Immunological insight into IgA nephropathy: Dissecting immune cell responses and transcriptomic profiles for targeted therapeutic strategies

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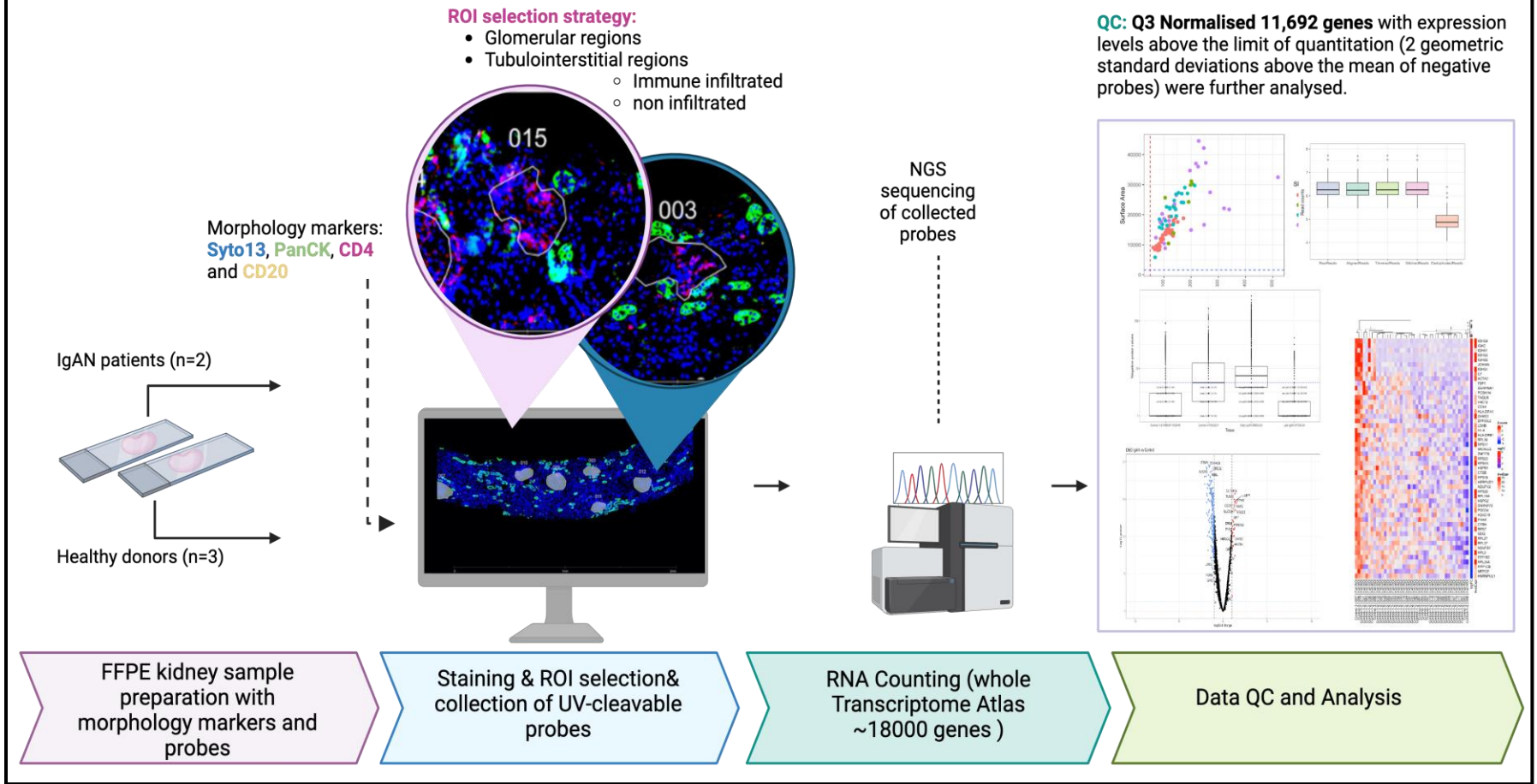
INTRODUCTION

IgA nephropathy (IgAN) is a prevalent form of glomerulonephritis characterized by the deposition of galactose deficient IgA1 in the kidney's glomerular mesangium. Kidney transplantation is emerging as the best treatment for progressive IgAN. However, the long-term survival rates following transplantation remain suboptimal, primarily due to the threat of IgAN recurrence.

To enhance our understanding of the tissue specific mechanisms of pathogenesis of IgAN and its recurrence post-transplantation, we conducted **deep spatial profiling** of IgAN kidney biopsies across the whole human transcriptome.

