Mum's the word: Understanding the role of maternal obesity and inflammation during pregnancy in elevating the risk of offspring neuroendocrine disorders

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A mother's obesity during pregnancy is well-recognised for its ability to elevate her offspring's risk of obesity and the metabolic syndrome. Because the physiology of the mother and her offspring interact most intimately during gestation, we have been characterising the changes that take place to the fetal environment during development in an obese mother, with particular focus on the placenta and regions of the brain that regulate feeding behaviors later in life.

Female C57B/6J mice were fed a high-fat diet (45% kcal from fat) for 6 weeks beginning one week after weaning. This protocol resulted in >30% increase in body weight compared to control-fed age-matched females, and offspring showed elevated body weight and blood glucose when fed a high-fat diet.

At birth, we observed significant anatomical changes in neuronal connectivity between the arcuate (ARC) and paraventricular nuclei of the hypothalamus, two interconnected brain areas that regulate feeding behaviors. We then used NextGen sequencing and quantitative PCR to determine whether anatomical changes could be accounted for by altered developmental gene expression. At gestational day 15.5 (GD15.5) and GD17.5, the ARC of fetuses developing in obese mothers show altered expression of developmental genes. Several of these genes encode axon guidance receptors, including Deleted in colorectal cancer (DCC) and Unc5d, and immunohistochemical analysis showed that they were expressed specifically by ARC neurons that control body weight.

To understand the cellular mechanisms linking maternal obesity to altered developmental gene expression, we have investigated a possible role for cytokines. We have used a multiplex cytokine assay to identify significantly elevated interleukin-6 (IL6), IL17A, and interferon gamma in the fetal circulation at GD17.5. Investigation of the placenta at this age revealed increased macrophage activation and elevated expression of IL1b, IL6, tumor necrosis factor, and IL10 mRNA. Thus, although the placenta expressed increased inflammatory markers, they were not all transferred directly to the fetus. This suggests that some relay or transformation of the placental inflammatory environment occurs to shape the cytokine profile in the fetal circulation.

In an attempt to draw parallels between elevated fetal cytokines and ARC axon growth defects, explants of GD17.5 ARC were treated with IL6 (1 ng/ml) *in vitro*, and their axon growth and gene expression were evaluated. This analysis showed that IL6 significantly reduced ARC axon growth; and that this was accompanied by altered developmental gene expression that mimicked that seen *in vivo*.

Taken together these observations suggest that elevated inflammatory cytokines in the brains of fetuses developing in obese mothers may act to alter developmental gene expression and thereby derail normal formation of the neural circuitry that controls body weight later in life. Understanding how the prenatal environment has an impact on later life health and disease is one of the first steps toward developing strategies for ensuring a healthy start to life and life-long health for the babies of obese mothers.