



P3.310 SLC39A8 (ZIP8) Orchestrates IFN–STAT1–CXCL9/10 Signaling and T Cell Infiltration Through Complete Mediation in Small Cell Lung Cancer



Maki Kimura¹, Masato Inazu^{1,2}, Naoko Tajima¹, Tsuyoshi Yamanaka¹ ¹Department of Preventive Medicine, ²Institute of Medical Science, Tokyo Medical University, Tokyo JAPAN.
Correspondence: inazu@tokyo-med.ac.jp

INTRODUCTION



- Small cell lung cancer (SCLC) is an immune-cold malignancy with limited response to immune checkpoint inhibitors (ICIs). The molecular mechanisms underlying immune exclusion remain incompletely understood. [1]
- SLC39A8 (ZIP8) is a zinc transporter that mediates Zn²⁺ uptake, which is essential for IFN–STAT1 signaling, CXCL9/10 expression, and effective T-cell immune responses. [2,3]
- We hypothesized that ZIP8 is selectively suppressed in SCLC tumor cells while retained in immune cells, thereby contributing to impaired T-cell recruitment through disruption of the IFN–STAT1–CXCL9/10 axis.

METHODS



- Datasets
- GSE149180 (scRNA-seq)
 - GSE60052 (bulk RNA-seq)
 - cBioPortal (n = 77)



- Analyses
- Differential expression
 - Cell-type specificity
 - Correlation analysis
 - Survival analysis
 - Mediation analysis
 - DPT pseudotime
 - TF activity