METHODS

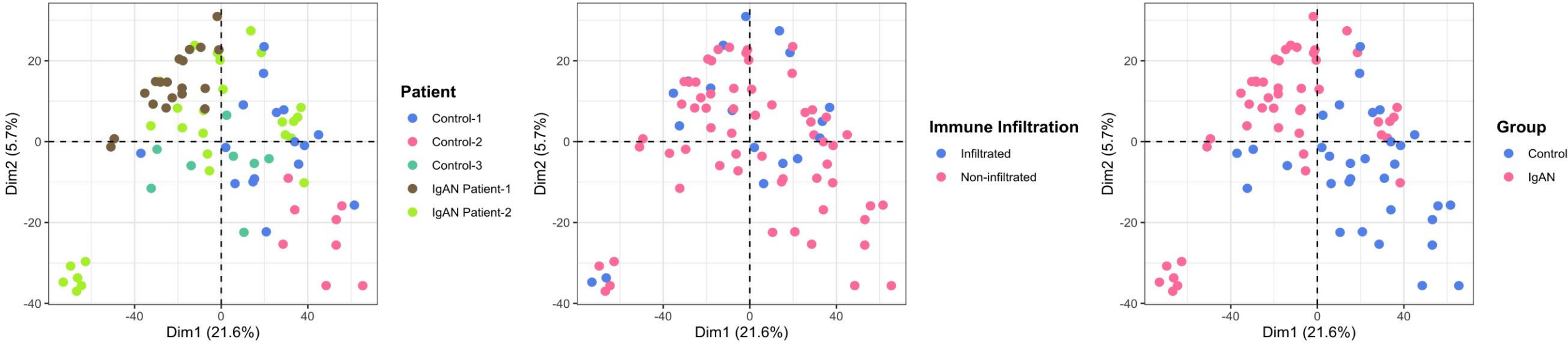


AIMS

Identification of disease-associated gene expression patterns in IgAN kidney biopsies:
To characterise gene expression profiles in glomerular and tubulointerstitial regions in kidney biopsies from patients with IgAN.

Analysis of immune cell infiltration kidney structures in relation to disease progression:
To understand how structural changes within the kidney tissue are influenced by disease progression and the extent of immune cell infiltration, using spatial transcriptomics to map these variations at a high resolution.

RESULTS



Principal component analysis of the entire dataset revealed three distinct clusters, with the one IgAN sample which is the most fibrotic and damaged forming a separate cluster, indicating a notable biological difference linked to disease stage.

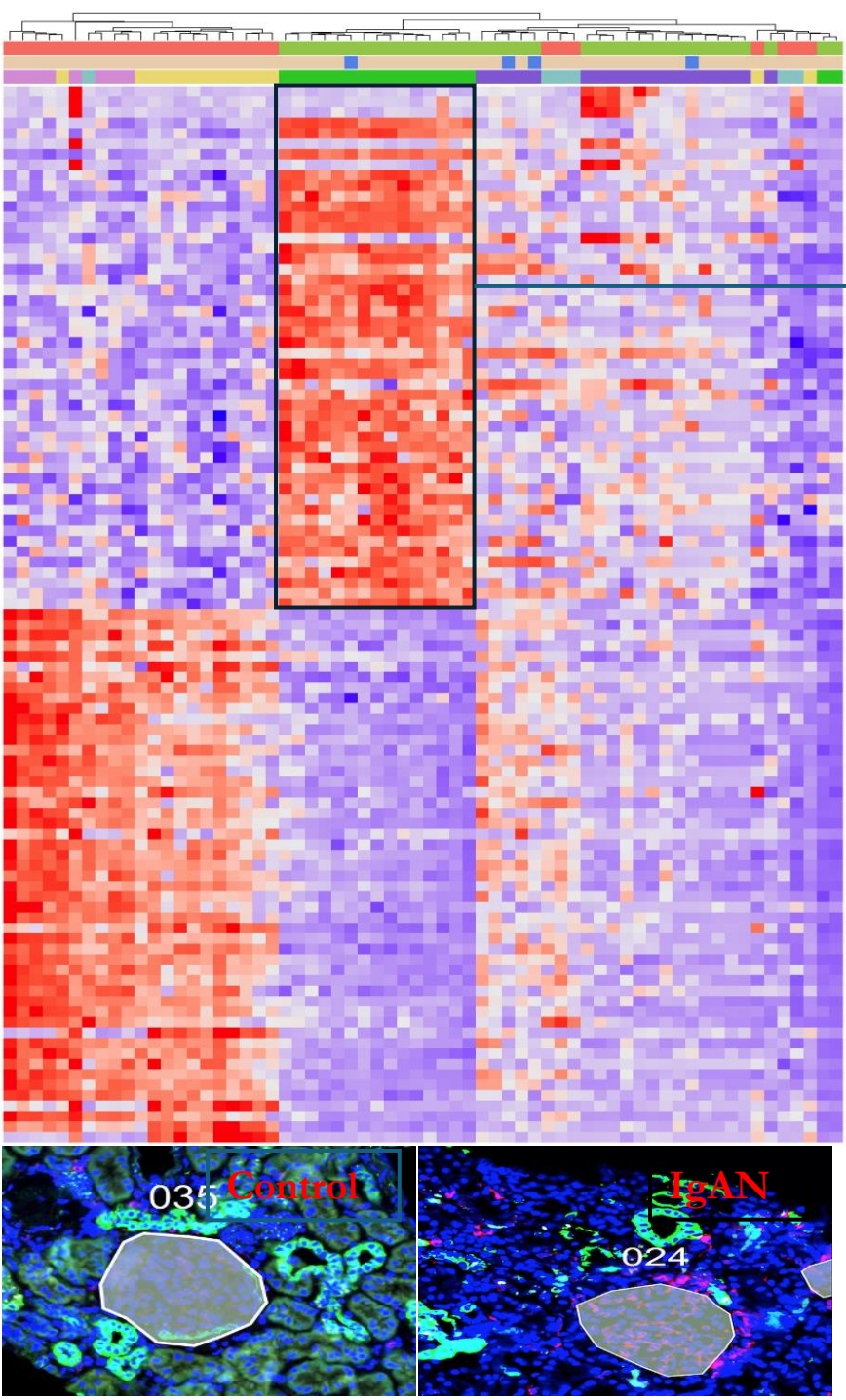
How do **glomerular regions** in IgAN tissue differ from those in healthy controls in terms of structure, gene expression, and immune cell infiltration?

