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Single Nucleus RNA-sequencing and Mendelian Randomization Analysis of IgA Nephropathy Progression from Onset to Chronic Kidney Disease

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Objectives : IgA nephropathy is a prevalent form of glomerulonephritis, often progressing to chronic kidney disease, placing a substantial burden on global healthcare and financial resources. Hence, it is crucial to unravel the entire progression of IgA nephropathy from onset to impaired kidney function.
Methods : We obtained renal biopsy tissues from 9 individuals with normal eGFR (> 90 ml/min/1.73m²) and 11 with low eGFR. These were further subdivided into 3 samples with normal eGFR and 3 with low eGFR, combined with the GSE151302 dataset (comprising 5 normal kidney snRNA-seq results) act as control group. The 10x Genomics protocol was employed, followed by analysis using Cell Ranger, Seurat, CellChat, pySCENIC, GSEA, Monocle2, and TwoSampleMR.
Results : Following basic Seurat analysis, we identified key kidney cell types. CellChat analysis highlighted substantial variations in cell-to-cell interactions, especially in fibroblasts and parietal epithelial cells (PEC) during IgAN progression. pySCENIC analysis confirmed blurred boundaries between podocytes and PEC, as well as between mesangial cells and fibroblasts throughout the disease progression. GSEA analysis identified distinct pathways: normal eGFR group showed upregulation in myeloid cell-mediated immune processes compared to the control group. In contrast, the low eGFR group exhibited enrichment in T cell-mediated immune processes, humoral immune processes, and interferon pathways compared to the normal eGFR group. Subsetting and re-clustering podocytes, PEC, fibroblasts, and mesangial cells unveiled unique transitional states in IgAN. Utilizing fibroblast, PEC, and T cell markers, our Mendelian randomization analysis suggested potential contributions of RPL34 and PRRT3 to IgAN, while implicating OIP5 in chronic kidney disease.
Conclusions : Collectively, podocytes, PEC, mesangial cells, and fibroblasts likely play a crucial role in IgAN progression to chronic kidney disease. Upregulated expression of RPL34 and PRRT3 may contribute to IgAN, while elevated OIP5 expression could lead to chronic kidney disease.

Figure1.png

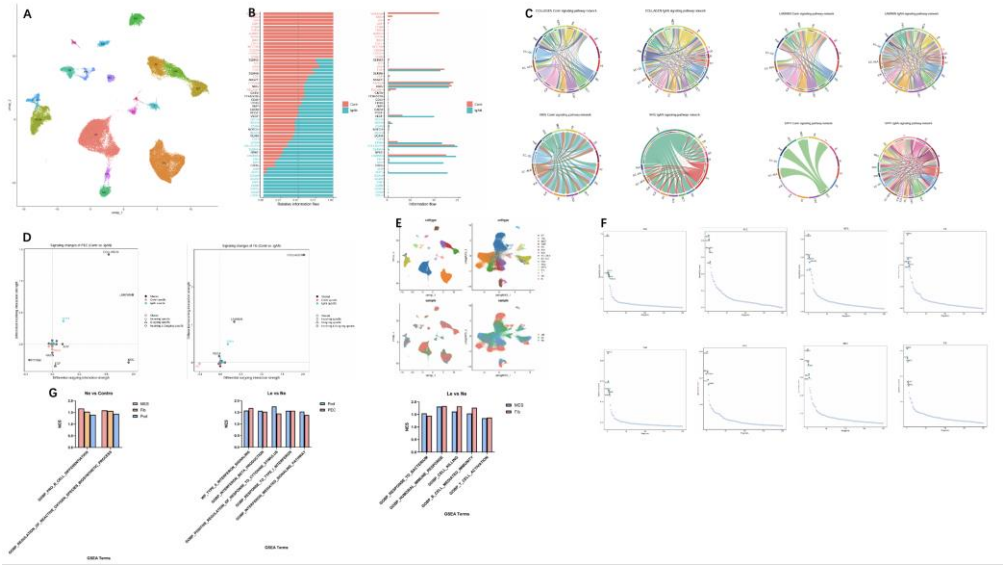

Figure1.png