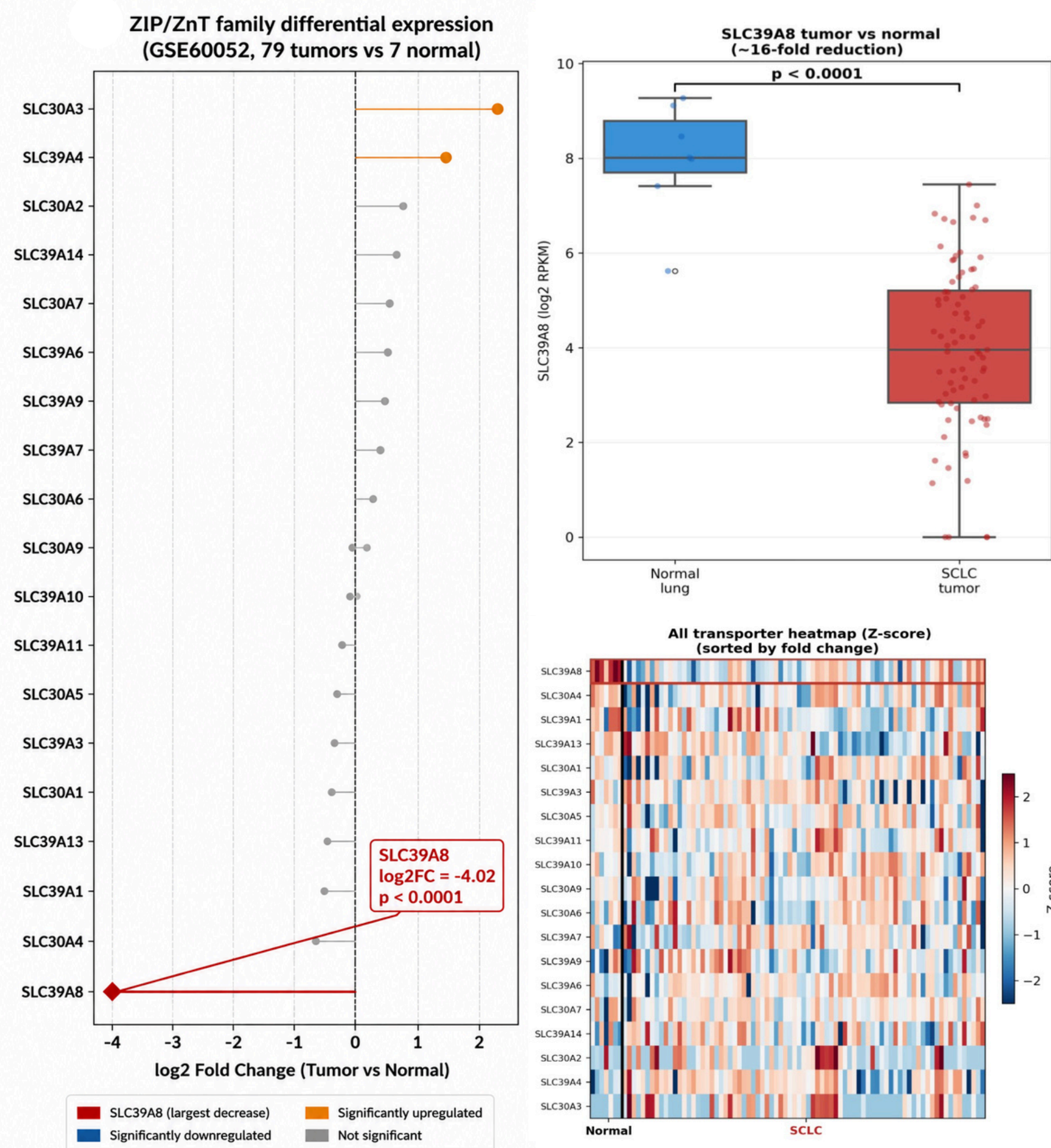
DESIGN



Multi-cohort integrative analysis combining bulk RNA-seq, scRNA-seq, clinical cohorts, mediation analysis, DPT pseudotime, and TF activity to investigate the role of ZIP8 in SCLC immune regulation.

RESULTS

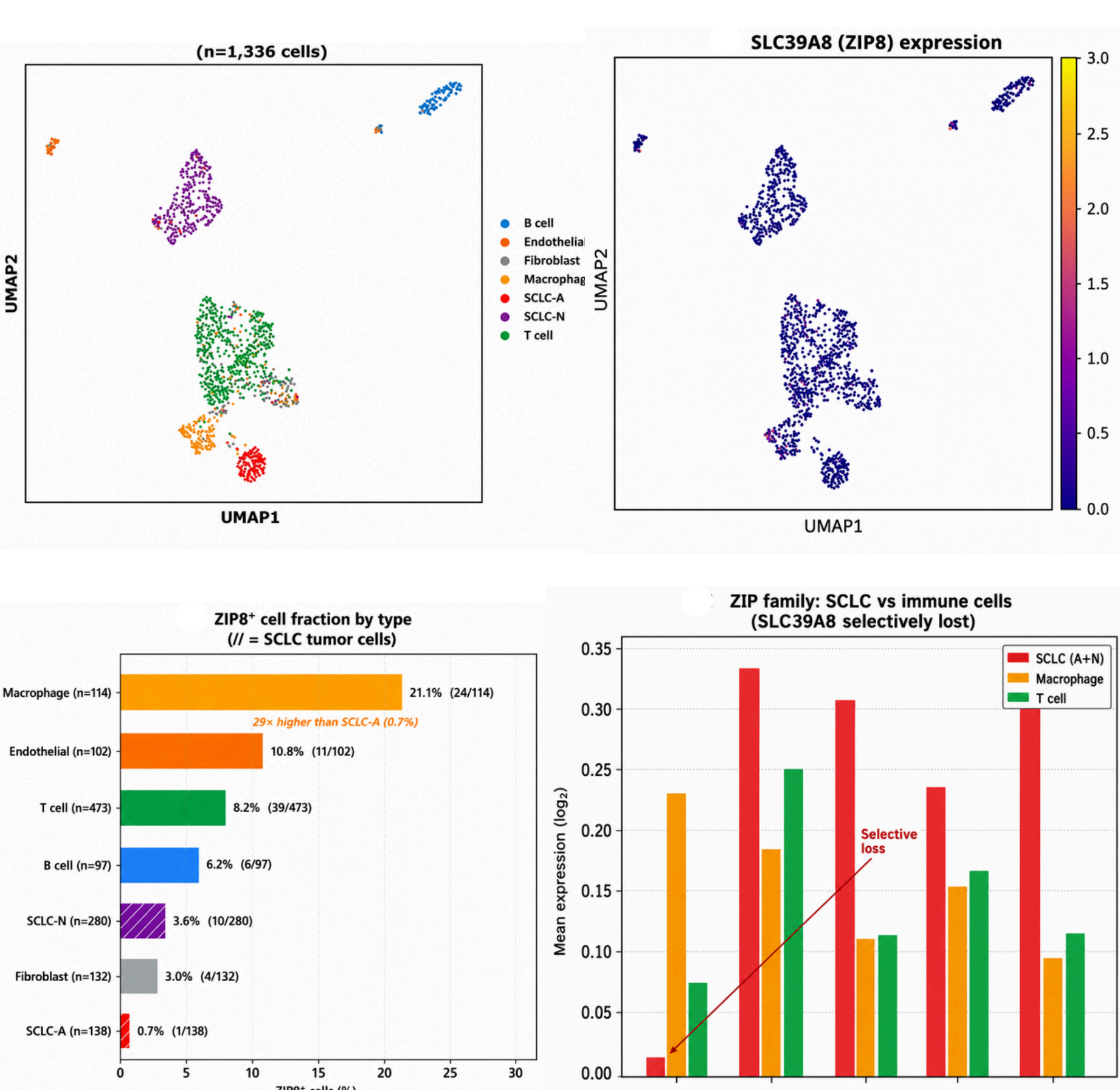
1. SLC39A8 is the most profoundly downregulated zinc transporter in SCLC (bulk RNA-seq)



SLC39A8 shows the largest reduction (log₂FC = -4.02, p < 0.0001; ~16-fold) across all ZIP/ZnT members.

