Spatially Anchored Molecular Neighborhoods in Lupus Nephritis

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Background:

Lupus nephritis (LN) affects 1 in 3 individuals with systemic lupus erythematosus. Suboptimal treatment precipitates irreversible kidney damage, leading to end stage renal disease. Kidney damage in lupus is characterized by immune cells injuring epithelial, endothelial, and stromal cells. We characterized molecular neighborhoods composed of immune cells interacting with resident cells of the kidney through spatial transcriptomics (ST).

Methods:

Visium ST experiments were conducted in 8 healthy controls (233 glomeruli) and 3 LN samples (48 glomeruli). Cell type labels from the Kidney Precision Medicine Project single cell RNA-seq atlas were transferred to deconvolute ST spots into specific cell types. Using histology and *NPHS2* expression, glomeruli were selected as functional tissue units. Data were normalized, dimensionally reduced, and clustered with Seurat v4. Spatially anchored gene signatures of LN were identified. Glomeruli were re-clustered according to cell composition, to identify associated neighborhoods by fisher's exact test. We characterized the cell composition, differentially expressed genes (DEGs), and pathways of relevant neighborhoods.

Results:

Between LN and control glomeruli, we identified *HSPA8, PLEK, COL1A2* DEGs, associated with hypoxia, fibrosis, and immune response. We identified glomerular neighborhoods consistent with immune complex deposition, endothelial dysfunction (e.g. wire loop lesions), and mesangial cell expansion enriched in LN ($p<0.05$). Immune complex-mediated injury neighborhoods were characterized by interferon signaling, endothelial cell migration, and vascular genesis, consistent with DEGs *BST2, CXCL12,* and *ENG*. Endothelial dysfunction neighborhoods present cellular adhesion, immune cell signaling, and hypoxic pathways. DEGs included *ITGB2, HLA-DPB1,* and *EGR1.* Pathways enriched in mesangial expansion neighborhoods included matrix adhesion, podocyte development, and ERK1 and ERK2 cascade, aligned with *ITGB3, NPHS1,* and *APOE* DEGs.

Conclusion/ Clinical Impact and Implications:

Neighborhood characterization provides insight into cell-cell interactions that drive kidney disease progression. Future directions will change how kidney biopsy specimens drive treatment by delineating specific cell-cell interactions, linking molecular and histopathological signatures, and defining genes associated with therapeutic resistance.