Abstract

Maternal *diabetes mellitus* negatively affects embryonic development and increases the risk for congenital malformations. Besides direct teratogenicity, diabetic intrauterine milieu can predispose an individual to chronic diseases later in life, including cardiovascular diseases, obesity, and *diabetes mellitus,* in a process termed fetal programing. Molecular mechanisms of embryonic and fetal responses to maternal diabetes are still not fully elucidated. Using mouse model, we show that maternal diabetes induces gene expression changes in the hearts of developing embryos. The most significant changes in the expression of 11 selected genes were detected at the developmental stage associated with completion of cardiac septation, myocardial mass expansion, and increased insulin production in the embryonic pancreas. These affected genes encode products involved in the epithelial-to-mesenchymal transition, a crucial process in heart development. Using immunohistochemistry, we detected increased hypoxia in the diabetes-exposed hearts at the critical stage of cardiac development. Correspondingly to increased hypoxia, the expression of hypoxia-inducible factor 1α (HIF1α) and vascular endothelial growth factor A was increased in the heart of diabetes-exposed embryos.

Based on our results indicating the involvement of HIF-1-regulated pathways in diabetic embryopathy, we investigated the combinatorial effects of *Hif1a* mutation and maternal diabetes exposure on the heart of the offspring of diabetic pregnancy. We analyzed the diabetes-exposed adult offspring with heterozygous deletion of *Hif1a* (*Hif1a*$^{+/-}$). Echocardiographic analyses showed impaired heart function in the 12 weeks old *Hif1a*$^{+/-}$ offspring of diabetic pregnancy. Transcriptome profiling by RNA-Sequencing showed significant changes associated with development, metabolism, apoptosis and blood vessel physiology in the diabetes-exposed *Hif1a*$^{+/-}$ offspring compared to diabetes-exposed *wild-type* mice. In contrast, immune system processes and inflammatory responses were affected in both *Hif1a*$^{+/-}$ and *wild-type* offspring of diabetic mothers. Immunohistochemical analyses showed that the combination of *Hif1a*$^{+/-}$ genotype and maternal diabetes leads to impaired macrophage infiltration, increased advanced glycation end products accumulation and changes in the large coronary vessels.

In summary, our results show that maternal diabetes affects gene expression in the developing heart, and that the adult offspring of diabetic pregnancy have impaired heart function and significant changes in the transcriptome of the left ventricle. Additionally, we show a negative role of the combination of maternal diabetes exposure and *Hif1a* gene mutation in the development of cardiovascular diseases in the adult offspring.