Medical school identifies placental protein as possible birthweight regulator

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New findings from the University of Minnesota Medical School are helping uncover why some people are more likely to be overweight and develop Type 2 diabetes—and it starts in the womb.

Previous association studies have shown that low birthweight among infants is a strong determinant for eventual obesity and Type 2 diabetes. The placenta of infants with a low birthweight have reduced levels of mTOR (mechanistic target of rapamycin), and the placenta of bigger infants have increased levels of mTOR. Building off of that research, a U of M Medical School study, published in *JCI Insight*, is the first to directly implicate mTOR, a nutrient-sensor protein in the placenta, as a possible regulator of an infant's birthweight.

"It is clear from human and preclinical studies that Type 2 diabetes has fetal origins, but we do not yet know the mechanisms of how this programming of metabolic dysfunction or Type 2 diabetes occurs," said senior author, Emilyn Alejandro, Ph.D., an associate professor in the Department of Integrative Biology and Physiology. "Our study is the first to show a direct role of a placental protein, like mTOR."

They found that in preclinical studies:

- After eliminating mTOR in the placenta, female offspring had lower birthweights and had an increased risk for obesity and insulin resistance in adulthood.
- In contrast, after increasing mTOR signaling in the placenta, female adult offspring were protected from high-fat diet induced obesity.

"A causal relationship between placental mTOR and the metabolic health of the offspring has not been tested before, and our study suggests that manipulating mTOR in the placenta is sufficient to cause permanent and lasting impact on the health trajectory of the offspring," said Brian Akhaphong, first author and a post-baccalaureate trainee in the Alejandro Lab. "Our hope is that we can identify proteins that we may target therapeutically through maternal health to reduce the prevalence of Type 2 diabetes."

The research team will continue their study, probing which metabolic tissues in the offspring are permanently impacted by placental mTOR signaling. Megan Beetch, Ph.D., a postdoctoral fellow, will look at the epigenetics, or heritable changes in gene expression, that do not involve changes to the underlying DNA sequence.

More information: Brian Akhaphong et al, Placental mTOR-Complex1 regulates fetal programming of obesity and insulin resistance in mice, *JCI Insight* (2021). DOI: 10.1172/jci.insight.149271

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