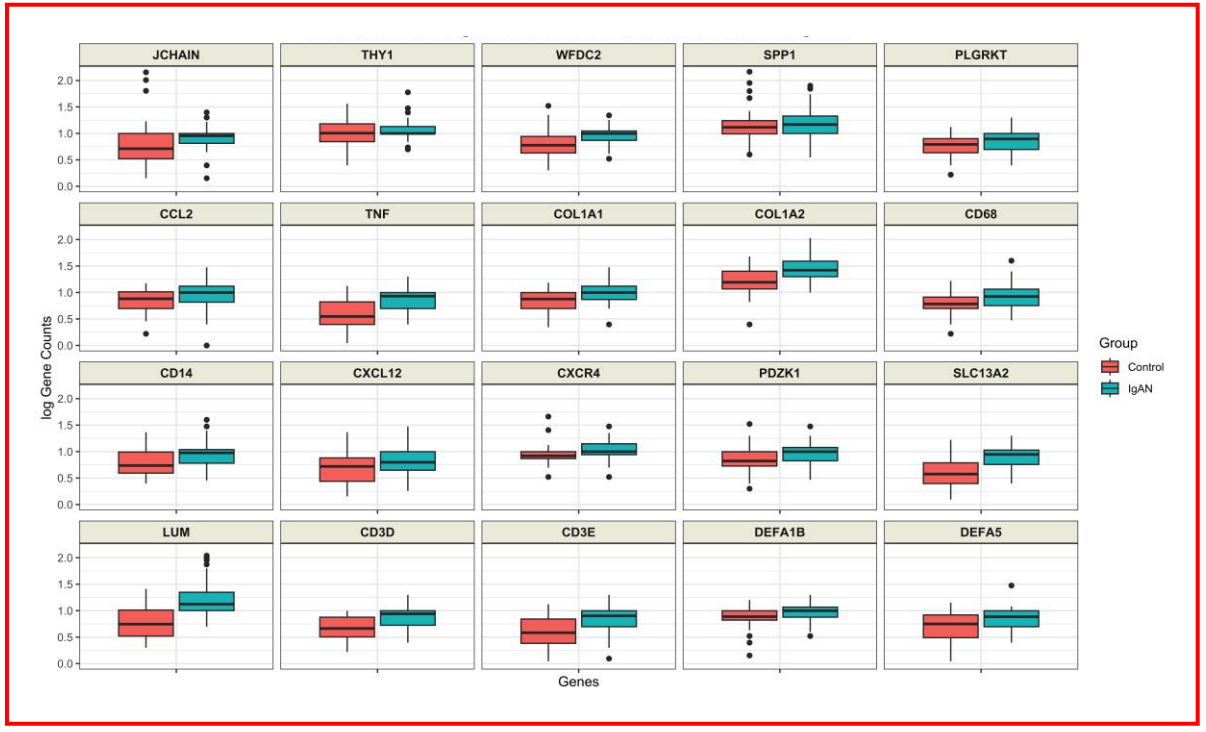
IgAN glomerular regions:

- 763 significantly upregulated genes, many linked to inflammation, fibrosis, and tissue damage.

