Abstract Type : Oral presentation
Abstract Submission No.: A-0156
Abstract Topic : Glomerular and Tubulointerstitial Disorders

Single-Cell Transcriptomics Reveals Distinct CD8+ T cell Differentiation Trajectories in early IgA nephropathy

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Objectives : IgA nephropathy (IgAN), the most prevalent primary glomerulonephritis, is a significant cause of chronic kidney disease. The heterogeneous clinical presentation and prognosis pose challenges in identifying patients at risk during the early stage of IgAN when kidney function is relatively preserved. This study aimed to characterize immune cell heterogeneity and transcriptional dynamics in IgAN patients stratified by disease severity.
Methods : Peripheral blood samples were collected from 9 healthy controls and 17 biopsy-proven IgAN patients, who were classified into early- and late-stage disease groups based on estimated glomerular filtration rate at the time of blood collection. Single-cell RNA sequencing revealed distinct immune cell profiles and transcriptional changes between groups.
Results : Notably, early-stage IgAN featured a enrichment of IL-7Ra^{high} and IL-7Ra^{med} effector memory (EM) CD8^{+} T cells, which showed distinct developmental trajectories relative to late-stage IgAN. These findings suggest a shift from memory CD8^{+} T cells in early-stage disease to IL-7Ra^{low} EM CD8^{+} T cells in late-stage disease, correlating with disease progression (Figure 1). Trajectory and gene expression analyses revealed early-stage specific signatures, including pathways regulating T cell activation and differentiation (Figure 2). In contrast, CD4^{+} T cells and B cells exhibited limited correlation with disease progression. These results provide novel insights into immune cell dynamics in early-stage IgAN and underscore the prognostic significance of CD8^{+} T-cell subpopulations in IgAN progression.
Conclusions : The findings highlight the potential of CD8^{+} T-cell subpopulation as therapeutic targets and offer a new strategy to delay IgAN progression.

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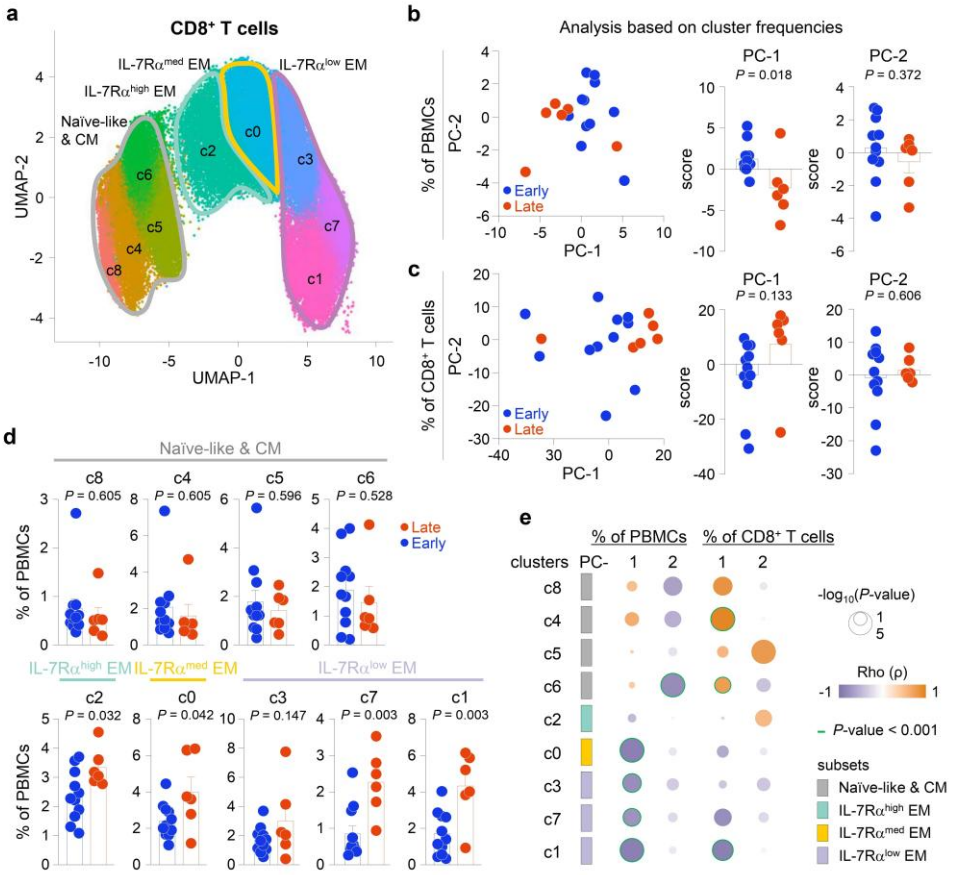

