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Promoting Sustainable Kidney Health: The Asia-Pacific and Beyond

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Spatially Resolved Transcriptomics Profiling for Glomerular and Tubulointerstitial Gene Expression in Human Diabetic Kidney Disease

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Objectives : Diabetic kidney disease (DKD) is the leading cause of chronic kidney disease worldwide. We aimed to investigate the substructure-specific gene expression profile of DKD using spatial transcriptomics.
Methods : We performed spatial transcriptomic profiling using GeoMx with kidney biopsy specimens obtained from 26 DKD patients. Total 73 glomerular and 77 tubulointerstitial ROIs were configured. We used DESeq2 method to identify differentially expressed genes (DEG) depending on proteinuria or eGFR. We performed gene ontology (GO) annotation through the ToppGene suite, and mapped interactions among the DEGs using the STRING database.
Results : A total of 85 highly expressed DEGs were identified in the tubulointerstitium when comparing low eGFR (30≤eGFR<60) over high eGFR (eGFR≥60). The DEG with the highest fold change was TSPY1, followed by RPS4Y1, MGP, COL3A1. Extracellular matrix structural constituent and structural molecule activity were among the top enriched GO terms. A total of 220 lowly expressed DEGs were identified in the tubulointerstitium when comparing low eGFR over high eGFR, including metallothionein gene family members (MT1H, MT1G, MT1X) which are known to mediate SFN renal protection from type 2 diabetes. A total of 25 and 14 DEGs were expressed respectively highly and lowly in the tubulointerstitium when comparing high proteinuria (random UPCR ≥ 3g/g) over low proteinuria (random UPCR < 3g/g). The DEG with the lowest p-value was FKBP5, which is known to regulate endocrine stress responses. A total of 29 and 19 DEGs were expressed respectively highly and lowly in the glomeruli when comparing low eGFR over high eGFR. In contrast, the glomerular transcriptome profiles were similar between low and high proteinuria.
Conclusions : We found significant transcriptomic differences in DKD according to the severity of kidney dysfunction. Finding more significant DEGs in the tubulointerstitium than in the glomeruli may suggest that tubulointerstitial damage is more important than glomerular damage in the pathogenesis of DKD.

Figure 1 glomerular, tubular ROI.jpg

Glomerulus Tubule

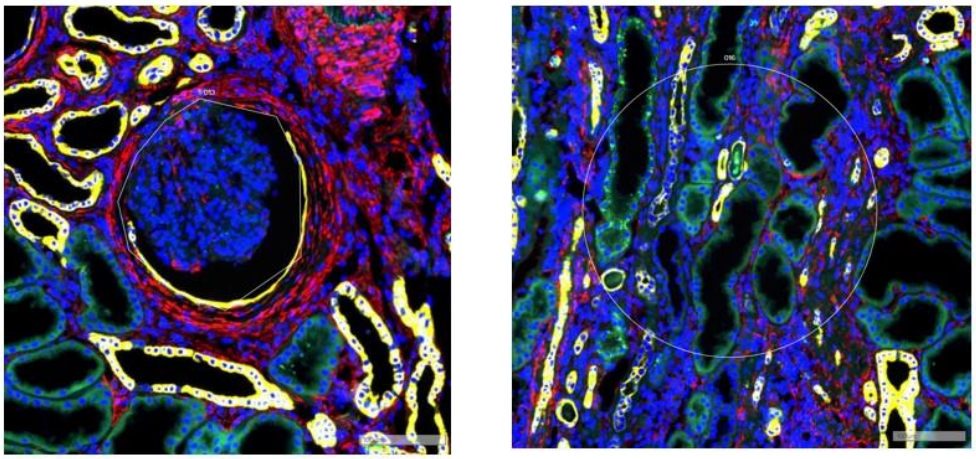
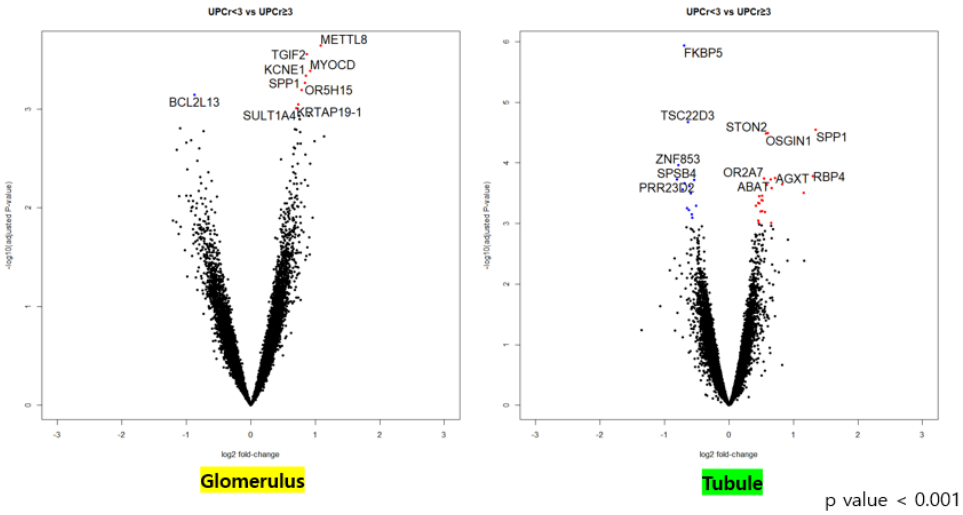


Figure 1 glomerular, tubular ROI.jpg



Glomerulus Tubule

p value < 0.001