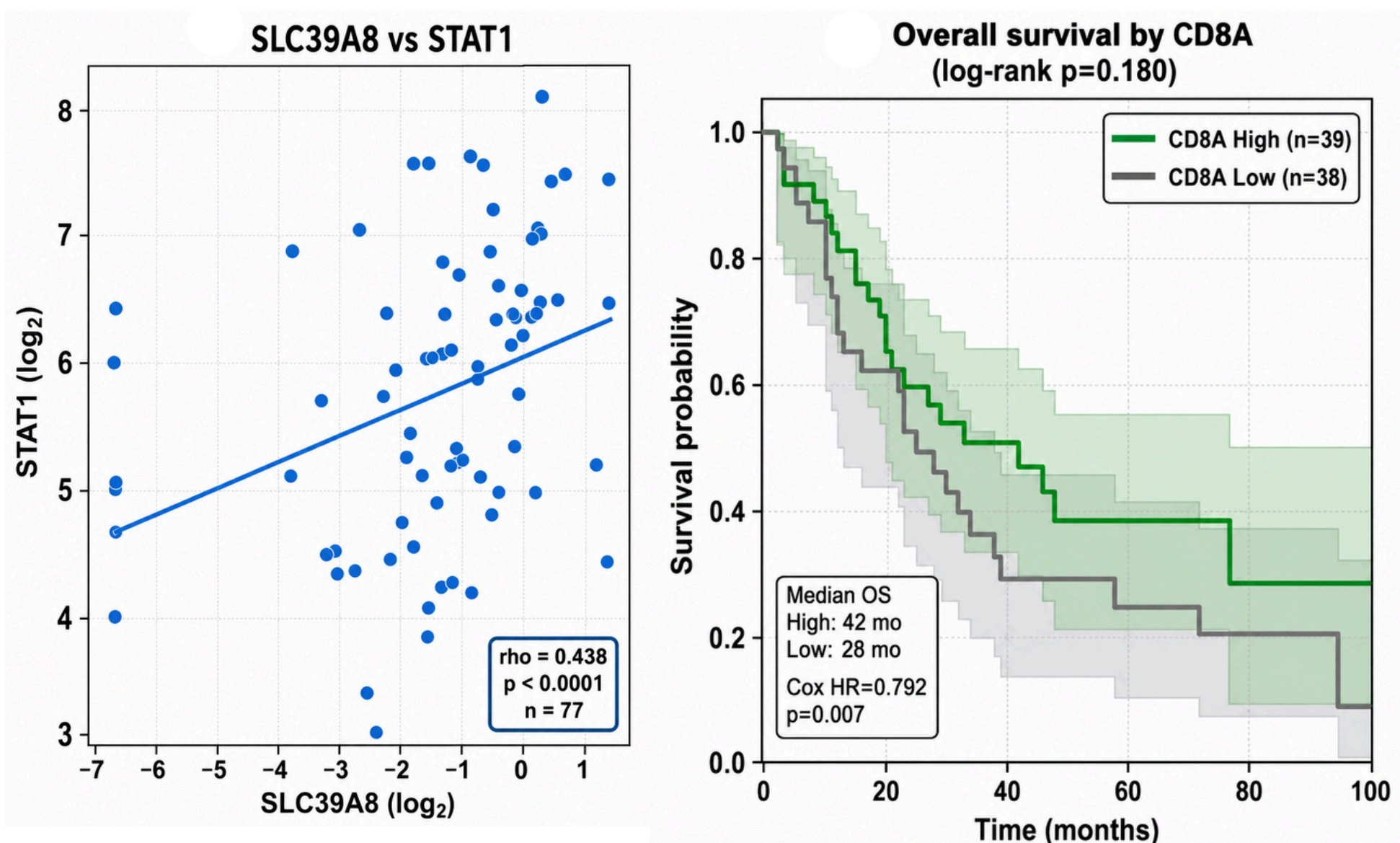
Note: This panel reflects bulk tumor tissue analysis (GSE60052). It represents overall reduction in ZIP8 expression in SCLC tumors, not cell-type-specific effects.

