No. YIA_004

Predicting IgA Nephropathy Progression Through CD8+ T-Cell Chromatin Accessibility Analysis

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Disclosures

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Introduction

- IgA nephropathy (IgAN)
- Most common primary glomerulonephritis worldwide
- Leading cause of CKD

- Various clinical courses : asymptomatic hematuria to ESKD

→ Up to 40%, progress to ESKD

→ difficulty in identifying high-risk patients during early stage status

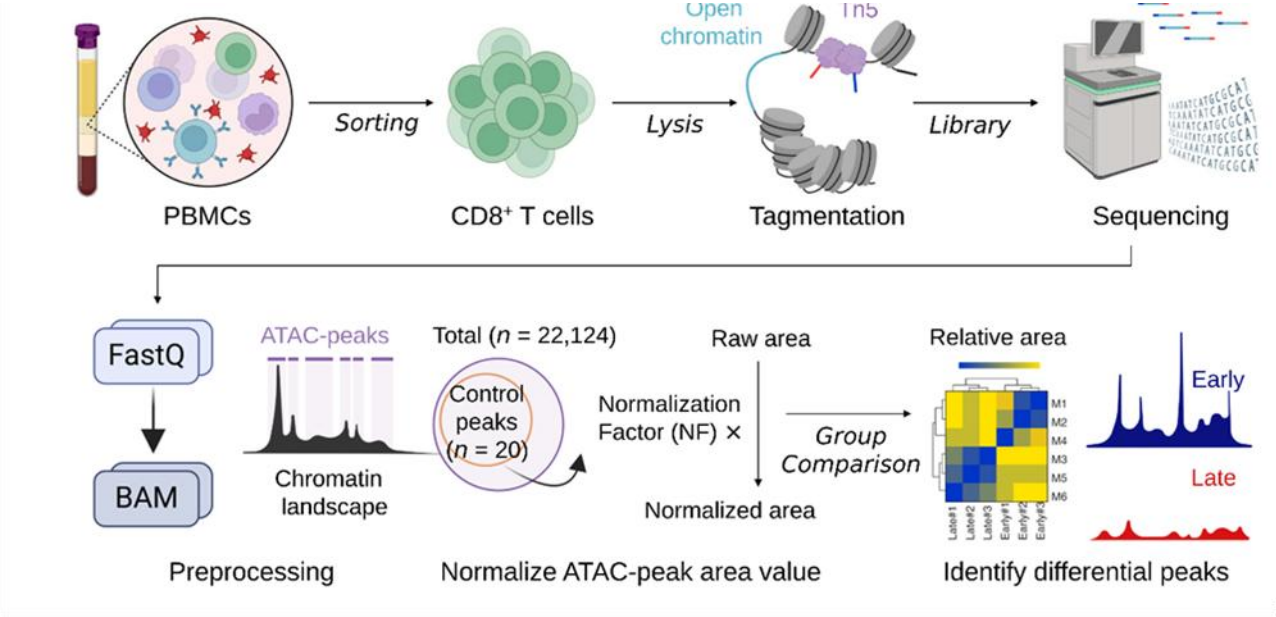
J Am Soc Nephrol. 2011 Oct; 22(10):1795-803.
N Engl J Med. 2013;368:2402–2414.
Clin J Am Soc Nephrol. 2019 Mar 7; 14(3): 469–481.

Study objective

- Aimed to identify epigenetic biomarkers in circulating $CD8^+$ T cells that distinguish patients with IgAN at risk of disease progression, using transposase-accessible chromatin sequencing (ATAC-Seq) to assess chromatin accessibility

- Especially, identification of stage-specific chromatin accessibility profiles associated with early IgAN.

Methods



17 Adults patients with biopsy proven IgAN

- Early-stage (n = 11) and late-stage (n = 6) groups
- Early-stage : eGFR ≥ 60 mL/min/1.73 m², an average eGFR ≥ 30 mL/min/1.73 m² or UPCR < 3 g/g

CD8⁺ T cells were isolated from PBMC and analyzed using ATAC-Seq to assess chromatin accessibility.
Differentially accessible regions were identified, and selected biomarkers were validated using ATAC-qPCR.

