

Dysregulation of Notch signaling in cardiac cells of the patients with tetralogy of Fallot

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Introduction.

Tetralogy of Fallot (TF) is the most common cyanotic congenital heart defect. The cellular and genetic mechanisms of this defect are obscure. Mutations in several genes important for heart development have been described including mutations in the genes related to Notch pathway. Now is clear that fine-tuned sequential activation of Notch genes is responsible for the proper heart chamber development. The aim of this study was to analyze the activity of Notch pathway in the cardiac mesenchymal cells derived from TF patients.

Methods.

Cardiac mesenchymal cells were isolated from 42 patients with TF and from 14 patients with ventricular septal defects (VSD), which was used as a comparison group. Notch pathway was analyzed by estimating the expression of Notch genes and receptors as well as the main Notch target genes by qPCR. Differentiation and proliferation capability of the cells was also estimated. For in vitro Notch activation Notch-intracellular domain bearing lentiviruses were used. Notch activation in hypoxic and normoxic conditions of in vitro culture was analyzed.

Results.

The cells derived from TF patients demonstrated different pattern of gene expression profiles of Notch related genes comparing to the cells from the patients with VSD. Notch activation level by classic targets HEY1/HES1 correlated with the level of NOTCH1 transcripts in the cells from the patients with tetralogy of Fallot. Both in vivo and in vitro high Notch activation level was associated with enhanced differentiation and proliferation capacity of the cells. Hypoxic condition caused a very moderate elevation in Notch signaling in the cells from the patients with Tetralogy of Fallot.

Conclusion.

Our data suggest a contribution of dysregulated Notch to the pathogenesis of tetralogy of Fallot; elevated level of Notch signaling could contribute to the increased plasticity of cardiac mesenchymal cells derived from the patients with tetralogy of Fallot. Our data confirm that fine-tuned Notch signaling is one of the key factors responsible for the appropriate heart development.