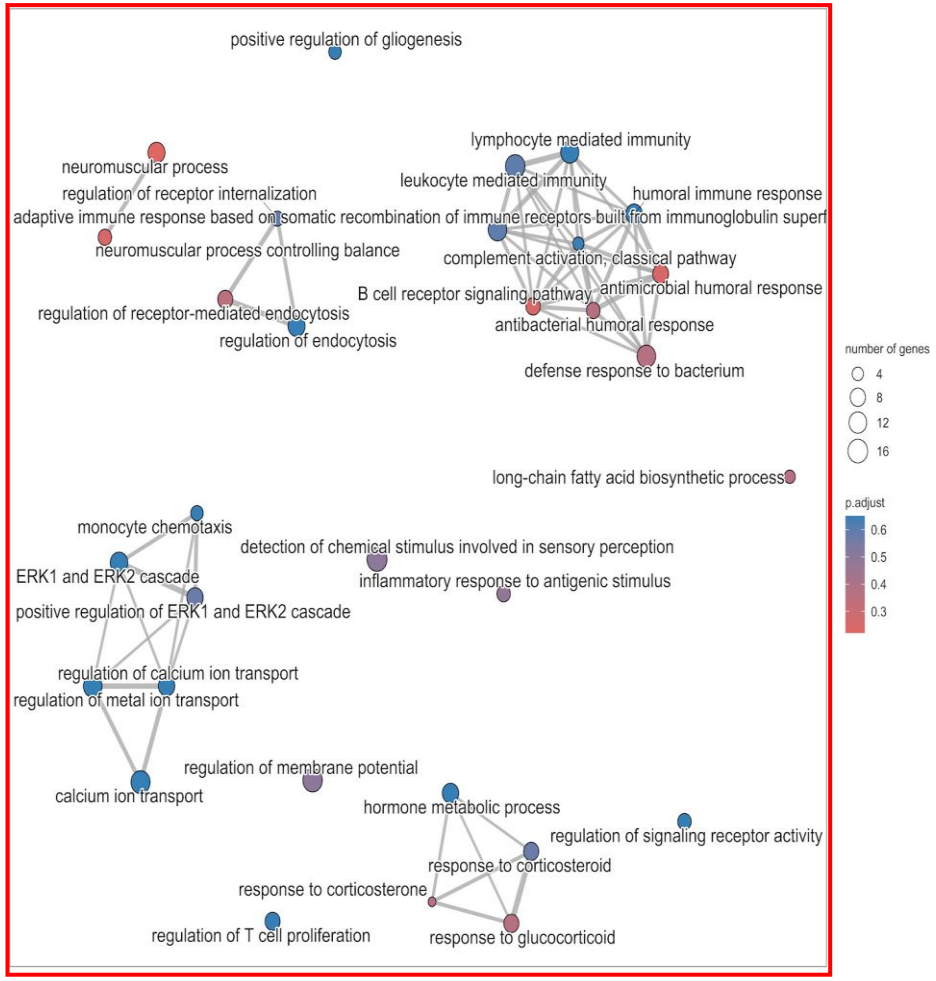
Upregulation:

- CLEC10A (inflammation, immune response), TGFB3 (inflammation),
- GPR4 (glomerular development), DEFB1 (mucosal immunity), KRT28 (fibrosis)
- CCR1 (monocyte and dendritic cell chemotaxis),
- CD79B, ZNF346, and CYP2W1 (immune signaling),
- LUM and IGHG subclasses (complement activation and humoral immunity).

