Single nuclei RNAseq reveals cell-type specific responses to disease and enalapril in the ggdY mouse model of IgAN

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Background

IgA Nephropathy (IgAN) is the leading cause of chronic kidney disease worldwide, with limited treatment options. Mouse models of early onset IgAN have been previously described that induce atrasentan response signature (angiotensin converting enzyme inhibitor, enalapril) associated with albuminuria.

Methods/Study Design

Mouse IgAN model:

- Generation and characterization of ggdY mice with early onset IgAN have been previously described. ggdY mice were used as control, while ggdY mice treated with the ACEI enalapril showed a disrupted ACEI response signature.

RNA sequencing and data processing:

- Nuclei were isolated from snap-frozen kidney cortex, sequenced using the 10x Genomics Platform and analyzed using Seurat. Single nuclei transcriptomes were projected into distinct cell types using the Seurat method. The top 20 principal components were used for downstream analyses.

Data analysis:

- Atrasentan-induced cell clusters at the L1 level of precision. Failed repair proximal tubular epithelial cells were associated with a failed repair proximal tubule signature and TNF-α signature. Enalapril-induced cells were associated with the ACEI-Lakanalaam expression.

Cellular Composition

- Graphical representation of the cellular composition of the ggdY kidney with early onset IgAN.

Results

1. Identification of Failed Repair Tubular Epithelial cells (FR PTEC) in the ggdY IgAN model

- A cluster with the highest score for the FR PTEC signature and high scores for TNF-α signature was identified as FR PTEC.

2. FR PTEC are the most expanded kidney cell type in ggdY

- FR PTEC were the most expanded cell type in ggdY compared to control, with ~8x the proportion of nuclei in ggdY compared to control.

3. FR PTEC are a source of chemokines and cytokines for immune cells and fibroblasts

- FR PTEC signature may be induced by TNF-α signaling.

4. TNF-α signaling is enriched in FR PTEC

- FR PTEC were associated with increased TNF-α signaling in the ggdY model.

5. Treatments have differing effects on gene expression

- In FR PTEC, atrasentan and ACEI treatment reversed TNF-α signaling.

6. Comparison of pathway enrichments for atrasentan and ACEI treatment

- Pathway enrichment analysis for atrasentan and ACEI treatment identified differentially expressed genes.

Conclusions

- FR PTEC are identified as the cell type that is most highly induced by atrasentan treatment in the ggdY mouse model.

Ongoing efforts to characterize gene expression associated with atrasentan response

- Characterization of the ggdY FR PTEC atrasentan response signature in the anti-Thy1,1 model

Disclosures

- Atrasentan is an investigational drug that has not been approved by regulatory authorities. Efficacy and safety have not been established. There is no guarantee that it will become commercially available for the use(s) under investigation.