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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.

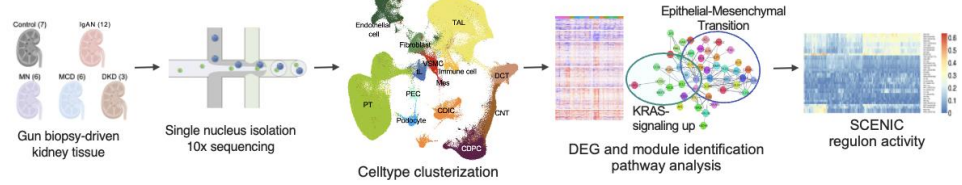
Methods : We obtained snap-frozen kidney biopsy specimens from 6 patients with IgAN and 7 nephrectomy control cases. The disease control group included 3 cases of diabetic kidney disease, 6 cases of minimal change disease, and 6 cases of PLA2R-Ab-positive membranous nephropathy. snRNA-seq was performed 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

SnRNA sequencing to identify target molecule



in vitro experiment using primary cultured mesangial cell

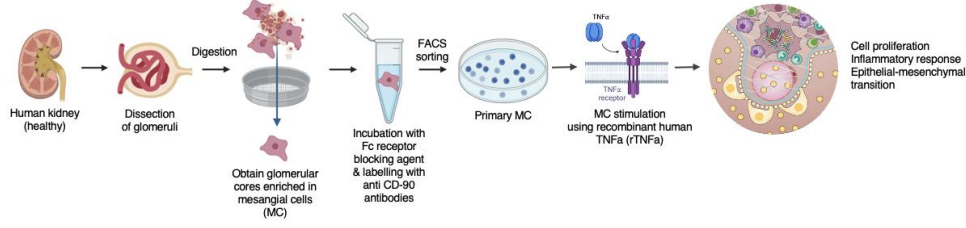


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