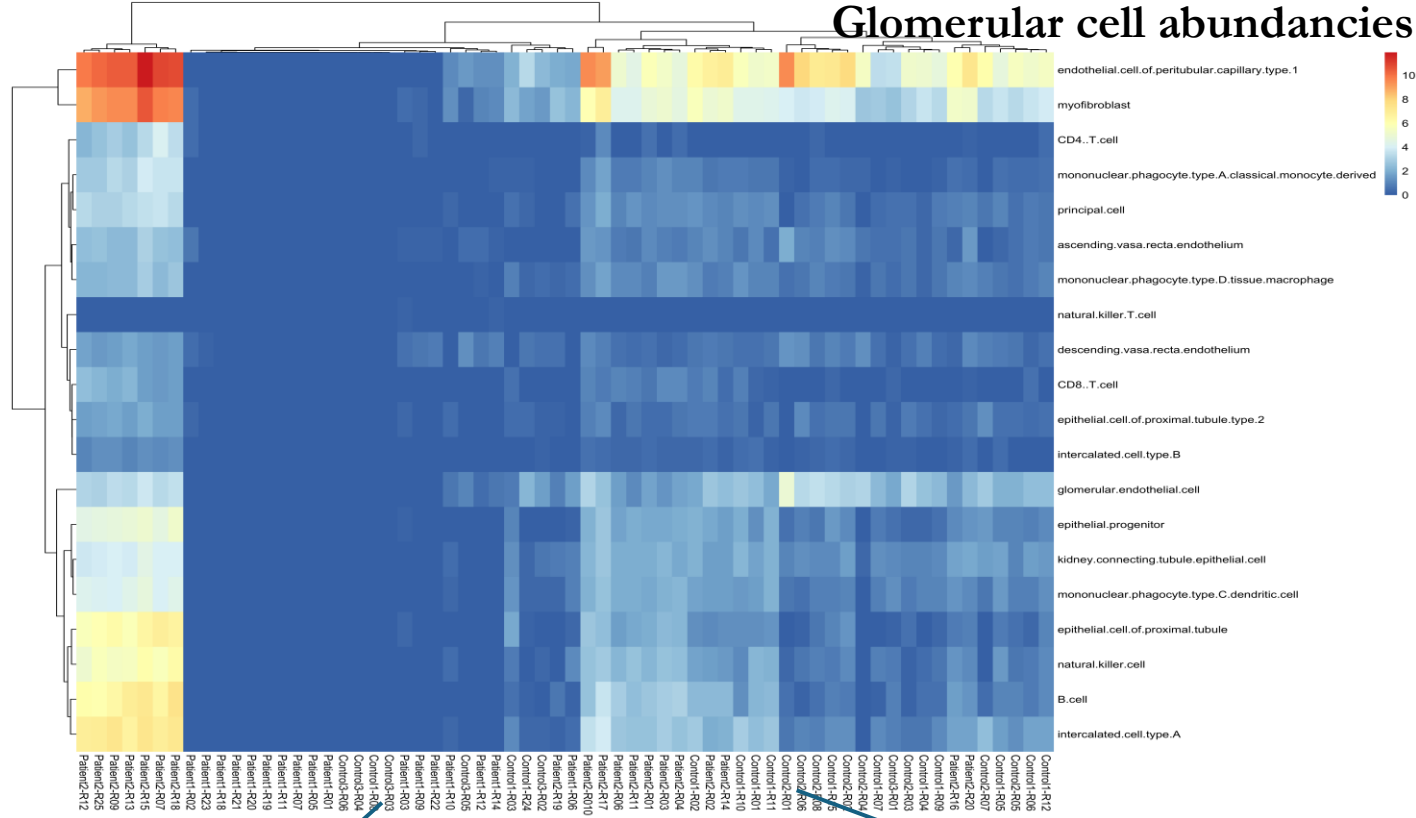




Over-Representation Analysis (ORA) of significantly upregulated genes in IgAN glomerular regions
- enrichment in pathways related to cellular migration, activation, regulation and adaptive immunity.

