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Investigation of molecular insights into the disease-specific pathophysiology of IgA nephropathy using the single cell RNA-sequencing analysis

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Objectives : IgA nephropathy (IgAN) is the most prevalent primary glomerulonephritis worldwide. It is difficult to explain the heterogeneity of the clinical presentation and prognosis as the pathogenesis is not completely understood yet. We performed transcriptome profiling of peripheral immune cells of IgAN to explore the role of immune cells in the pathogenesis of IgAN.
Methods : Peripheral blood mononuclear cells were obtained from 20 IgAN patients and 9 healthy controls. The cells were FACS sorted into B, CD4 T, and CD8 T subsets. Single cell RNA sequencing (scRNA-seq) was performed using NovaSeq6000. The patients were divided into mild to moderate and severe group, according to the eGFR and proteinuria value. The differentially expressed genes (DEG) were identified. Pathway analysis was performed with Ingenuity Pathway Analysis.
Results : After quality control, 32,742 B cells, 101,637 CD4 T cells, 63,029 CD8 T cells were retained for further analysis. Annatated cell clusters were presented in UMAP. (Figure 1) Ninety five genes were commonly upregulated in all subsets of IgAN, including AKT1, CD81, JUN and TGFB1. (Figure 2) Compared to the mild to moderate IgAN group, severe IgAN group exhibited the significant increase in DEG expression; 40, 148, 132 upregulated and 233, 77, 78 downregulated DEGs in B, CD4 T, CD8 T cell subsets, respectively. Upregulated DEGs in B and CD4 T cell subsets were associated with eukaryotic translation pathways. The upstream analysis predicted the top transcriptional regulators; ETV3 was significantly activated upstream regulator in all subsets of severe IgAN and regulated the downstream target genes including IFIT3, SAMD9L and XAF1.
Conclusions : The present transcriptome profiling showed different gene expression profiles according to the severity of IgAN. The study provides new insights into the role of immune cells in understanding the pathogenesis of IgAN. The present study may contribute to the investment of the novel disease specific biomarkers of IgAN.

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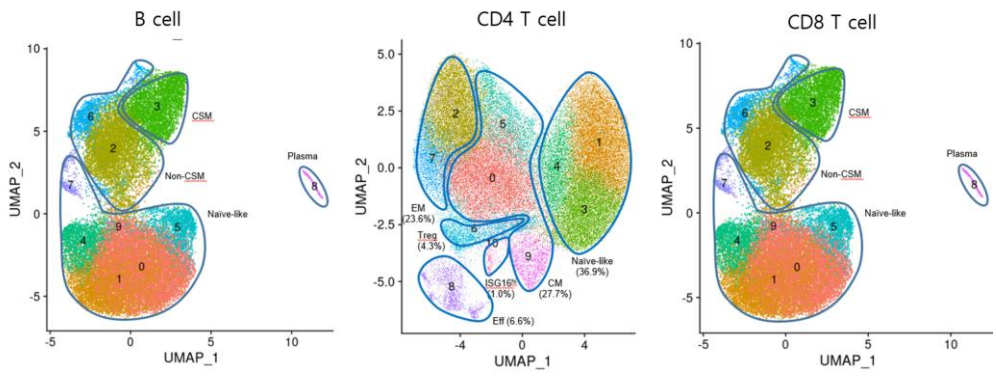
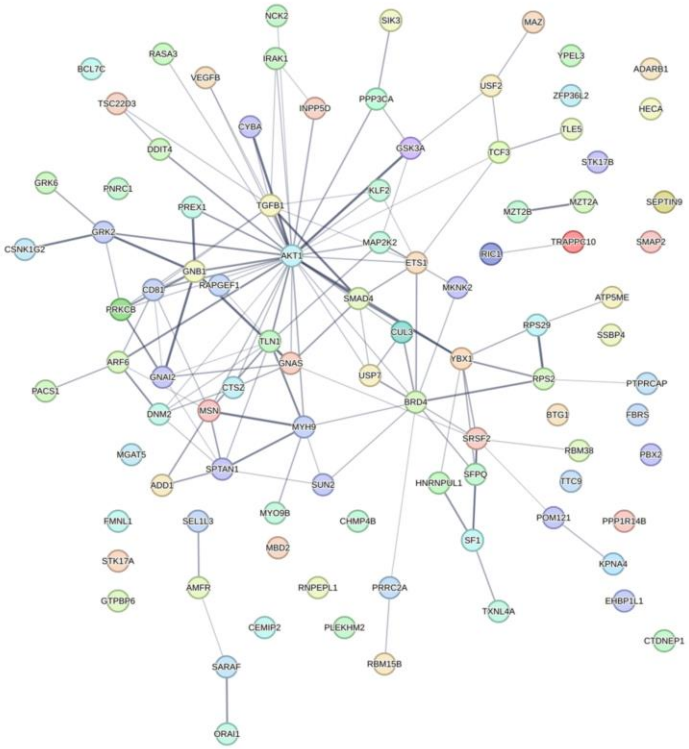
Figure 1



ksn fig 1.jpg

Figure 2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SIK3
MAZ
RASA3
IRAK1
YPEL3
ADARB1
BCL7C
VEGFB
USF2
ZFP36L2
TSC22D3
INPP5D
PPP3CA
HECA
CYB4
TLE5
DDIT4
GSK3A
TCF3
STK17B
GRK6
PNRC1
KLF2
TGFB1
MZT2B
MZT2A
SEPTIN9
PREX1
GRK2
MAP2K2
TRAPPC10
SMAP2
CSNK1G2
AKT1
RIC1
ETS1
GNB1
RAPGEF1
MKNK2
CD81
SMAD4
ATP5ME
PRKCB
CUL3
RPS29
TLN1
SSBP4
ARF6
GNAS
YBX1
GNAI2
USP7
RPS2
PTPRCAP
PACS1
CTS2
BRD4
DNM2
MSN
BTG1
FBRS
MYH9
SRSF2
MGAT5
RBM38
PBX2
SPTAN1
SFPQ
ADD1
SUN2
HNRNPUL1
ITCH
MYO9B
FMNL1
SEL1L3
CHMP4B
POM121
PPP1R14B
SF1
MBD2
STK17A
KPNA4
AMFR
RNPEPL1
PRRC2A
EHBP1L1
GTPBP6
TXNL4A
CEMIP2
PLEKHM2
CTDNEP1
SARAF
RBM15B
ORAI1