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Spatially resolved transcriptomic analysis for glomerular and tubulointerstitial gene expression profile of C3 glomerulonephritis

Jung Hun Koh[1], Sehoon Park[2], Jeong Min Cho[2], Semin Cho[3], Yaerim Kim[4], Hyun Je Kim[5], Dong Ki Kim[2]
[1]Department of Internal Medicine, Seoul National University Hospital, Korea, Republic of
[2]Department of Internal Medicine-Nephrology, Seoul National University Hospital, Korea, Republic of
[3]Department of Internal Medicine-Nephrology, Chung-Ang University Gwangmyeong Hospital, Korea, Republic of
[4]Department of Internal Medicine-Nephrology, Keimyung University Dongsan Medical Center, Korea, Republic of
[5]Department of Biomedical Sciences, Seoul National University College of Medicine, Korea, Republic of

Objectives: C3 glomerulonephritis (C3GN), a type of membranoproliferative glomerulonephritis, is a relatively rare but clinically significant kidney disease. However, little is known about its transcriptomic profile. We aimed to investigate the substructure-specific gene expression profile of C3GN using the recently introduced spatial transcriptomics technology.

Methods: We performed spatial transcriptomic profiling using GeoMx Digital Spatial Profiler with formalin-fixed paraffin embedded kidney biopsy specimens obtained from three C3GN cases and eight controls from donor kidney biopsy. Profiles from other types of glomerulonephritis, including focal segmental glomerulosclerosis, membranous nephropathy, and minimal change disease, were included as the disease controls. We compared the gene expression levels by DESeq2 method. Differentially expressed genes (DEGs) were identified if their expression showed a significant difference (false-discovery rate <0.05) with that in the donor controls along with a notable difference ($P<0.05$) with the same directional change in that of the disease controls. We performed gene ontology (GO) annotation by the ToppGene suite, and Pathview was used to map the DEGs on relevant pathway graphs.

Results: A total of 120 highly expressed DEGs were identified in the glomerulus of C3GN when compared to donor and disease controls. The DEG with the highest fold change rate was POSTN, followed by COL1A2, ST3GAL2, FN1, and AEBP1. Extracellular matrix structure formation (GO:0005201) and blood vessel development (GO:0001568) related GOs were the most notable annotated domains in the glomerulus of C3GNs. In contrast, while 494 lowly expressed DEGs were identified in the glomerular transcriptome of C3GN, the GO annotation did not identify notable GO domains enriched by the DEGs. In addition, the tubular transcriptome profiles of C3GN were similar to those of the donor and disease controls.

Conclusions: This is the first report of kidney substructure-specific transcriptomic profile of C3GN to date. Significant disease-specific transcriptomic alterations occur in the glomerulus of C3GN, providing insights regarding the pathophysiology.