Decoding the oxidative stress hypothesis in diabetic embryopathy through proapoptotic kinase signaling

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Maternal diabetes-induced birth defects occur in 6-10% of babies born to mothers with pregestational diabetes, representing a significant maternal-fetal health problem. Currently, these congenital malformations represent a significant maternal-fetal medicine issue, but are likely to create an even greater public health threat as 3 million women of reproductive age (19-44 years) have diabetes in the United States alone, and this number is expected to double by 2030. Neural tube defects (NTDs) and congenital heart defects are the most common types of birth defects associated with maternal diabetes. Animal studies have revealed that embryos under hyperglycemic conditions exhibit high levels of oxidative stress resulting from enhanced production of reactive oxygen species and impaired antioxidant capability. Oxidative stress activates a set of proapoptotic kinase signaling intermediates leading to abnormal cell death in the embryonic neural tube, which causes NTD formation. Work in animal models also has revealed that maternal diabetes triggers a series of signaling intermediates: protein kinase C (PKC) isoforms, PKCα, βII and δ; apoptosis signal-regulating kinase 1; c-Jun-N-terminal kinase (JNK)1/2; caspase; and apoptosis. Specifically, maternal diabetes in rodent models activates the proapoptotic unfolded protein response and endoplasmic reticulum (ER) stress. A reciprocal causation between JNK1/2 activation and ER stress exists in diabetic embryopathy. Molecular studies further demonstrate that deletion of the genes for *Prkc*, *Ask1*, *Jnk1*, or *Jnk2* abolishes maternal diabetes-induced neural progenitor apoptosis and ameliorates NTD formation. Similar preventive effects are also observed when apoptosis signal-regulating kinase 1, JNK1/2, or ER stress is inhibited. Cell membrane stabilizers and antioxidant supplements are also effective in prevention of diabetes-induced birth defects. Mechanistic studies have revealed important insights into our understanding the cause of diabetic embryopathy and have provided a basis for future interventions against birth defects or other pregnancy complications associated with maternal diabetes. The knowledge of a molecular pathway map identified in animal studies has created unique opportunities to identify molecular targets for therapeutic intervention.