THE KOREAN SOCIETY OF NEPHROLOGY
APCN & KSN 2024
June 13(Thu) - 16(Sun), 2024 Coex, Seoul, Korea
Promoting Sustainable Kidney Health: The Asia-Pacific and Beyond

Abstract Submission No.: A-0961

Multi-system alterations in the mesangium of IgA nephropathy mice using single-nucleus RNA-seq and single-nucleus assay for transposase-accessible chromatin

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Objectives : Immunoglobulin A nephropathy (IgAN) is the most common primary glomerulonephritis worldwide. One of the most prominent features of IgAN is mesangial proliferation with deposition of immune complexes. The role of the immune response in the development of IgAN is well-established. However, the genetics and pathways involved are not yet fully understood.
Methods : Mesangium from ddY mice (8 weeks gddY mice, n=3) and control mice (8 weeks Balb/c mice, m=3) were analyzed from three different system-level perspectives: genome level by single-nucleus assay for transposase-accessible chromatin sequencing (snATAC-seq), transcription level by single-nucleus RNA sequencing (snRNA-seq), and metabolic level by in-silico metabolic flux simulation. 'Pdgfrb', 'Pdgfra', 'Fhl2' and 'Itga8' were selected as mesangium-specific marker genes prior to analysis.
Results : The study found that there was a proliferation of cells in IgAN compared to the control, as determined through spatial deconvolution of single-nuclei RNA-seq. The cells in the mesangium were rearranged into three subgroups, including two IgAN-specific subgroups and one control-specific subgroup, each with system-level-specific alterations. From an epigenomic perspective, one of the IgAN-specific subgroups revealed a 'positive regulation of cell adhesion' and 'epithelial cell proliferation' compared to the control-specific subgroup. In transcription profile alteration, two IgAN-specific subgroups revealed either upregulation of immune-associated pathways or energy-associated pathways. Metabolic flux changes affected various metabolic pathways, including 'alanine and aspartate metabolism' and 'purine catabolism'. Three metabolic pathways, namely 'beta-alanine metabolism', 'nucleotide metabolism', and 'pyrimidine catabolism', showed multiple simultaneous alterations on all three system levels.
Conclusions : This study provides insight into the key molecular changes that occur during the development of IgAN-associated glomerular injury, particularly in the mesangium of mice.