2. Single-cell RNA sequencing reveals selective exclusion of ZIP8 from SCLC tumor cells (scRNA-seq)



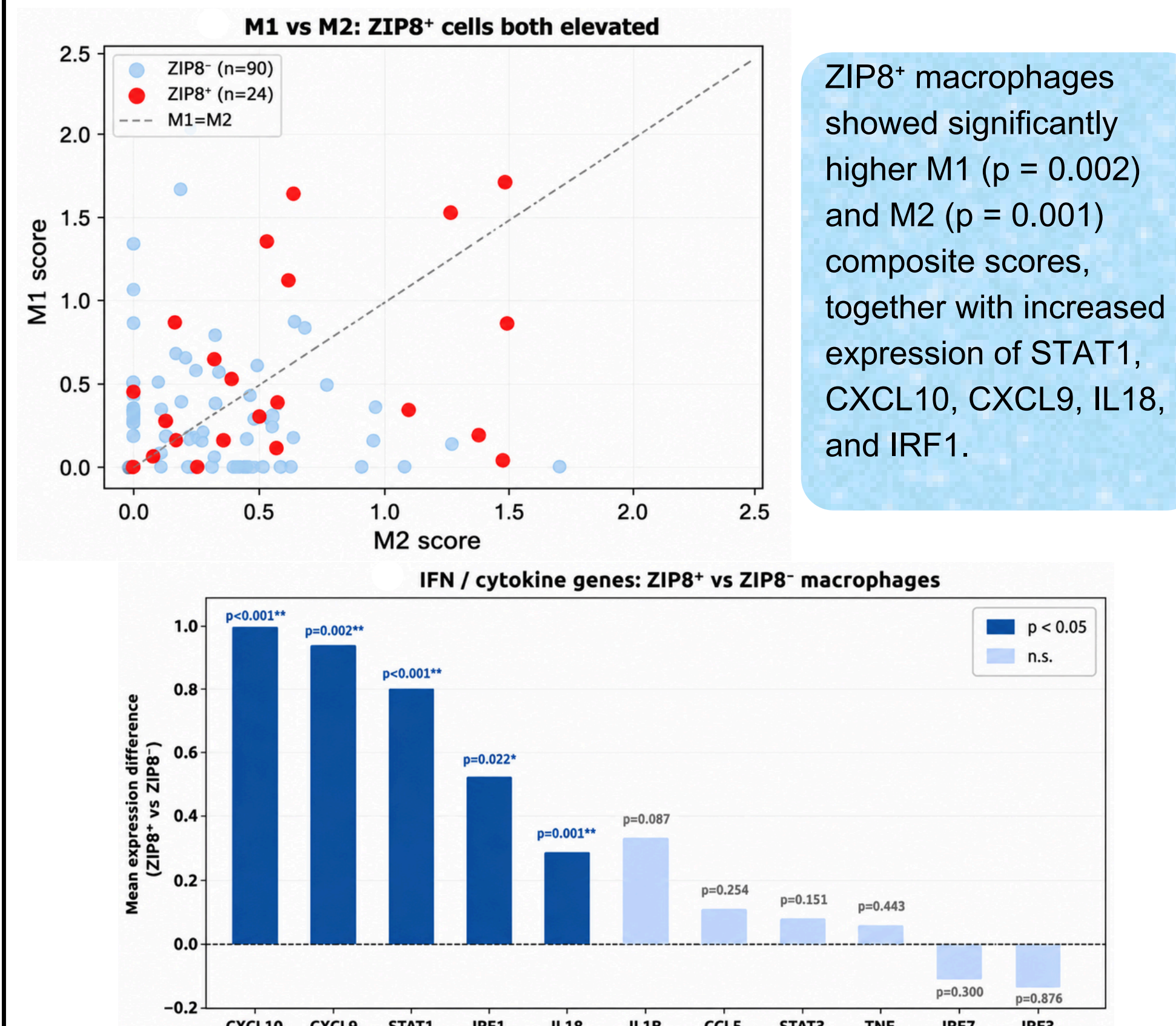
ZIP8 is almost absent in tumor cells (0.7% in SCLC-A), but abundant in macrophages (21.1%) and T cells (8.2%). This panel is independent from bulk RNA-seq and demonstrates cell-type-specific exclusion of ZIP8 in tumor cells.

