechanisms involved in the fetal origins of adult disease hypothesis. We have a well established non-human primate (NHP) model of obesity, now in its seventh year, to study the changes in histone modifications and DNA methylation in the fetal liver tissue upon exposure to a maternal high fat (MHF) diet. In our model of maternal obesity, we have observed a profound affect of *in utero* high fat diet exposure on the developing fetus which is independent of maternal obese phenotype. We have demonstrated that a majority (but not all) of the macaque dams chronically consuming a 35% high fat diet become obese and insulin resistant. However, regardless of maternal obesity and insulin resistance, all fetal offspring of high fat fed dams develop non-alcoholic fatty liver disease, hypertriglyceridemia, and premature gluconeogenic gene activation. Over the 180 day postnatal period, the high fat exposed fetuses demonstrate a 2-fold increase in body fat composition. Of interest, we have demonstrated that these fetal and postnatal alterations are accompanied by fetal chromatin modifications, epigenetically regulated alterations in fetal gene expression, and ensuing alterations in the fetal metabolome.

We are highly enthused by our recent significant successes in the laboratory with regards to the development and successful utilization of four high throughput modalities in our model system: exon-hybrid capture arrays for the identification of *de novo* SNPs, whole genome custom primate CpG gene arrays for the identification of gene-specific alterations in DNA methylation, chromatin immunoprecipitation with genome-wide sequencing (ChIP-Seq) for the identification of modified chromatin specific DNA sequences, and metabolomics for the tight correlation of phenotype to metabolites. Of particular interest, a characteristic fetal hepatic epigenomic signature (*i.e.,* hyperacetylation of H3K14 on the histone tail) does appear in offspring destined to obesity regardless of the maternal obese phenotype and is the focus of much of our research.

Taken together, our emerging data suggests that fetal epigenetic signatures may primarily reflective of the maternal diet, and not maternal obesity *per se*. Conversely, the metabolomic signatures in the fetus appear to be related predominantly to the obese maternal phenotype. Full interrogation of these observations will be instrumental in efforts aimed at deciphering the effect of the gestational milieu on the fetal epigenome, transcriptome and metabolome in relation to metabolic disorders in later life.