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The landscape of fetus metabolism in maternal hyperglycemia

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Abstract

Maternal hyperglycemia contributes to abnormal fetal development; yet, how it affects fetal metabolism is poorly understood. Perez-Ramirez and colleagues recently provided a comprehensive metabolic atlas of fetal organs isolated from normal and diabetic pregnant mice, identifying novel metabolites and alterations in tissue glucose utilization throughout mid-to-late gestation by maternal hyperglycemia.

Diabetes mellitus (DM), characterized by hyperglycemia and other metabolic dysregulations, is a teratogenic risk factor of congenital malformations; a mechanism that is still incompletely understood [1,2]. The rising incidence of DM worldwide and increased risk of congenital malformation in mothers with pregestational DM underscores the necessity of under-standing the impact of maternal hyperglycemia on fetus development [3]. Using the hyperglycemic, type I diabetes Akita (AK) mouse model harboring a heterozygous mutation in the insulin 2 gene, Perez-Ramirez *et al.* executed a comprehensive three-dimensional metabolomics analysis to interrogate the effect of maternal glycemic state on the tissue metabolome of the fetus (placenta, heart, liver, and brain) across different developmental stages (embryonic days 10, 12, 15, 18) [4] (Figure 1).

Targeted metabolomics reveals changes in fetal metabolism dependent on maternal glycemic state and developmental stage

To first identify metabolites that can explain the fetal developmental defects induced by maternal hyperglycemia, the authors performed targeted metabolomics in fetuses from wild-type (WT) and AK pregnant female mice (dams). Generation of this large dataset allowed the authors to discover that the glucose-derived metabolite sorbitol abnormally accumulated in late-stage fetal tissues from AK dams compared with mid-stage fetal tissues from WT dams (e.g., >tenfold in the brain). This finding implies that fetal tissues are chronically exposed to high sorbitol, which has been implicated in the development of diabetic complications such as retinopathy and kidney dysfunction [5]. In addition,

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Declaration of interests

No interests are declared.

they identified significantly decreased neurotransmitters such as gamma-aminobutyric acid (GABA), especially in earlier embryonic days (E10 and E12). Consistently, the amino acids that contribute to GABA synthesis (aspartate and glutamate) are also markedly decreased in fetal brains from AKdams. As the authors hypothesize, perhaps these metabolic abnormalities may explain birth defects associated with maternal hyperglycemia. Therefore, through the unbiased and comprehensive comparisons of metabolite abundance alone, the authors disclosed potential candidate metabolic defects caused by the hyperglycemic state, which would help shed light on unexplored contributors to fetal developmental defects.

^{13}C stable isotope tracing identified differences in fetal carbon utilization dependent on maternal glycemic state and developmental stage

In addition to measuring metabolite abundances, Perez-Ramirez et *et al.* further implemented *in vivo* isotope tracing using universally ^{13}C-labeled glucose as a tracer to infer the metabolic flux of central carbon metabolism across fetal tissues at different developmental stages. After carefully deducing the circulatory flow from the mother to the placenta to the fetal organs, the authors revealed fetal nutrient exchange between tissues in addition to metabolic pathway activities within each tissue. For instance, the authors discovered that fetal heart and liver tissue utilize central carbon metabolism to synthesize aspartate and glycine, respectively, independent from the dam. Furthermore, by carefully comparing isotopic labeling enrichments across glycolytic intermediates, the authors found that the maternal glycemic state strongly influenced fetal liver carbon metabolism. Specifically, while fetal livers from WT dams displayed isotopic labeling patterns expected from high gluconeogenic activities, fetal livers from AK dams displayed labeling patterns matching maternal circulation, suggesting that fetal livers from AK dams take up glucose from maternal circulation instead of making their own, possibly due to elevated glucose levels in maternal blood. Additionally, fetal tissues from either WT or AK dams consistently displayed a reduction in nucleotide labeling enrichment as the fetus progressed through mid-to-late gestation, regardless of maternal glycemic state. The authors' inability to achieve an isotopic steady state in nucleotides suggests that as fetal development progresses, nucleotide biosynthesis de-creases. To conclude, by utilizing *in vivo* isotope tracing, the authors were able to identify perturbations in fetal nutrient sourcing resulting from differences in maternal glycemic state and developmental stage. This information could improve dietary interventions used to manage diabetic pregnancies.

Untargeted metabolomics highlights highly enriched histidine metabolism during late gestation

Finally, the authors moved forward one more step by performing untargeted metabolomics to discover unknown metabolic features of fetal tissues across different developmental stages. This unbiased analysis bore fruit. They found that several histidine-derived metabolites selectively accumulated in fetal tissues on embryonic day 18 compared with day 10 from WT and AK dams, suggesting that developmental stage alone influences this phenotype. Histidine metabolism was one of five enriched metabolic processes identified

by the authors, revealing a host of potential biomarkers that can be used to monitor fetal development.