3. SLC39A8 is associated with IFN–STAT1 signaling and T cell effector activity

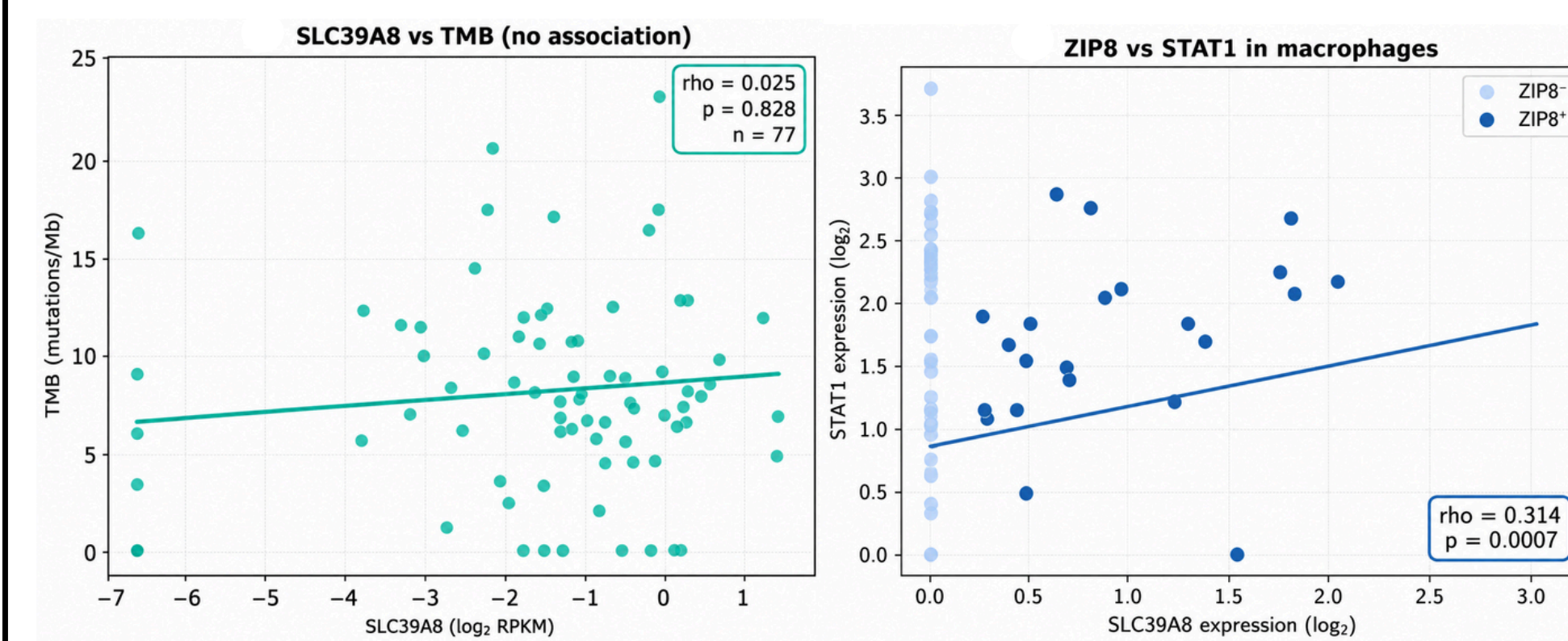


CD8A high expression was associated with favorable OS in Cox regression (HR = 0.792, p = 0.007), although the log-rank test was not significant (p = 0.180).

