Abstract: FR-PO001

A Network-Based View of AKI and CKD at Cell Subtype and Spatial Niche Resolution

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Background

Understanding functional relationships between genes and their regulators and how they are altered in acute kidney injury (AKI) and chronic kidney disease (CKD) is a crucial challenge. New computational methods are necessary to elucidate disease-specific gene regulation and function in spatial context.

Methods

We develop a computational framework to integrate spatial transcriptomics with single cell multiomics data (Table 1) and infer disease-associated gene networks at spatial niche and cell type resolution. We identify spatial niches using a biological-knowledge-informed matrix decomposition method, align single-cell multiome data with spatial transcriptome data, and infer functional regulatory relationships between genes using an integrated Bayesian framework.

Results

Using glomerular identification as an example, the spatial transcriptome-based niche pattern is concordant with image-based digital pathology. We build functional regulatory gene networks for ~50 kidney cell subtypes for each disease state. Focusing on the adaptive proximal tubule (aPT) networks, we rank >13000 gene ontology terms based on their differential network connectivity between disease states. The terms with highest differential connectivity include regulation of nephron tubule epithelial cell differentiation (CKD vs AKI), phospholipase A2 inhibitor activity (reference vs. AKI), and regulation of kidney size (CKD vs. reference). The regulatory networks mediated by HNF4A and NFKB1 in aPT cells are further validated on independent single cell data (Lake et al 2023). These disease-associated cell type networks are aligned to spatial niches, enabling a spatially-resolved, cell-type specific characterization of molecular pathways in kidney disease.

Conclusion

Our framework provides a network-based view of molecular differences between kidney disease states, cell subtypes, and spatial niche patterns.

Table 1. Number of biopsies for each disease state.

Data types	AKI	CKD	Reference
Spatial transcriptome	6	10	10
sc/sn-RNA-seq	14/21	36/42	20/54
sc-multiome	In process		9

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