Unpublished data

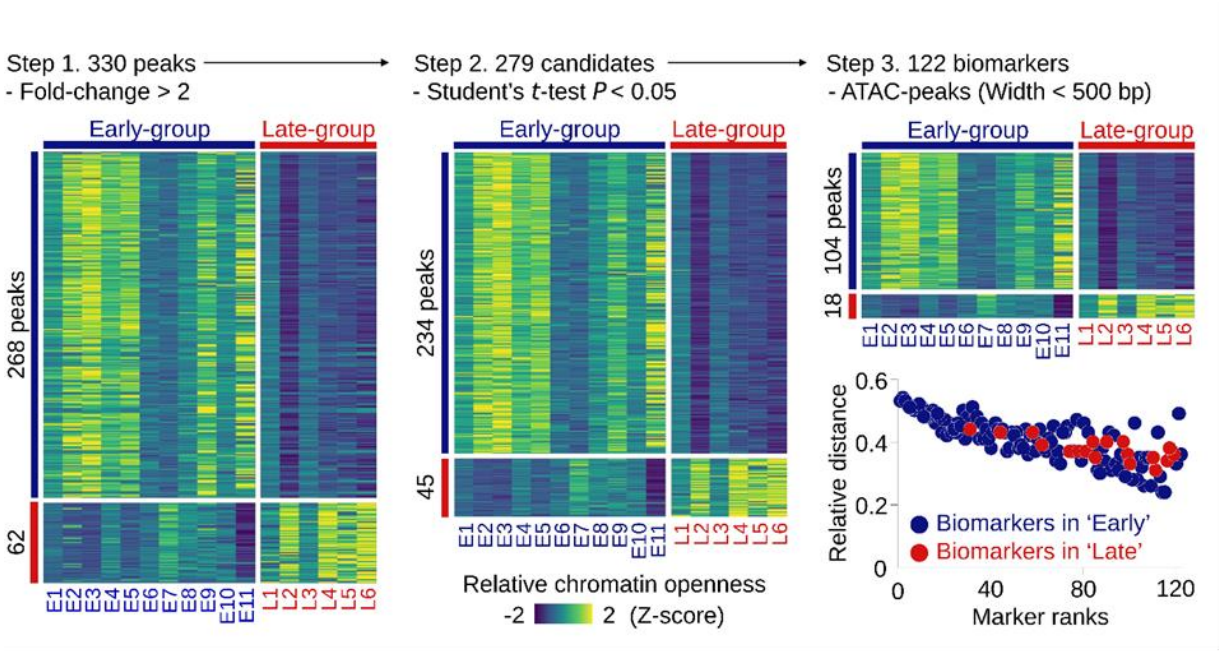
Baseline characteristics

	Early-stage (*n* = 11)	Late-stage (*n* = 6)	P-value
Age years	44.6 ± 9.5	46.7 ± 5.8	0.641
Male (N, %)	6 (54.55)	5 (83.33)	0.512
eGFR at sample (mL/min/1.73m²)	54.2 ± 23.2	18.8 ± 17.0	0.005
eGFR Decline (mL/min/1.73m² per year)	–4.5 ± 4.7	–6.0 ± 3.4	0.513
Average UPCR (g/g)	1.92 ± 1.60	2.79 ± 2.32	0.439
Oxford classification (MEST-C Score)	2.0 ±1.1	1.6 ± 1.0	0.483
serum IgA (mg/dL)	296.0 ± 65.2	405.0 ± 95.4	0.013
Albumin (g/dL)	4.2 ± 0.3	4.0 ± 0.1	0.944
P (mg/dL)	3.4 ± 0.3	4.6 ± 1.0	0.029
K (mmol/dL)	4.6 ± 0.5	5.5 ± 0.7	0.008

Unpublished data

Results

- **Identification of differential chromatin landscapes and stage-specific biomarkers**