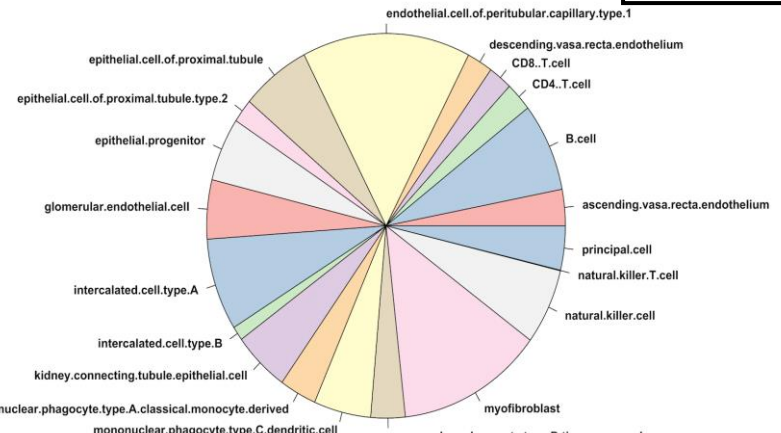


Glomerular cell abundancies

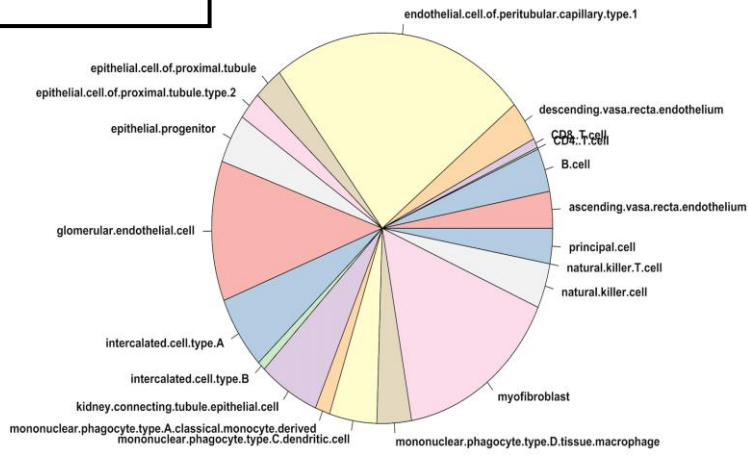


Spatial deconvolution analysis estimated the abundance of immune cells in glomerular regions of diseased tissue.

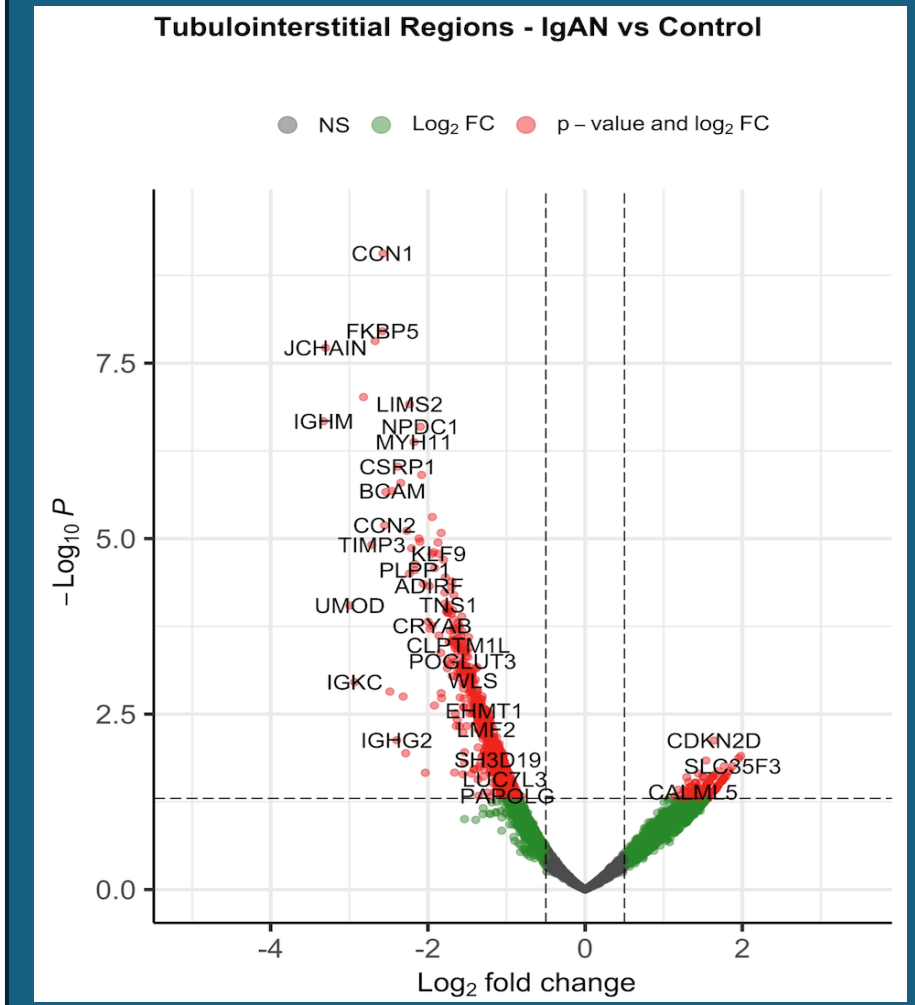
IgAN



Control



What are the differences in **tubulointerstitial regions** between IgAN tissue and healthy controls?

