High Resolution Immune Cell Atlas Reveals Epigenetic Reprogramming in Healthy Human Aging

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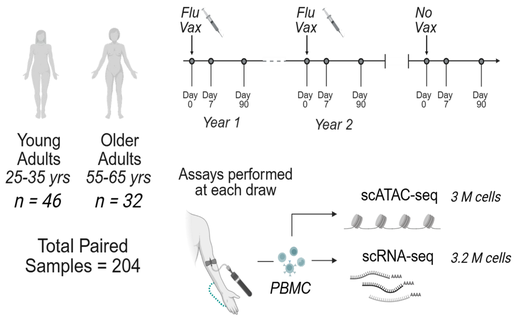
Introduction

Single-cell chromatin accessibility (scATAC-seq) profiles genome-wide regulatory elements that shape immune cell identity and function, but its interpretation is currently limited by low cell type resolution and small reference datasets. Existing datasets annotate fewer than 20 immune cell types and are too coarse to resolve heterogeneity and characterize cell type specific gene regulatory programs and functions. Here, we present a large-scale scATAC-seq resource that substantially improves immune cell annotation and regulatory inference.

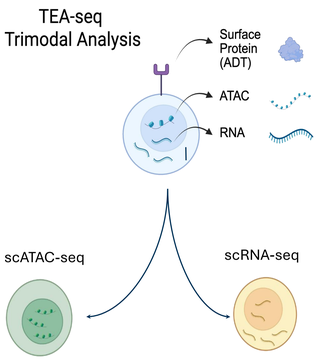
Large-Scale Paired Multimodal Dataset



What questions can we answer?

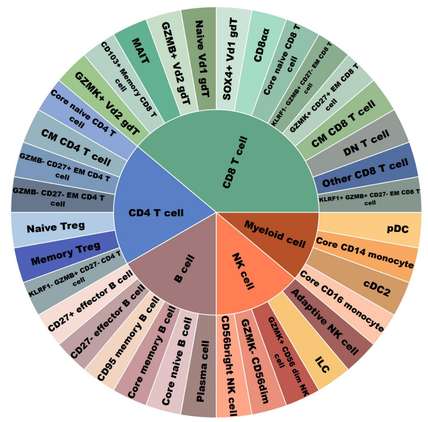
- How do regulatory landscapes and cell function shift with age?
- What regulatory mechanisms are not capture by gene expression?
- How does the epigenetic landscape change following influenza vaccination?
- Are epigenetic responses to vaccination different in younger vs. older individuals?

Fine Grained Cell Labeling via Trimodal Assay



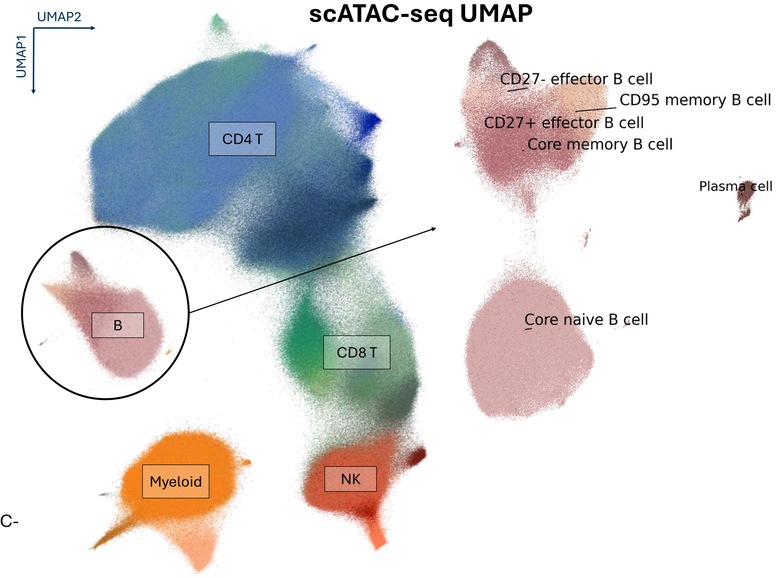
Machine learning framework unifies labeling onto single modality datasets

36 Cell Types in Hierarchy



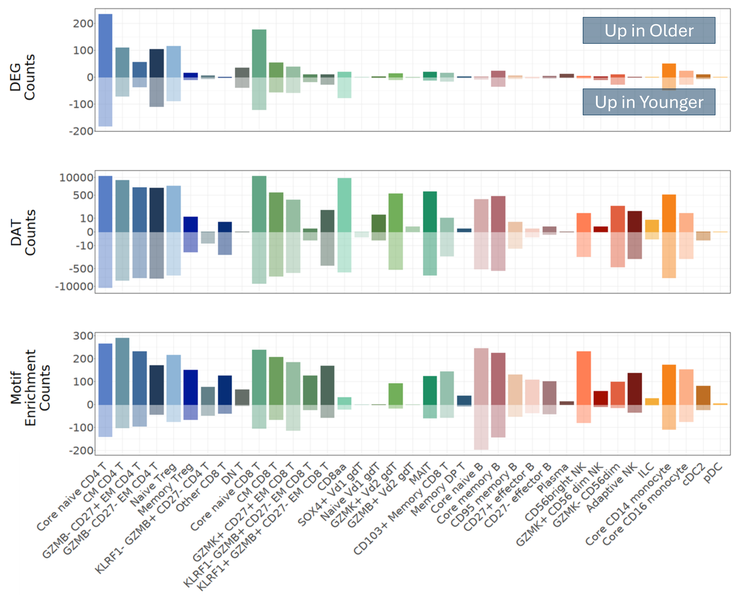
Cell frequencies from published scRNA-seq and new scATAC-seq labelings were highly correlated (median ρ = 0.84)

