Shift in transcriptional landscape of human right ventricle in chronic thromboembolic pulmonary arterial hypertension

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Background: Chronic thromboembolic pulmonary hypertension (CTEPH) is a sub group of pulmonary hypertension (PH). CTEPH is characterized by the existence of thromboemboli and vascular remodeling in pulmonary vessels. The effect of increase in pulmonary artery pressures causes right ventricle (RV) hypertrophy and dilatation and finally leads to right heart failure and death. Surgical intervention in operable patients makes the CTEPH as an only curable and unique form of ph. Pulmonary endarterectomy (PEA) is the surgical procedure to remove the thromboembolic clots from the pulmonary vasculature, which restores RV function back to normal with significant improvements in cardiovascular magnetic resonance.

Purpose: The aim of this study is to use transcriptomic profiling to identify signaling pathways, master regulators, and potentially new biomarkers that specifically indicate the effect of PEA on the RV of patients with chronic thromboembolic pulmonary hypertension.

Results: RNA -sequencing (RNA-seq) was performed on RV biopsies obtained from CTEPH patients at PEA baseline (before PEA surgery) and the results were compared with those from RV biopsies obtained during follow-up evaluation. Bioinformatic analysis of RNA-seq data identified 2799 genes (n=14, $-0.585 \leq$ Log2 fold change ≥ 0.585, FDR ≤ 0.05) differentially regulated between the PEA baseline and follow-up sample groups. The great number of genes (2799) differentially expressed after PEA surgery in CTEPH patients confirms a major shift in the transcriptional landscape of RV in these patients. To further identify potential biomarker candidates from the large pool of 2799 differentially expressed genes (DEGs), extensive bioinformatic analysis of different data sets shortlisted 250 DEGs that were functionally associated with cardiovascular development or disease. The findings of this study reveal prominent transcriptional changes that occur in response to PEA. Gene ontology enrichment and pathway analysis confirmed altered regulation of hypoxia-inducible factor 1 (HIF-1) signaling, advanced glycation end products and their receptors (AGE-RAGE), mitogen-activated protein kinase (MAPK) signaling, hippo signaling, the Janus kinase/ signal transducers and activators of transcription (Jak-STAT) signaling pathway, and proteoglycans after PEA compared with before PEA.

Conclusion: Comparison of the results of RNA-seq analysis of RV biopsies of CTEPH patients, pre and post PEA, revealed a major shift in the transcriptional landscape of these patients after reducing the pressure overload of the RV by PEA.