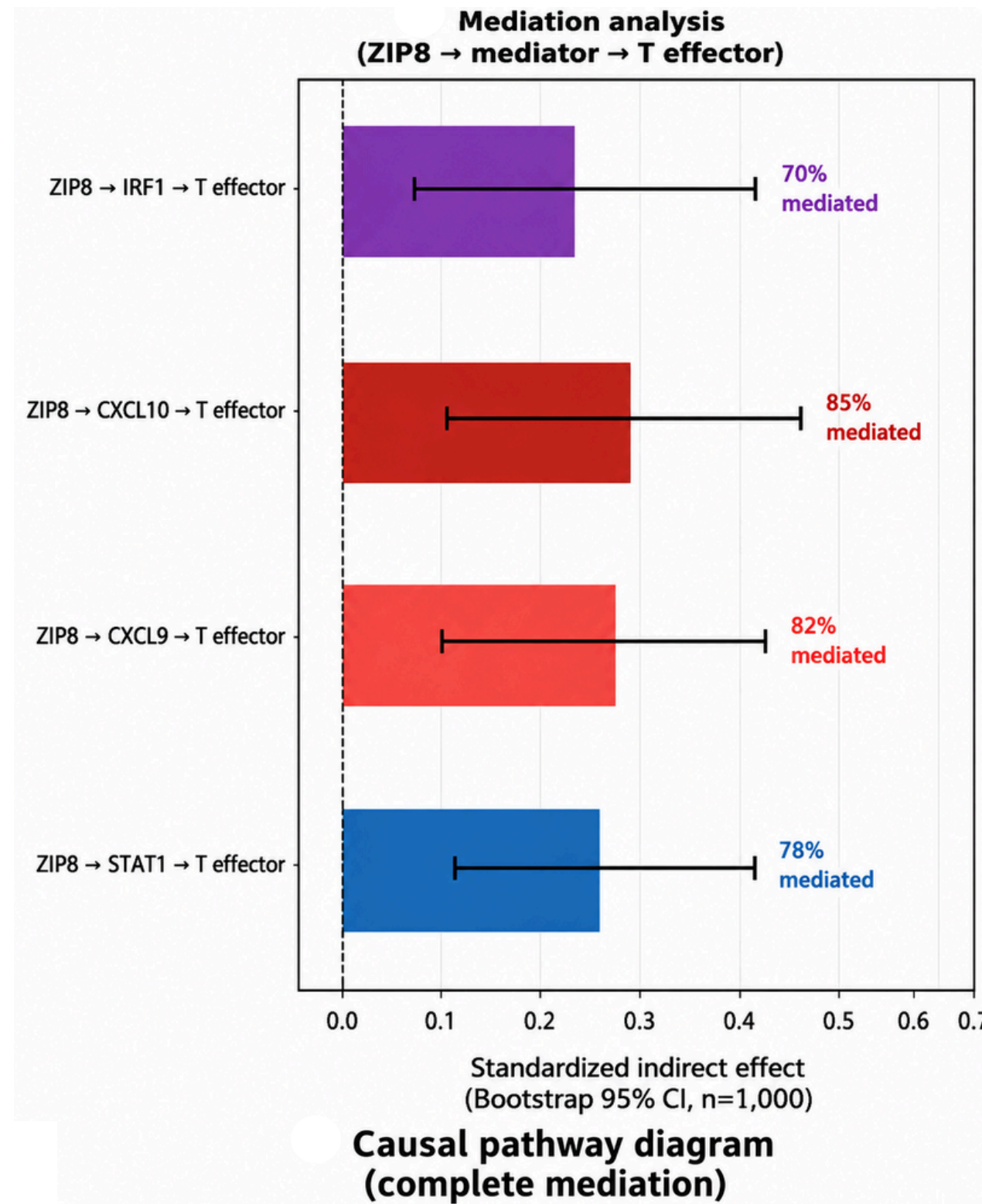
4. ZIP8-positive macrophages exhibit enhanced immune activation without association with tumor mutational burden



SLC39A8 showed no association with TMB (rho = 0.025, p = 0.828) confirming that ZIP8 loss is an intrinsic epigenetic event independent of genomic instability.