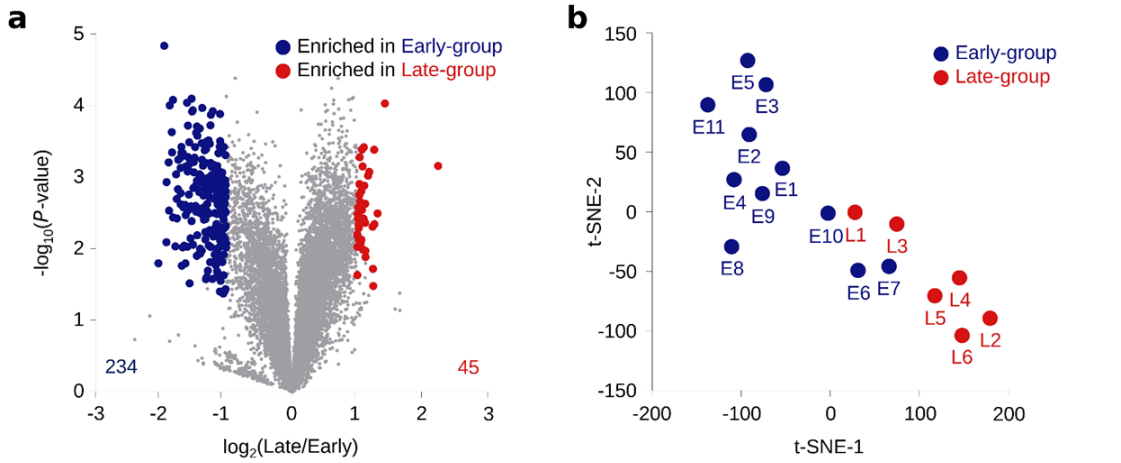
Biomarker selection process by comparing chromatin accessibility between the groups

- 279 differentially accessible regions (DARs) were identified based on a fold-change > 2 and $P < 0.05$
- 122 peaks < 500 base pair in width were classified as potential stage-specific biomarkers and ranked.
- Top-ranked biomarkers were predominantly enriched in early-stage group.

Unpublished data

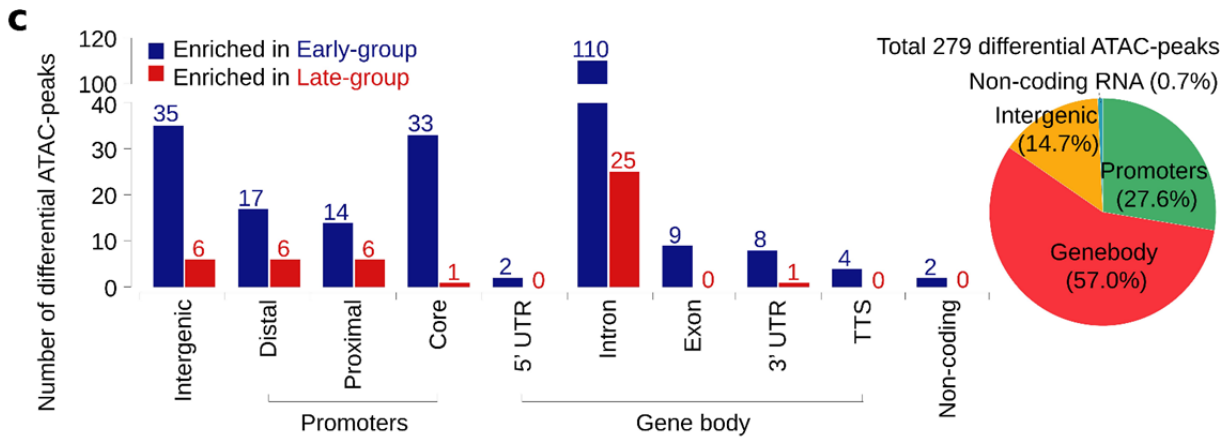
Results

- **Chromatin landscape analysis reveals stage-specific regulatory signatures**



234 DARs were enriched in early-, 45 peaks were enriched in late-stage group; higher overall chromatin accessibility in early-stage group.

Clustering using t-distributed stochastic neighbor embedding (t-SNE) based on normalized ATAC-peak area values revealed clear separation of groups.