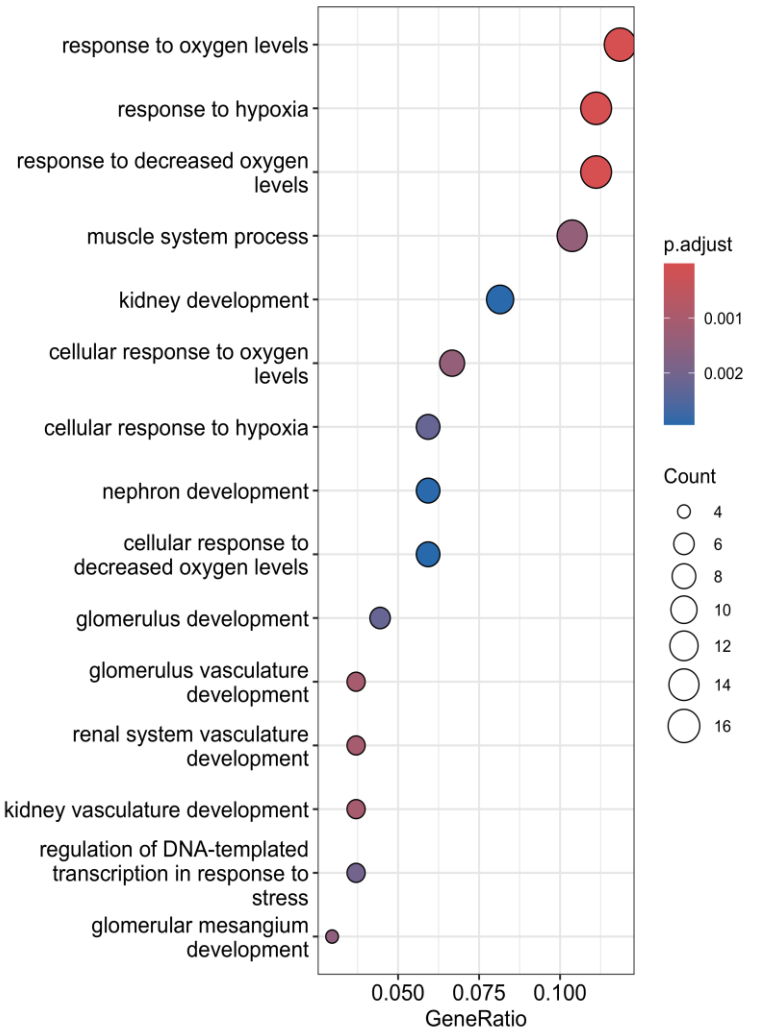


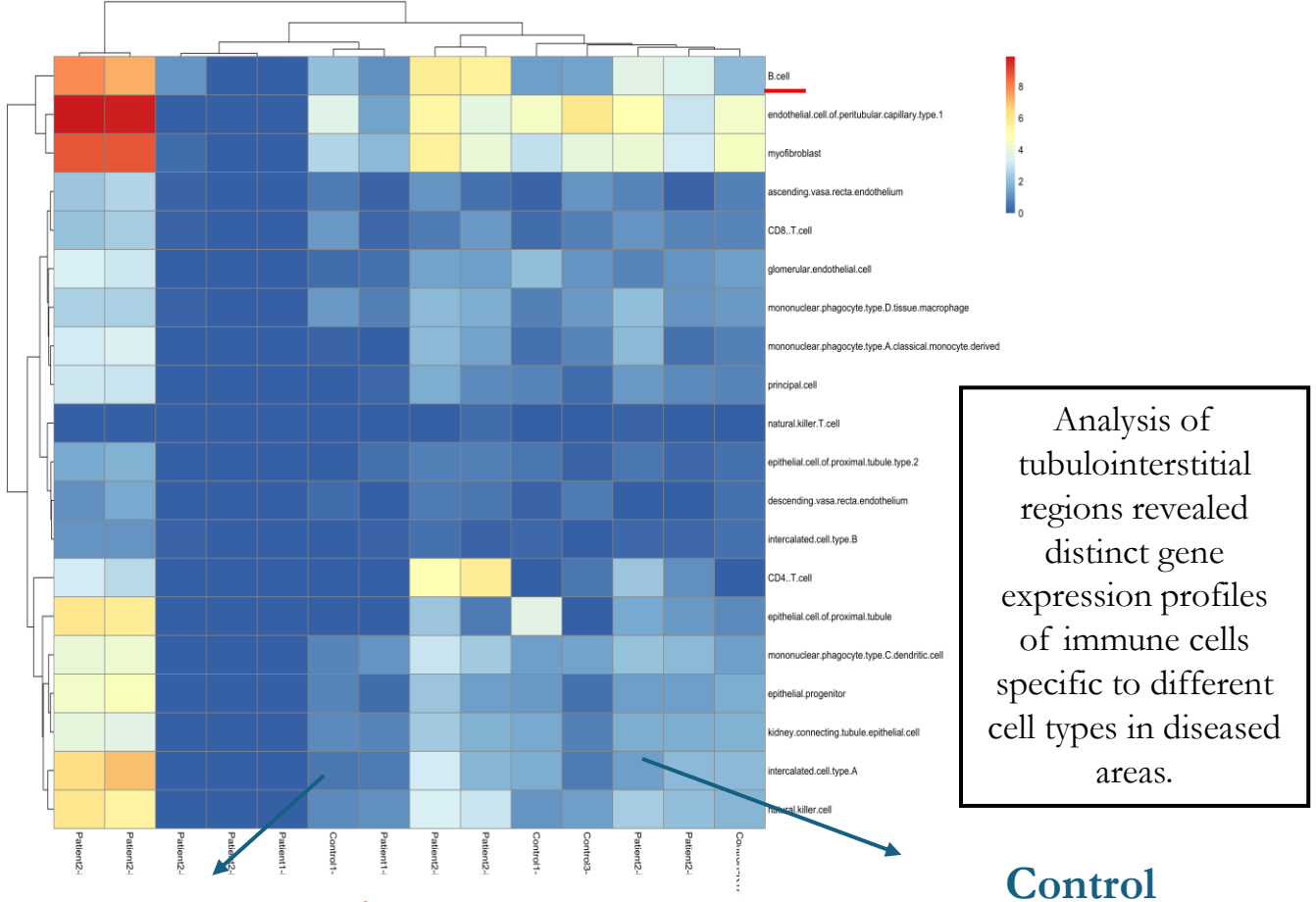
Intercellular crosstalk between different kidney regions can provide critical insights into disease progression. To explore this, we analyzed the tubulointerstitial regions within diseased and heathy biopsies.

