

RNA Expression Profiles and Regulatory Networks in Human Right Ventricular Hypertrophy due to High Pressure Load

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Introduction.

Right ventricular hypertrophy (RVH) and remodeling in high pressure afterload, for example in pulmonary arterial hypertension (PAH) or tetralogy of Fallot/pulmonary stenosis (TOF/PS), are associated with alterations in energy metabolism, neurohormonal and epigenetic dysregulation, and a reset of the developmental transcriptional program. We recently identified several interdependent mechanisms such as impaired lipid metabolism, epigenetic miRNA dysregulation, and revival of a fetal gene program, in the SuHx rat model of PAH/RVH/RV failure and in human endstage PAH/RVH/RV failure. However, RNA expression profiling in human non-failing (compensated) RVH has not been performed, and thus RVH-specific regulatory networks are largely unknown.

Methods.

We studied intraoperative RV tissue from 19 infants with TOF/PS and RVH (age 2–8 months) and 8 non-RVH age-matched control infants with ventricular septal defects (VSD; 2–12 months). RNA was extracted and sequenced, capturing mRNA, lncRNA, and circRNA (≥ 10 Gb of cleaned data, 5 million pairs of 100 bp PE reads). The reads were aligned to the GRCh38.p10 human genome reference using STAR, followed by differential expression analysis (EDASeq/DESeq/STARChip).

Results.

Using GO-Elite we performed over-representation analysis of the differentially expressed genes in KEGG pathways, cellular biomarkers, and GO-terms. We found differentially expressed genes (RVH vs. no-RVH), significantly overrepresented in pathways related to MAPK signaling, extracellular matrix (ECM)-receptor interaction, focal adhesion and adherens junctions. Additional IPA analysis revealed perturbations in inhibition of matrix metalloproteases, iron homeostasis signaling, tight junction signaling, cardiomyocyte differentiation via BMP receptors, and apelin cardiac fibroblast signaling pathways.

Conclusions.

To the best of our knowledge, this is the first unbiased, comprehensive RNA-Seq study of mRNA expression patterns in human RV hypertrophy (here: tetralogy of Fallot). Multiple genes and pathways identified overlap with the mRNA signature we had previously identified in rat and human adult RV failure. Our results advance our current understanding of RV hypertrophy and progressive RV failure, and highlight future therapeutic targets. The upcoming analysis of lncRNA and circRNA expression will allow us to investigate further the related complex transcriptional regulation and RNA biology specific for human RV hypertrophy in tetralogy of Fallot (in the absence of RV failure).