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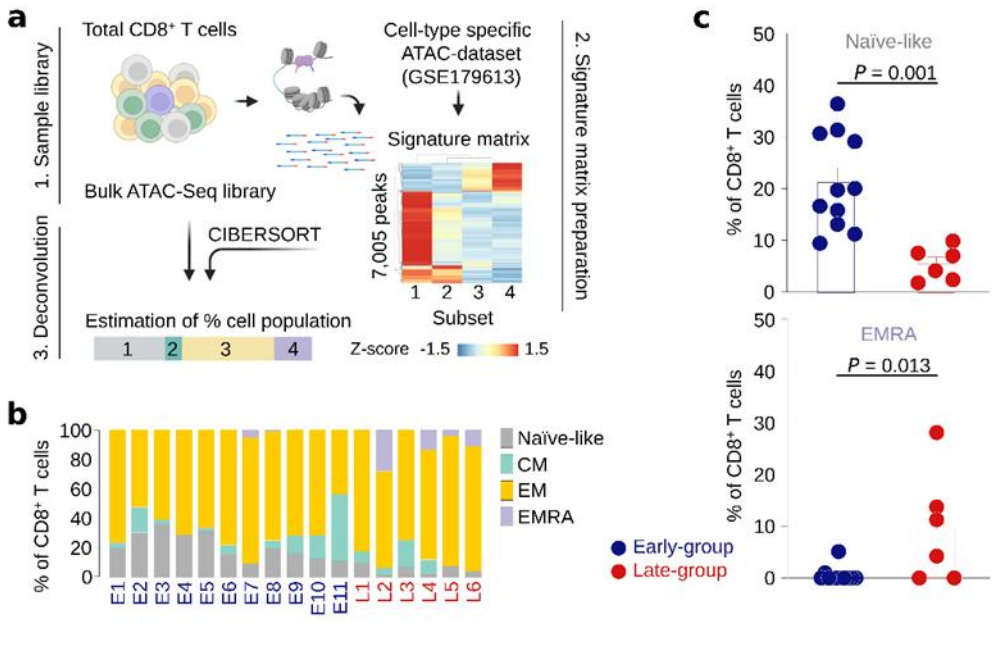
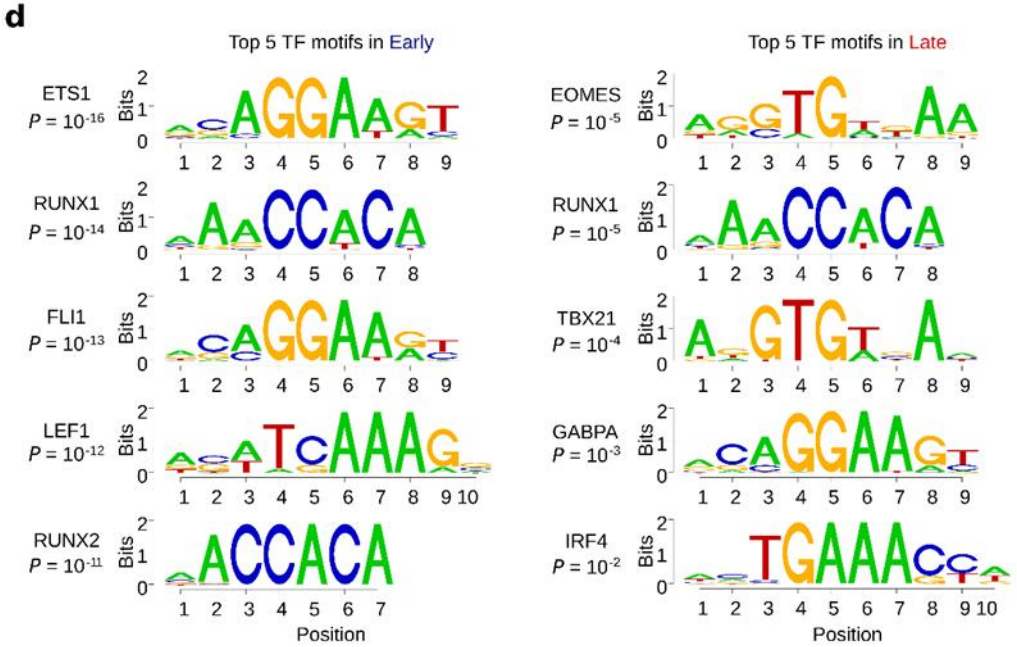
Results

