Abstract

Diabetic embryopathy is one of many serious complications associated with diabetes. It is known that maternal diabetes increases the frequency of congenital defects up to ten times. The most common defects are cardiovascular and neural tube defects. Molecular mechanisms of diabetic embryopathy are still not known. This work contributes to elucidation of molecular processes leading to development of cardiovascular defects in diabetic embryopathy. This study is based on observation that maternal diabetes affects transcriptional regulation of hypoxia-inducible factor 1 (HIF-1) in developing embryo. To study the influence of maternal diabetes on HIF-1 signaling pathway, we used mouse model heterozygous for "knock-out" of *Hif1α* gene. Our analyses showed the negative combinational effects of maternal diabetes and *Hif1α*$^{+/-}$ genotype on embryonic development and increased risk of diabetic embryopathy. Histological analysis demonstrated the increased incidence of cardiovascular defects, particularly defects of interventricular septum and hypoplastic compact left ventricular wall in embryonic day (E) 14.5 *Hif1α*$^{+/-}$ embryos compared to *wt* littermates from the diabetic pregnancy. Using qPCR, we analyzed gene expression changes in the embryonic hearts at E9.5 and E10.5. We selected genes important for the development of heart, and direct or potential target genes of HIF-1 signaling. These analyses showed changes in the expression of genes important for overall development of heart (*Vegfa* and *Wt1*), genes important for differentiation of cardiomyocytes (*Nkx2.5* and *Mef2c*), genes important for chambers specification (*Hand1* and *Hand2*), genes important for septation (*Gata4*, *Tbx5* and *Bmp4*) and gene important for the specification of precursor cells and their migration to the heart (*Isl1*). Embryonic mRNA expression of *Vegfa*, *Hand2*, *Mef2c*, *Gata4*, *Bmp4* and *Tbx5* was deregulated due to maternal diabetes. The expression of *Hand2*, *Nkx2.5*, *Gata4*, *Vegfa* and *Isl1* was significantly affected by the combination of the global reduction of *Hif1α* gene and maternal diabetes in the embryonic hearts. These results confirmed initial hypothesis that maternal diabetes deregulates transcriptional program in the embryonic heart and affects the expression of genes involved in the HIF-1 signaling in the developing embryos. Our analysis showed that partial HIF-1α deficiency alters gene expression in the developing heart and increases susceptibility to congenital defects in a mouse model of diabetic pregnancy.

Key words: diabetic embryopathy, gene expression, *Hif1α*, *Vegfa*, *Wt1*, *Hand1*, *Hand2*, *Nkx2.5*, *Mef2c*, *Gata4*, *Bmp4*, *Tbx5*