Concluding remarks

Altogether, Perez-Ramirez *et al.* present a comprehensive three-dimensional metabolomics dataset that reports maternofetal metabolic perturbations with respect to maternal glycemic state and developmental stage. What would be the next step? Given that most patients diagnosed with DM have type II diabetes while AK mice resemble type I diabetes [6-8], it will be important to perform a similar study in type II diabetes models to identify similarities and differences between type I and type II diabetes on the fetal metabolic perturbations. In terms of tracing experiments, similar studies in the fed state without anesthesia will be informative to identify the metabolic changes affected by overnight fasting or anesthesia [9]. This will be crucial be-cause defective insulin secretion and responses in diabetes are highly relevant in the fed state and anesthesia is known to affect organ metabolism. To conclude, this pioneering study represents an important advancement by providing a holistic picture of fetal metabolism during mid-to-late gestation regarding both maternal euglycemia and hyperglycemia. As the incidence of adverse pregnancy outcomes associated with DM rises worldwide [10,11], it is critical to dissect metabolic crosstalk between the mother and the fetus. In this regard, this resource provides important new insights as well as a framework for how to collect and analyze complex metabolomics datasets for future investigations of maternofetal metabolism.

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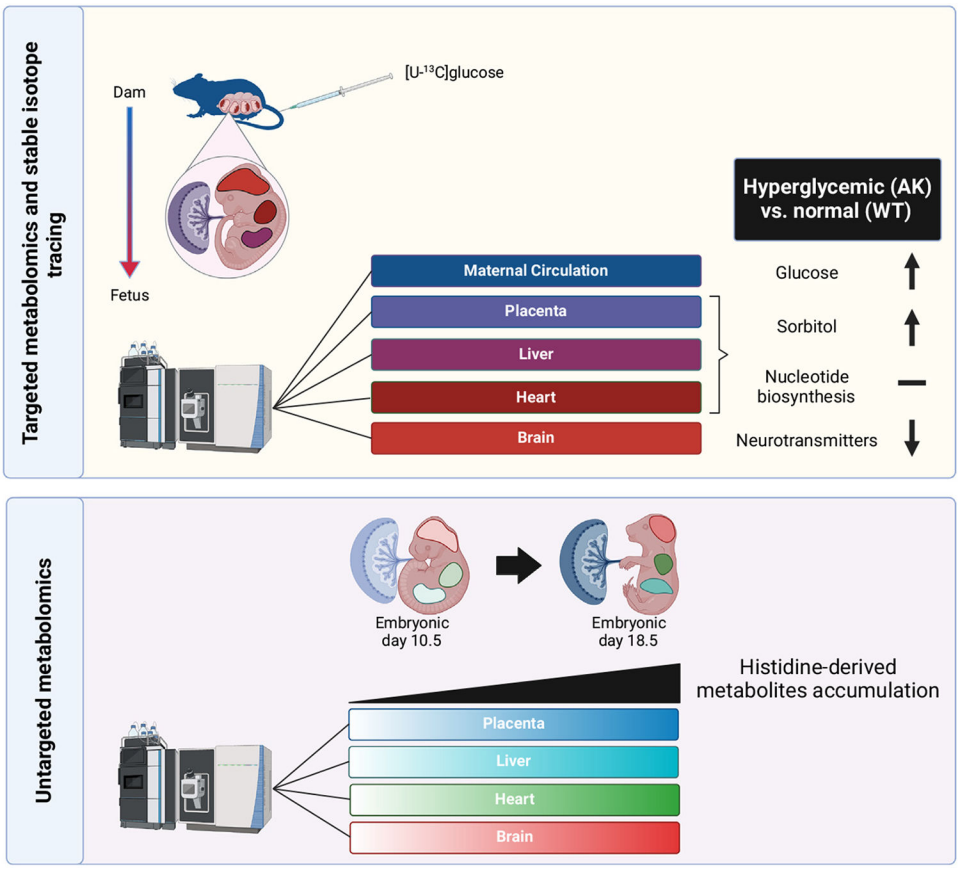

Figure 1. Schematic of the metabolomic platform used by Perez-Ramirez *et al.* [4] to assess fetal metabolism with respect to developmental stage and maternal glycemic state.

Wild-type (WT) and Akita (AK) dams were infused with universally labeled ^{13}C glucose ([U-^{13}C]glucose). The placenta and fetal liver, heart, and brain were subsequently harvested and analyzed using liquid chromatography-mass spectrometry (LC-MS). Targeted metabolomics, ^{13}C glucose tracing, and untargeted metabolomics analysis were performed to establish metabolic profiles for fetal tissues exposed to different maternal glycemic states at various stages during mid-to-late gestation. Created with Biorender.com.