IgAN tubulointerstitial areas most of the DEGs were downregulated, including:
- CCD1, FKBP5, and IGHM,

IgAN tubulointerstitial areas upregulated:
- CDKN2D, SLC35F3, and CALML5

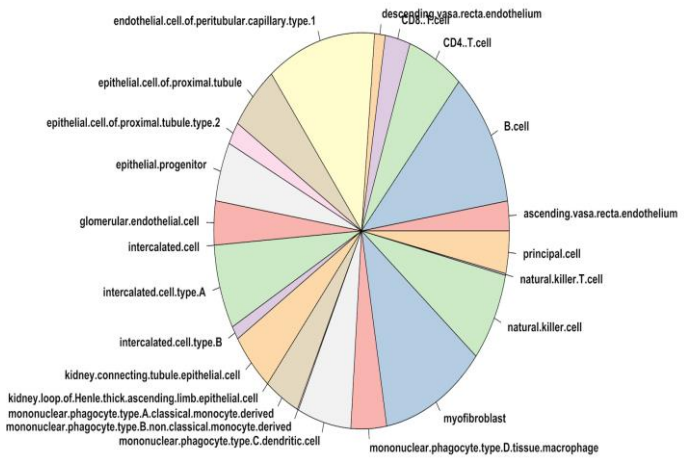
- Pathway enrichment analysis : pathways critical for healthy kidney development and function, indicating that these essential biological processes are disrupted as the disease progresses.





Analysis of tubulointerstitial regions revealed distinct gene expression profiles of immune cells specific to different cell types in diseased areas.

IgAN



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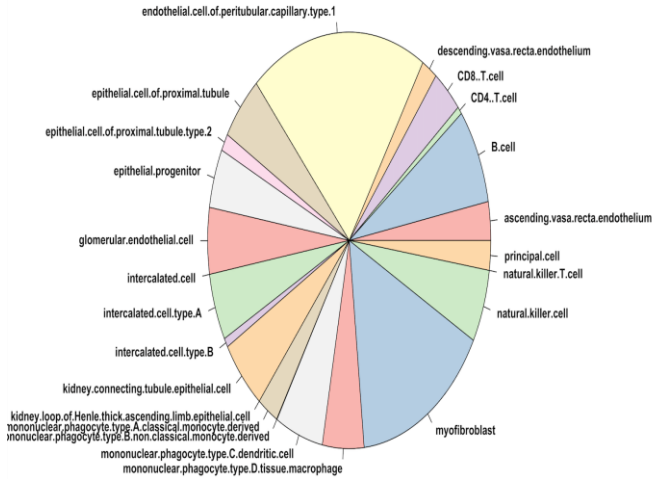

KEY POINTS

- Spatial transcriptomic analysis of biopsies from IgAN patients allows for the precise mapping of immune cell distributions and interactions within glomerular regions.
- Our data demonstrates that the progression of IgAN affects different kidney structures in distinct ways, with specific genes and immune cells exhibiting unique spatial patterns.
- We expect that our findings will provide valuable insights into the complex immune mechanisms associated with IgAN, both in its native form and post-transplantation.
- Future temporal and disease course analyses will shed further light on dynamic processes.

British Society for immunology

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