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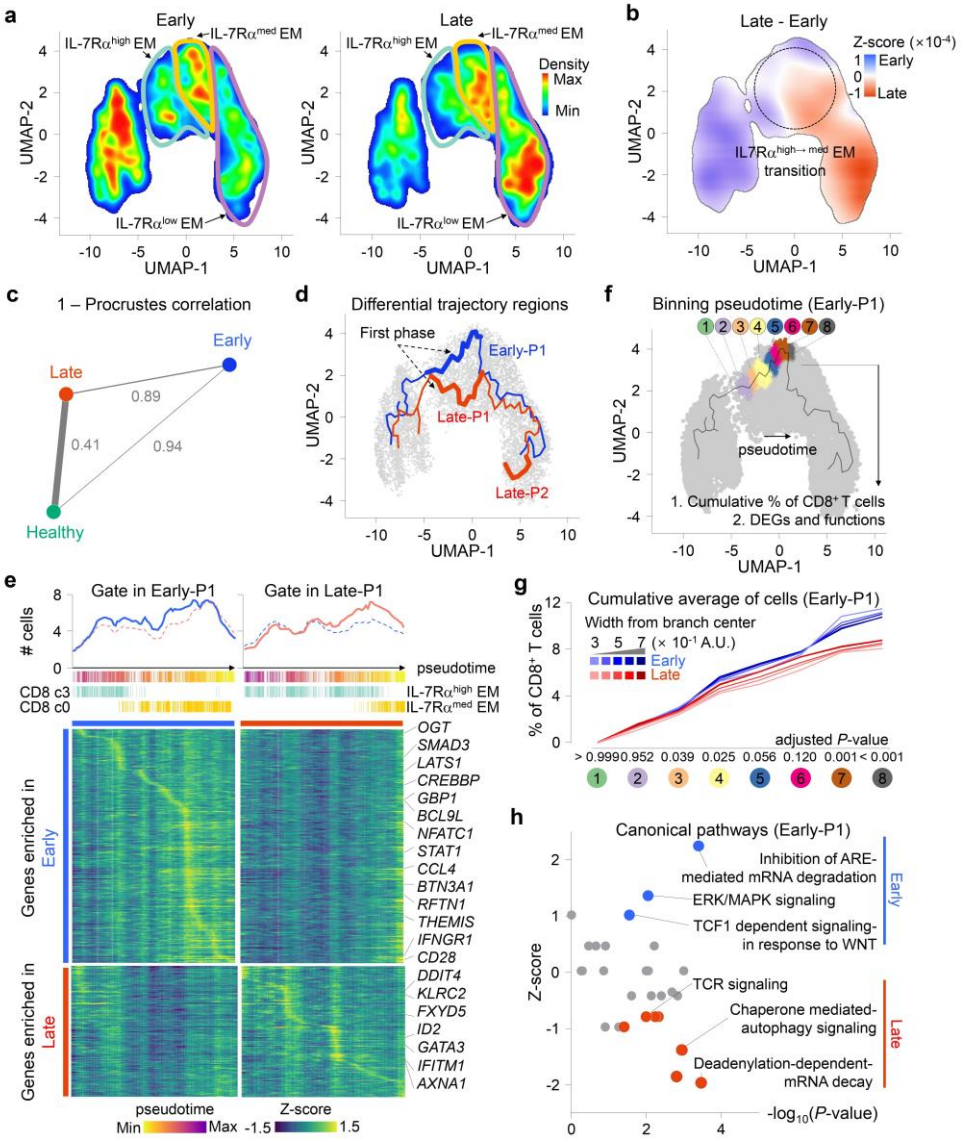
THE KOREAN SOCIETY OF NEPHROLOGY
KSN 2025
SEOUL, KOREA
June 19 (Thu) – 22 (Sun), 2025 Coex, Seoul, Korea
Beyond Challenges, Towards Healthier Kidney


a
Early
Late
IL-7Rα^high EM
IL-7Rα^med EM
IL-7Rα^low EM
Density
Max
Min
UMAP-1
UMAP-2
b
Late - Early
Z-score (×10^-4)
Early
Late
IL7Rα^high→med EM transition
c
1 – Procrustes correlation
Early
Late
Healthy
0.89
0.41
0.94
d
Differential trajectory regions
First phase
Early-P1
Late-P1
Late-P2
f
Binning pseudotime (Early-P1)
pseudotime
1. Cumulative % of CD8⁺ T cells
2. DEGs and functions
e
Gate in Early-P1
Gate in Late-P1
cells
pseudotime
CD8 c3
CD8 c0
IL-7Rα^high EM
IL-7Rα^med EM
Genes enriched in Early
Genes enriched in Late
OGT
SMAD3
LATS1
CREBBP
GBP1
BCL9L
NFATC1
STAT1
CCL4
BTN3A1
RFTN1
THEMIS
IFNGR1
CD28
DDIT4
KLRC2
FXYD5
ID2
GATA3
IFITM1
AXNA1
pseudotime
Min
Max
Z-score
-1.5
1.5
g
Cumulative average of cells (Early-P1)
Width from branch center
3 5 7 (× 10^-1 A.U.)
Early
Late
% of CD8⁺ T cells
adjusted P-value
> 0.999 0.952 0.039 0.025 0.056 0.120 0.001 < 0.001
h
Canonical pathways (Early-P1)
Inhibition of ARE-mediated mRNA degradation
ERK/MAPK signaling
TCF1 dependent signaling in response to WNT
TCR signaling
Chaperone mediated-autophagy signaling
Deadenylation-dependent-mRNA decay
Z-score
-log10(P-value)
Early
Late