- **CD8+ T-cell subset deconvolution and Transcription factor motif analysis**





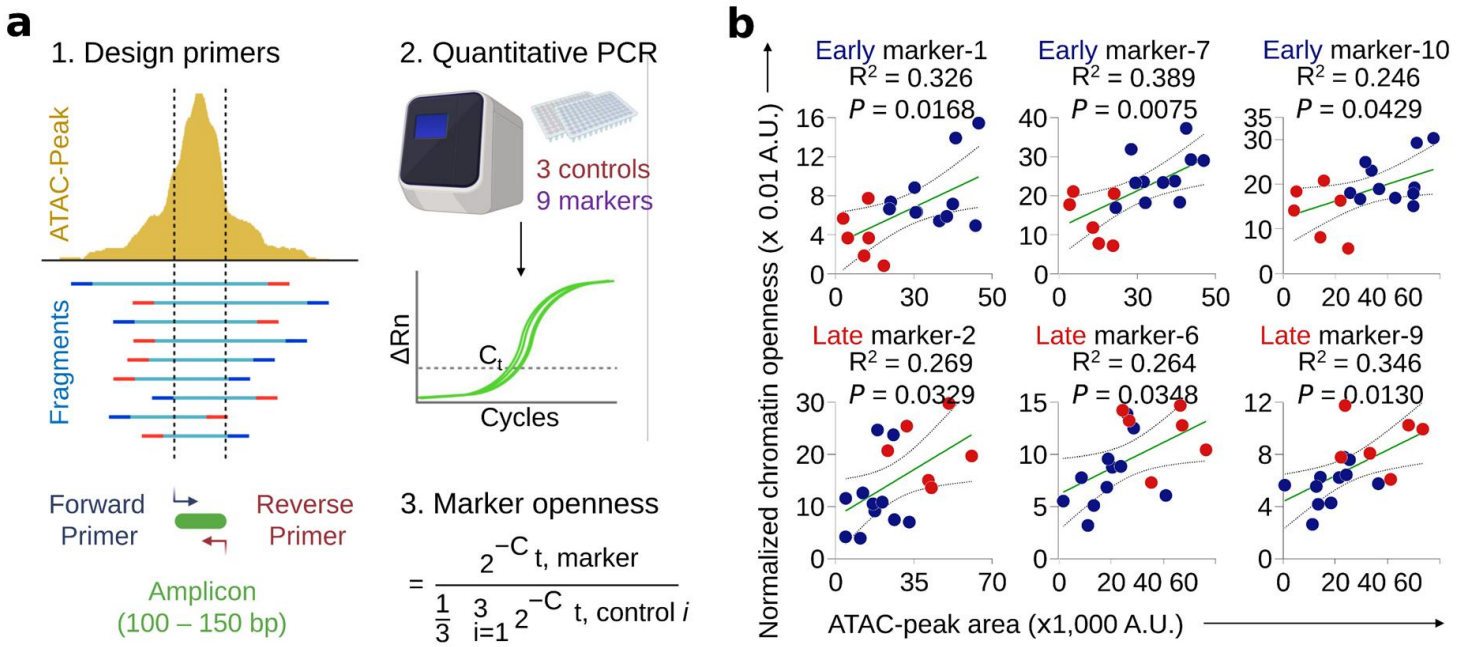
Deconvolution analysis with CIBERSORT
Effector memory cells were the dominant subset
Early; high proportion in naïve CD8⁺ T cells
Late; terminally differentiated EMRA cells

Transcription factor motif analysis
Early : ETS1, LEF1, FLI1, and RUNX2, active cytotoxic regulation
Late : EOMES, TBX21, IRF4, and GABPA, terminal differentiation and exhaustion under chronic immune activation

Unpublished data

Results

- **Exploratory ATAC-qPCR assessment of ATAC-Seq derived biomarkers**



Due to challenges in practical use of ATAC-seq, ATAC-qPCR to simply assess chromatin accessibility

- Require few cells, minimal equipment, lower cost, enable target assessment of specific regulatory loci
- ATAC-qPCR signal showed correlation with ATAC-Seq peak intensities in both early and late group biomarkers

Diagnostic utility of the markers: AUROC values of 0.772 and 0.893 (early), 0.848 to 0.924 (late); good predictive accuracy

The results support ATAC-qPCR as a feasible and translatable tool for assessing disease stage in IgAN

Unpublished data

Conclusion

- The study comprehensively profiled the chromatin accessibility landscapes of circulating $CD8^+$ T cells in IgAN and identified distinct epigenetic signatures associated with disease progression using ATAC-Seq.

- Stage-specific chromatin accessibility profiles showed that early-stage disease characterized by naïve/memory-linked accessibility and late-stage disease showing terminal differentiation and exhaustion signatures.

- 279 DARs, stage-specific distinct patterns of chromatin openness, indicate chromatin accessibility signatures that precede clinical disease progression and offered their utility as discriminatory tools for disease status stratification.

Discussion and limitations

- Peripheral blood sampling was performed at non-uniform time points, introducing possible temporal variability.
- The study population included only Korean patients, limiting generalizability to broader ethnic groups and necessitating validation in diverse cohorts.
- Analyses focused solely on circulating $CD8^+$ T cells, which may not fully capture immune or epigenetic changes occurring within the renal microenvironment.

- Future research with kidney tissue data may be beneficial for the comprehensive understanding.

Thank you for your attention