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Spatially-Resolved Transcriptomic Profiling of Mesangial Cells in IgA Nephropathy via Laser-Activated Cell Sorting

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Objectives : IgA nephropathy (IgAN) is the most common primary glomerulonephritis, characterized by mesangial IgA deposition, and hypercellularity. Mesangial proliferation is a key histologic feature associated with disease severity and prognosis, yet its underlying molecular mechanisms remain poorly understood. To elucidate the spatial transcriptomic landscape of mesangial cells in IgAN, we applied Spatially-Resolved Laser-Activated Cell Sorting (SLACS), an advanced technique for isolating region-specific cell populations from kidney biopsy tissues.
Methods : We performed spatial transcriptomics on kidney biopsy tissues from IgAN patients (M0: n=7, M1: n=7), normal controls (n=3), and disease controls (Diabetic kideny disease: n=3) using SLACS. Mesangial regions were selected based on glomerular morphology, followed by laser microdissection for precise isolation of target areas. Differentially expressed genes (DEGs) were identified through pairwise comparisons, and Gene Set Enrichment Analysis (GSEA) was conducted to explore biological pathways.
Results : A total of 561 DEGs were identified in the IgAN-M1 vs. M0 comparison, with 317 genes significantly upregulated and 38 genes downregulated (Fold change > 0.5, $p < 0.05$). Upregulated genes, including TBK1, RXRA, IGF2BP1, CFHR5, CHD7, and NFATC2, were associated with immune regulation, complement activation, and cell proliferation. Conversely, genes involved in cellular repair and extracellular matrix stability, such as ATG7, ZEB2, FGF1, and BGN, were significantly downregulated in IgAN-M1 compared to IgAN-M0. Despite both IgAN and DKD exhibiting mesangial proliferation, their transcriptomic profiles differed. DKD showed differential expression of 116 genes (89 upregulated, 27 downregulated) compared to IgAN, with upregulation of genes such as FOXO6, ITGA3, VEGFC, NOS1, GRINA, and ADCY6, suggesting a stronger association with metabolic dysregulation, oxidative stress, and vascular remodeling.
Conclusions : This study provides the first spatially-resolved transcriptomic profile of mesangial cells in IgAN, revealing stage-specific molecular signatures that contribute to disease progression. The distinct mesangial transcriptomic landscapes in IgAN emphasize the need for further investigation into disease-specific mechanisms and potential therapeutic targets.