Immunological Insight into IgA Nephropathy: Dissecting Immune Cell Responses and Transcriptomic Profiles for Targeted Therapeutic Strategies

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IgA nephropathy (IgAN) is a prevalent form of glomerulonephritis characterized by the deposition of galactose deficient IgA1 in the kidney's glomerular mesangium. The consequential development of end-stage renal disease shortens life expectancy by a decade, with kidney transplantation 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 pathogenesis and clinical implications of IgAN and its recurrence post-transplantation, and to identify tissue-localised immune biomarkers and mechanisms, we conducted deep spatial profiling of IgAN biopsies across the whole human transcriptome. Two IgAN disease samples were compared to 3 healthy controls. PanCK, CD20, and CD4 morphology markers were used to select regions of interest (ROIs) with immune infiltration in glomerular and tubular areas. Bulk next-generation sequencing analyses were performed on these regions to identify differentially expressed genes in the different kidney structures affected by the disease and compared to control biopsies.

Principal component analysis of the entire dataset revealed three distinct clusters, with the late IgAN sample forming a separate cluster, indicating a notable biological difference. Subsequent spatial deconvolution highlighted an increased abundance of immune cells in the severe disease sample, specifically B cells, CD4 and CD8 T cells, as well as NK cells in the ROIs. A differential gene expression analysis uncovered over 30 genes, primarily associated with kidney function, exhibiting heightened expression in IgAN. Enriched immunoregulatory and immune-to-non-immune cell interaction gene markers, such as ICAM3, ITGA4, and VCAM1, were identified.

This ongoing work strongly suggests that IgAN is associated with a broad immune cell infiltration in the kidney, exhibiting a distinct gene signature and immune pathway activation. Our findings will contribute valuable insights into the complex immune biomarkers and mechanisms associated with IgAN, both in its native form and post-transplantation, aiming for targeted treatment strategies. Future temporal and disease course analyses will shed further light on dynamic processes.