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Single-Nucleus RNA sequencing reveals ETS1 as a key driver of IgA nephropathy pathogenesis

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Objectives : IgA nephropathy (IgAN), the most common primary glomerular disease worldwide, is a leading cause of kidney failure. We aimed to characterize cell-specific transcriptomic alterations in the kidney using single nucleus RNA sequencing (snRNA-seq) and identify novel therapeutic targets to mitigate IgAN progression.
Methods : We obtained snap-frozen kidney biopsy specimens from 6 patients with IgAN and 7 nephrectomy control cases. The disease control group included 3 cases of diabetic kidney disease, 6 cases of minimal change disease, and 6 cases of PLA2R-Ab–positive membranous nephropathy. snRNA-seq was performed on kidney tissues, and cell types were identified through UMAP clustering. We assessed differences in kidney cell-type proportions and identified differentially expressed genes (DEGs). Additionally, we examined key genetic loci previously reported in a multiethnic genome-wide association study (GWAS). To explore the therapeutic potential of a target gene, in vitro experiments using primary human mesangial cells and an ETS1 inhibitor were conducted.
Results : We successfully generated transcriptomic profiles of over 50,000 kidney cells from IgAN samples, with a notable enrichment of intraglomerular cell populations. DEG analysis revealed a substantial number of DEGs in intraglomerular cells in IgAN compared to nephrectomy and disease control samples. Gene set enrichment analysis demonstrated activation of the epithelial–mesenchymal transition pathway from IgAN samples. Among various GWAS-identified loci, ETS1 was significantly overexpressed in mesangial cells from IgAN cases, consistently across all control groups. In vitro, ETS1 expression was upregulated in primary human mesangial cells following TNF-α stimulation which mimics IgAN-associated pathological changes, along with increased expression of inflammatory and fibrotic markers. Notably, these effects were attenuated by ETS1 inhibition.
Conclusions : Our snRNA-seq analysis identified key cell-specific transcriptional changes and enriched molecular pathways in IgAN. ETS1 may serve as a kidney-resident driver of IgAN pathophysiology, representing a promising target for therapeutic intervention.

Fig1. study flowgram.png

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