5. Bootstrap mediation analysis demonstrates complete mediation via the IFN–CXCL9/10 axis

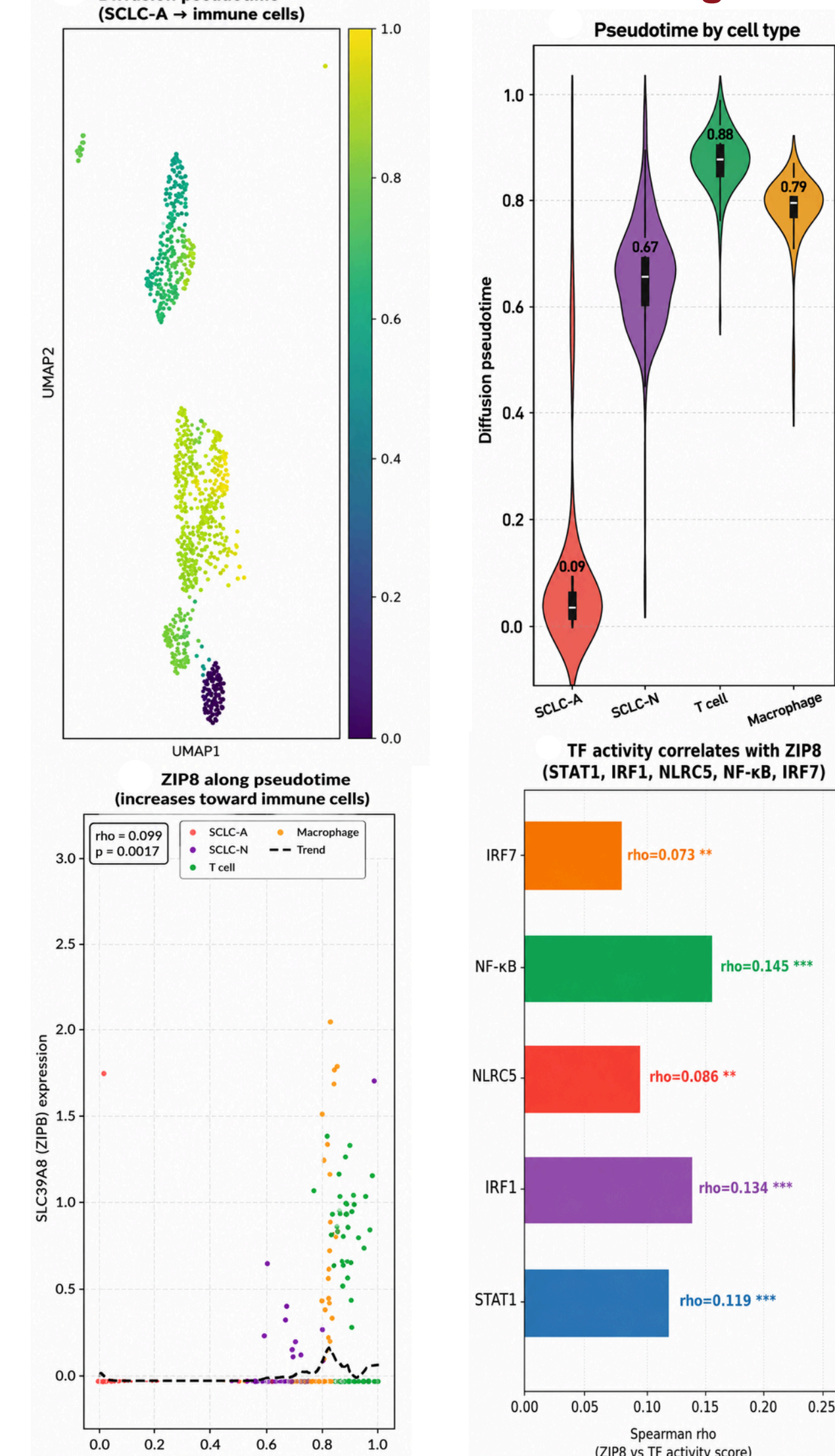


Bootstrap mediation analysis demonstrated significant indirect effects for CXCL10, CXCL9, STAT1, and IRF1. Mediation proportions were 84.5%, 81.8%, 78.0%, and 70.0%, respectively.

All four mediators showed significant indirect effects (bootstrap 95% CI excluding zero). Direct effects were non-significant in all four models (p = 0.13–0.38), confirming complete mediation.

Note: ZIP8 regulates T cell effector activity through STAT1/IRF1–CXCL9/10 signaling.

