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Abstract Title

Mapping the role of porphyrin metabolism genes in developing fetal lungs using human single-cell transcriptomics and bulk proteomics of the nitrofen-induced CDH rat model

Authors

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Background

Nitrofen-treated rat pups recapitulate human congenital diaphragmatic hernia (CDH). Nitrofen’s herbicidal activity is through protoporphyrinogen oxidase enzyme inhibition, it is important for us to examine the effect of nitrofen on porphyrin metabolism genes. Prior work done by Hirako et al. attributed iron (II)-dependent oxidative stress by nitrofen treatment to cause CDH in 2017.

Objective

Since iron (II) initiates the Fenton reaction, we hypothesize that nitrofen induced dysregulations in porphyrin genes cause iron and cytotoxicity. Exploring integration of single-cell and bulk multi-omics cross species data helps us to understand porphyrins in CDH abnormal lung development. Here, we aimed to examine the effect of nitrofen on porphyrin metabolism genes.

Methods

Six Sprague-Dawley rat dams were treated with olive-oil suspended nitrofen via oral gavage at embryonic day (E)9.5 to induce CDH in fetuses, and gender-balanced pups were taken from were collected at E15, E18 and E21. Proteins from a total of 106 samples were extracted and processed with LC-MS/MS. We performed all statistical analyses and visualizations to gain proteomic insights in the nitrofen-induced CDH fetal rat lungs in R using the tidyverse, lme4, and ggplot2 libraries. We also utilized the publicly available Early Fetal Lung Atlas, generated by Quach et al., 2024. from NCBI GEO, GSE264407 and analyzed with R Seurat library.

Results

We demonstrated through Weighted Gene Co-expression Network Analysis that porphyrin metabolism pathway is prematurely upregulated in the nitrofen-treated lungs. Our initial screening of the Early Fetal Lung Atlas revealed interesting spatial patterns of porphyrin metabolism transcripts in stromal, fibroblast-like intermediate progenitors, especially during the pseudoglandular stage.

Conclusion

Our preliminary results demonstrate disruption of porphyrin metabolism in nitrofen-induced hypoplastic lungs. Building on these exploratory findings, we will elucidate cell-type specific roles of porphyrin metabolism genes in the branching fetal lung in future studies, and infer effects of disruption using nitrofen-induced CDH bulk lung proteomics data.