Investigating the Effects of Perinatal Hypoxia on the Neonatal Heart Transcriptome Maturation

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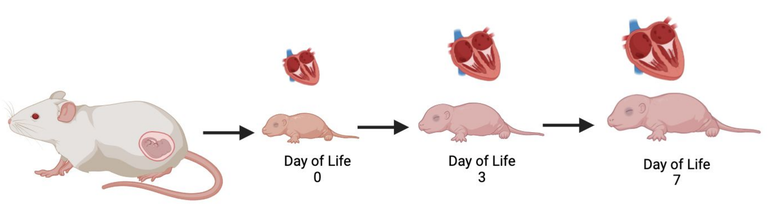
ABSTRACT

The development of the heart postnatally can be heavily influenced by perinatal stress factors. Environmental perinatal stress factors, such as hypoxia, have been shown to have significant pathological effects on the heart and can contribute to the progression of cyanotic congenital heart defects (CHDs). This project seeks to elucidate chamber-specific effects of perinatal hypoxia on neonatal heart transcriptome regulation. We are conducting transcriptome-wide analysis of both the right ventricle (RV) and left ventricle (LV) under hypoxic and normoxic conditions in neonatal mouse hearts over three time points of postnatal transition: day of life zero, three, and seven. Through sequential analysis of RNA-seq derived from a transcriptome dataset, significant differentially regulated genes and pathways will be identified. By uncovering how hypoxia changes the transcriptome of the neonatal heart, we can enhance our understanding of patients with cyanotic CHDs, and potentially identify novel therapeutic approaches to improve outcomes.

BACKGROUND

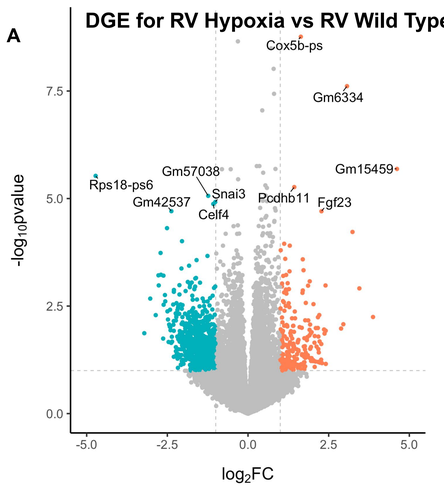
- Early postnatal development of the mammalian heart involves significant morphological, cellular, and transcriptional changes. Functional maturation of the heart's ventricles after birth is critical but can be altered by perinatal stress factors, like hypoxia.
- Transcriptome programming drives cardiac chamber development, but chamber-specific transcriptome changes during hypoxic perinatal transition remain poorly understood.
- Previous studies have shown transcriptome changes in the right ventricle under hypoxia may contribute more to the development of cyantonic CHDs, compared to the left ventricle.
- Current knowledge and clinical approaches to right ventricular diseases often rely on knowledge derived from left ventricular studies, potentially overlooking critical chamber-specific mechanisms.

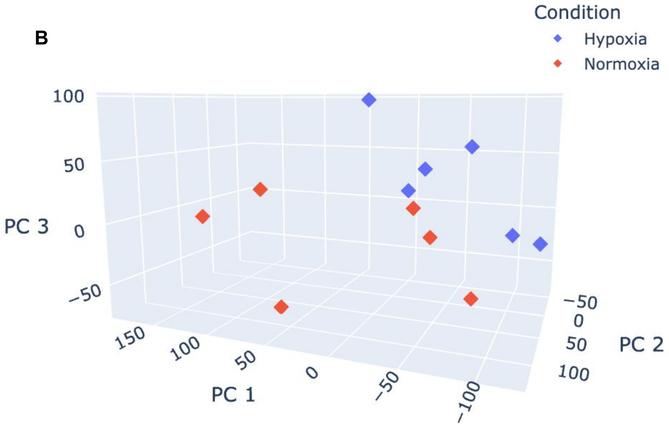
METHODS

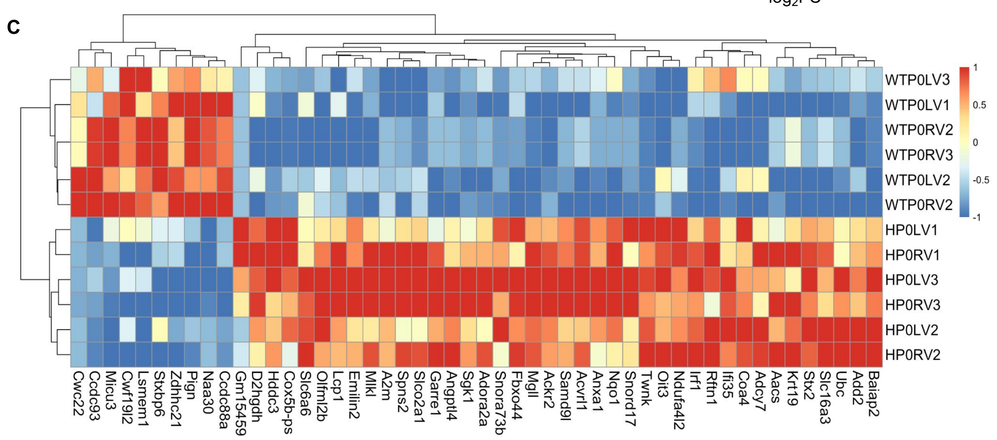


- Samples were obtained from RV and LV on postnatal day 0 (P0), P3, and P7 in both ambient air and hypoxic conditions.
- Full transcriptome (bulk RNA-seq) was performed to obtain differential gene expression data, normalized via the median of ratios method, with a p-value ≤ 0.05 considered significant.

RESULTS







A. *Volcano Plots of Chamber-Specific Differential Gene Expression (DGE)).* The significant upregulated (red) and downregulated genes (green) were defined at (log_2FoldChange ≥ 1, -log_{10}p-value ≥ 0.05) with the most significant genes labeled.

B. *3-Dimensional PCA Plot of Transcriptomes.* Linear separability between hypoxic and normoxic features across the transcriptomic profiles demonstrates the distinction between the two conditions [Hypoxia (blue), Normoxia (red)] at P0.

C. *Heatmap of Differentially Expressed Genes.* The expression patterns of significantly differentially expressed genes between hypoxic and normoxic conditions across both the left and right ventricles at P0. The clear segregation of samples based on their gene expression profiles further supports the strong impact of hypoxia on cardiac transcriptome regulation.

CONCLUSION

FINDINGS

- Numerous genes show statistically significant upregulation and downregulation, indicating robust transcriptional responses to perinatal hypoxia.
- The identified differentially expressed genes suggest the activation and suppression of specific molecular pathways that could underlie the early development of hypoxia-related cardiac conditions.

FUTURE DIRECTION

- Expand analysis and comparison across all three time points.
- Continue to explore the most significant genes and related pathways identified and their influence on heart development.
- While minimal ventricular differences at day zero were identified, studies suggest chamber-specific differences may emerge as the heart matures, we must monitor for changes at later points.

References

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