scATAC-seq UMAP

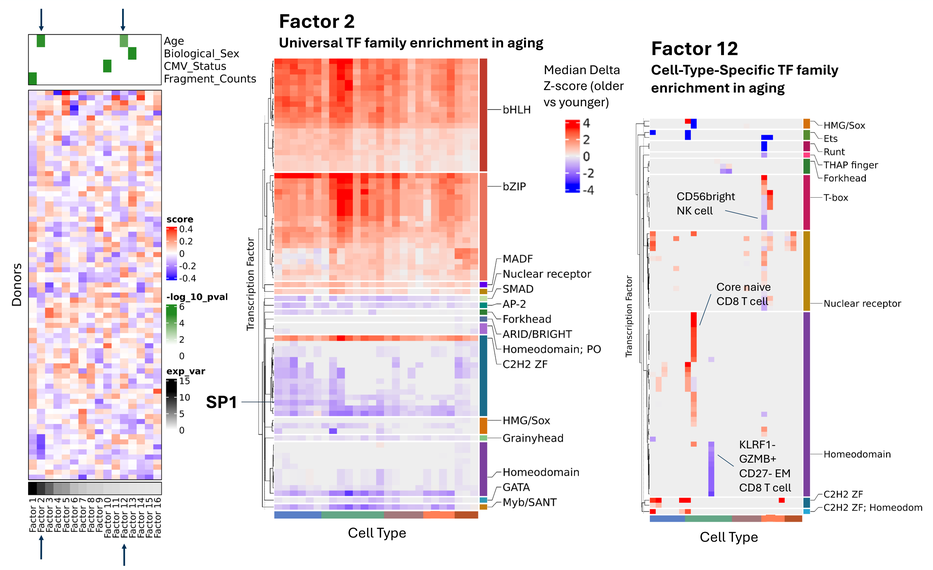


Age-Related Epigenetic Changes Distinct From Gene Expression

Gene expression changes with aging are largely restricted to T cells, however, chromatin accessibility and transcription factor (TF) motif enrichment change broadly across both T and non–T cells, suggesting widespread regulatory reprogramming in healthy aging that may precede or enable future transcriptional shifts.

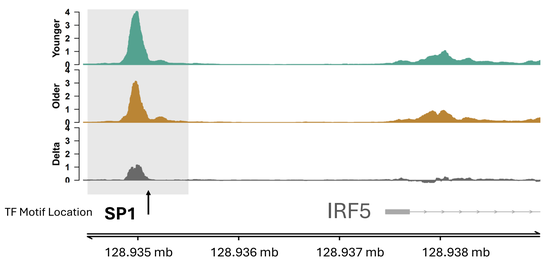


Identification of Universal and Cell-Type-Specific Aging Factors



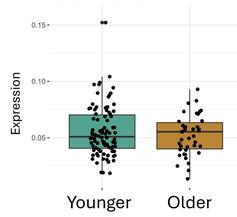
Factor 2, representing ~15% of the variance in motif enrichment, is driven by TFs that are similarly enriched across cell types. Factor 12, accounting for < 5% of variance identifies cell-type-specific TFs.

Age-associated Differential Accessibility at IRF5 Promoter in Core Memory B cell



- Lower accessibility in older adults vs younger within the IRF5 promoter region containing an SP1 TF motif suggests an SP1-mediated regulatory circuit in aging.
- Despite these changes, IRF5 expression remainsz unchanged, indicating potential reduced regulatory responsiveness in memory B cells during aging.

IRF5 Gene Expression
- no difference



References

1. Gong Q, Sharma M, Kuan EL, Glass MC, Chander A, Singh M, et al. Longitudinal Multi-omic Immune Profiling Reveals Age-Related Immune Cell Dynamics in Healthy Adults. Nature. 2025. doi:10.1038/s41586-025-09686-5

2. Zaim, S. R. Pebworth, M.P. *et al.* MOCHA's advanced statistical modeling of scATAC-seq data enables functional genomic inference in large human cohorts. *Nat. Commun.* **15**, 6828 (2024).

Figures created in https://BioRender.com

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Take-Home Message

- **Using a large, paired multi-omic human PBMC atlas, we developed a machine learning model that enabled precise, automated immune cell identification in scATAC-seq data.**
- **We detect age-associated shifts in chromatin accessibility, including universal and cell-type-specific changes in transcription factor activity across many immune cell subsets.**
- **These regulatory changes provide insight into immune aging and disease that precede or are not captured by transcriptional measurements alone.**

Human Immune Health Atlas scRNA here: scATAC data coming soon

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