

Analysis of Notch pathway activity in cardiac progenitor cells of the patients with congenital heart defects

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Introduction. Recently fine-tuned sequential activation of Notch genes has been shown to be responsible for the proper heart chamber development. In addition, mutations in several genes of the Notch pathway have been shown to be associated with Tetralogy of Fallot (TOF) and hypoplastic left heart syndrome (HLHS). To elucidate more precisely the role of Notch pathway in these congenital defects we aimed to estimate expression of Notch signaling related genes in cardiac progenitor cells (CPC) in the patients with TOF, HLHS and ventricular septal defect (VSD).

Methods. Cardiac progenitor cells were isolated from leftovers after surgical intervention (VSD – 17, HLHS – 10, TOF– 40 patients) by collagenase digestion and were cultured for several passages in vitro. The cells were immunophenotyped by flow cytometry using CD31, CD146, CD117, CD34, CD90, CD166. Gene expression of Notch family genes (NOTCH1, NOTCH2, NOTCH3, NOTCH4, HEY1, HEY2, JAG1, DLL4, BMP2, BMP4) was assessed by qPCR. Notch receptors and ligands surface expression were also estimated by flow cytometry.

Results. In cardiac progenitor cells derived from patients with hypoplastic left heart syndrome, NOTCH4 and DLL4, as well as BMP4, was significantly lower than in cells from patients with a ventricular septal defect. In the cells from patients with tetralogy of Fallot, the expression of Notch family genes had large variability ranging from low to high expression level by both flow cytometry and qPCR.

Conclusion. Our data on cardiac progenitor cells derived from VSD, HLHS and TOF patients suggest direct involvement of Notch pathway dysregulation in the pathogenesis of the HLHS. Regarding tetralogy of Fallot, the role of Notch pathway remains questionable and requires further research.