6. Diffusion pseudotime and TF activity establish ZIP8 as an apex immune regulator

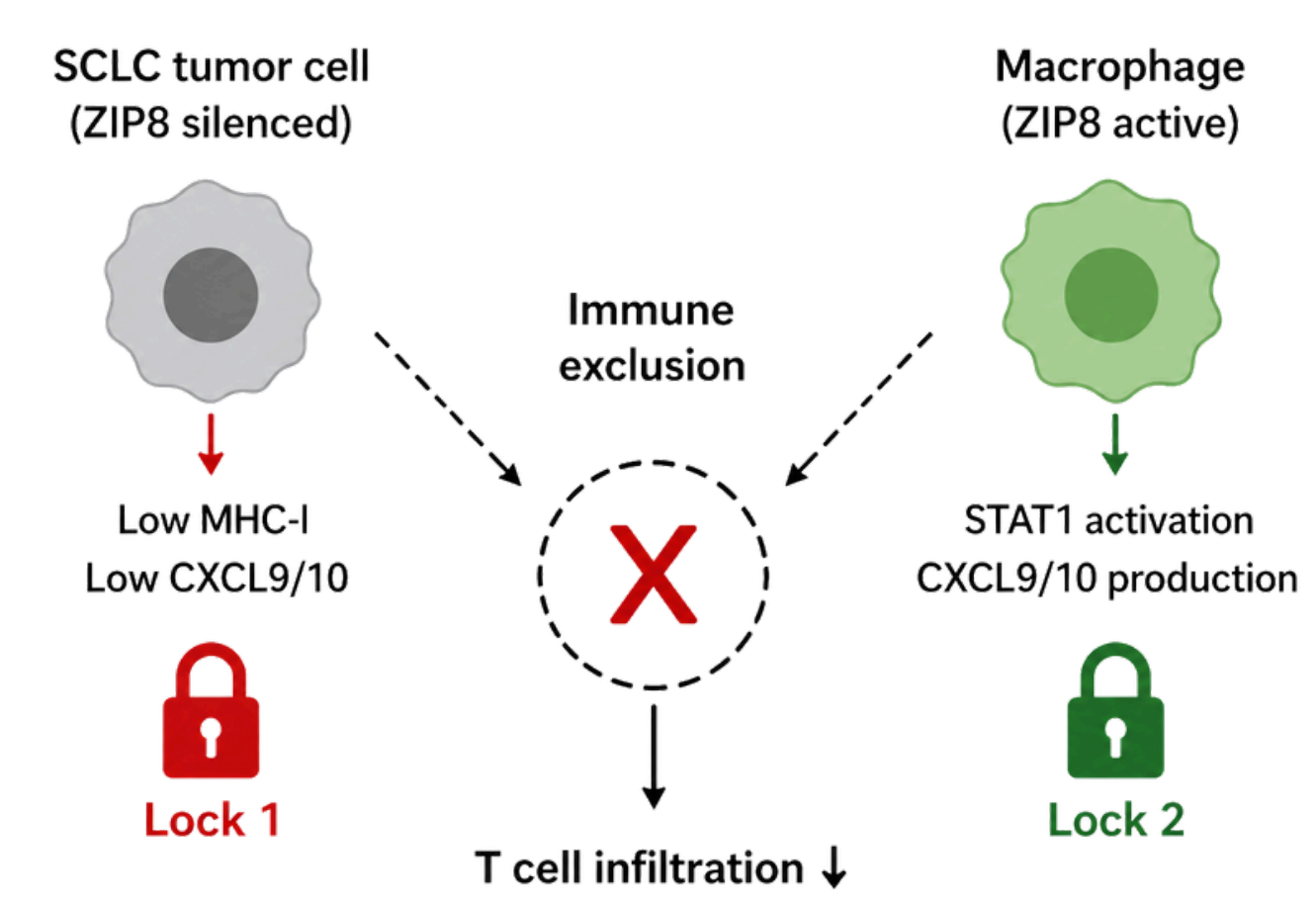


DPT analysis established a clear developmental trajectory: SCLC-A (mean PT = 0.086) → SCLC-N (0.670) → Macrophage (0.790) → T cell (0.878). SLC39A8 expression increased along the trajectory (rho = +0.099, p = 0.002). TF activity scoring demonstrated that STAT1, IRF1, NLRCS, NF-kB, and IRF7 all positively correlated with SLC39A8 (all p < 0.001).

ZIP8 sits at the apex of a broad immune regulatory network.

DISCUSSION AND CONCLUSION

Double-lock immune evasion model in SCLC



Key Conclusions

- SLC39A8 (ZIP8) is the most downregulated zinc transporter in SCLC.
- ZIP8 is selectively excluded from tumor cells but enriched in macrophages and T cells.
- ZIP8 sustains IFN–STAT1–CXCL9/10 signaling and T cell effector activity.
- Bootstrap mediation analysis demonstrates that the association of ZIP8 with T cell infiltration is consistent with mediation via CXCL9/10–STAT1–IRF1.
- Pseudotime and TF activity analyses position ZIP8 as the apex of the immune activation trajectory.

Actionable Take Away Message

Targeting the ZIP8–STAT1–CXCL9/10 axis may overcome immune evasion and sensitize SCLC to ICI therapy.

Future Directions

- Validate ZIP8 modulation in preclinical models.
- Explore combination strategies with ICIs.
- Identify epigenetic mechanisms silencing ZIP8 in tumor cells.
- Develop ZIP8 activators or zinc delivery approaches.

ACKNOWLEDGEMENTS

We thank all patients and investigators who contributed data to the public datasets used in this study.

AI USE DISCLOSURE

Claude (Anthropic) assisted with bioinformatics research and code generation. ChatGPT (OpenAI) assisted with literature searching, layout, and language editing. All analyses, interpretations, and conclusions are the sole responsibility of the authors. All scientific content was independently reviewed and approved by the authors.

REFERENCES

- Horn L, et al. First-line atezolizumab plus chemotherapy in extensive-stage SCLC. N Engl J Med. 2018;379:2220–2229.
- Nebert DW, Liu Z. SLC39A8 gene encoding a metal ion transporter. Hum Genomics. 2019;13:51.
- Kim B, Lee WW. Regulatory Role of Zinc in Immune Cell Signaling. Mol Cells. 2021;44:335–341.