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Cellular and Molecular Causes of Pre-Pregnancy Diabetes-Induced Birth Defects

Maternal diabetes existing prior to pregnancy increases birth defect risk in the offspring. We developed a mouse model of diabetic pregnancy to study how these birth defects occur. Neural tube defects (NTDs) and cardiac outflow tract defects (COTDs), two of the most common malformations in human offspring of diabetic women, are significantly increased in embryos of diabetic mice. Maternal diabetes inhibits expression of Pax3, a gene that is expressed in neuroepithelium and neural crest and is required for neural tube closure and cardiac outflow tract septation. We showed that maternal hyperglycemia, above 14 mM (250 mg/dl) is necessary and sufficient to inhibit Pax3 expression and to induce malformations. Early embryos express the high K_M (~15 mM) GLUT2 glucose transporter, and GLUT2-mediated glucose transport is required for malformations in response to maternal hyperglycemia. Increased glucose transport and metabilism induces oxidative stress. Oxidative stress stimulates AMP-activated protein kinase and DNA methyltransferase 3b activities, which inhibit Pax3 expresson. As a result of PAX3 protein insufficiency, neuroepithelial and cardiac neural crest cells undergo p53-mediated apoptosis. Thus, when maternal diabetes inhibits Pax3 expression, p53 protein levels rise, p53 induces neuroepithelial or cardiac neural crest cell apoptosis, and NTDs or COTDs result.

While GLUT2 confers susceptibility of embryos to maternal hyperglycemia, it does not function as an efficient glucose transporter during nomoglycemica. GLUT2 can transport the amino sugar, glucosamine (GlcN), a substrate for protein glycosylations. We showed that GLUT2 is required for GlcN-stimulated embryo cell proliferation and stimulates metabolic pathways needed for growth. GLUT2-mediated glucose transport significantly inhibits GlcN transport, suggesting that some of the adverse effects of high glucose are due to inhibition of GlcN-dependent pathways.

Keywords: Diabetic pregnancy, birth defects, PAX3, hyperglycemia, GLUT2

Biography

Mary R. Loeken is a Research Investigator at the Joslin Diabetes Center and Associate Professor of Medicine at Harvard Medical School in Boston, MA. She has served on the Editorial Board of the journal, Diabetes, and is a Co-Editor of the journal, Diabetes Metabolism Research and Reviews. She has served as the Chair and Post-Chair of the Pregnancy and Reproductive Health Professional Interest Group of the American Diabetes Association. She is recognized for her research on the mechanisms for birth defects induced by diabetic pregnancy, diabetic embryopathy.

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