Project 1: Mechanisms of sex-specific programming of obesity and type 2 diabetes risk by periconceptional exposure to a maternal obesogenic milieu.

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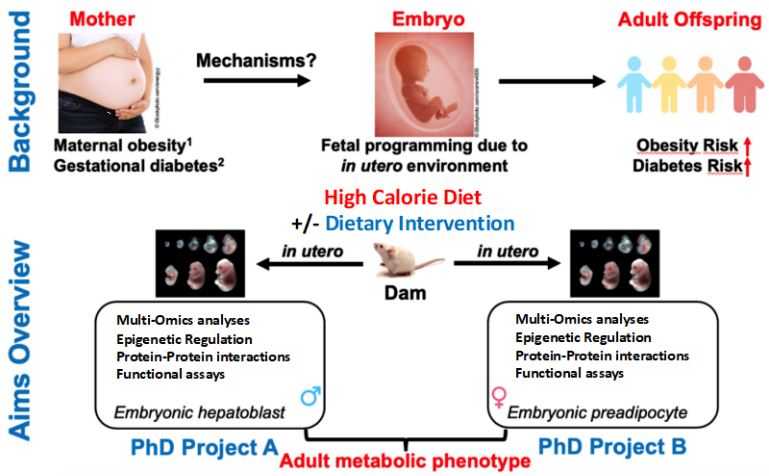
Background: Maternal obesity continues to increase dramatically in developed countries. Preclinical and clinical data have demonstrated that the offspring born to overweight or obese mothers have an increased risk for metabolic disease such as obesity and type 2 diabetes, which also holds true in animal models. However, the molecular mechanisms linking prenatal obesogenic exposure to the later development of diabetes and obesity in offspring remain poorly defined.

Own previous work: We previously established a mouse model of peri-conceptional maternal diet-induced obesity. We demonstrated that, even in the absence of any postnatal obesogenic influences, adult offspring developed adverse outcomes, i.e. increased body weight, insulin resistance and hepatic steatosis in males and impaired fasting glucose and altered adipose tissue expansion in females, indicating that peri-conceptional obesity induces metabolic disease in offspring in a sex-dependent manner[1]. Moreover, we and others demonstrated that intracellular signaling pathways can be altered by specific bioactive lipids[2] or microRNAs[3]. Nonetheless, it remains unknown how exposure to maternal diet and diet composition *in utero* mechanistically affects development of liver, adipose tissue as well as pancreatic beta cells.

Aim of the project: In Project A we aim to analyze the effects of maternal obesity on the developing fetal liver using a multi-Omics approach, and verify relevance of altered signaling pathways in murine fetal hepatoblasts and human hepatocytes (**PhD Project A**). **PhD student B** will perform parallel studies on the developing adipose tissue in murine and human preadipocytes (**PhD Project B**).

Work program: We have identified regulated pathways in hepatocyte and adipocyte precursors by Transcriptomics and Proteomics studies in the first period of vivid. These pathways including novel candidate genes and their relevance to metabolic dysfunction will be investigated in mouse hepatoblasts and human hepatocytes (**PhD Project A**) as well as in murine and human preadipocytes (**PhD Project B**) by RNA interference and CrispR/Cas9, followed by advanced phenotyping. Epigenetic regulation of these candidate genes will be assayed by e.g. Chromatin immunoprecipitation (ChIP). Secondly, periconceptional dietary interventions that may be able to ameliorate negative effects of maternal obesity on liver and adipose tissue dysfunction of the offspring will be tested by **PhD students A and B**, and they will use molecular and cell biology as well as Omics technologies to define the cellular pathways affected by these interventions.



References: [1]Dahlhoff et al., Biochim Biophys Acta. 2014. [2]Griess et al., Nat Cell Biol. 2023. [3]Belgardt et al., Nat Med. 2015