

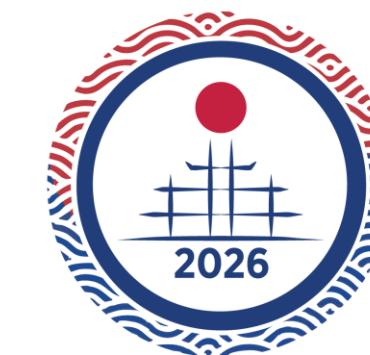


Single-Cell Profiling Identifies a Highly Metastatic Tumor Subpopulation in Early Lung Adenocarcinoma

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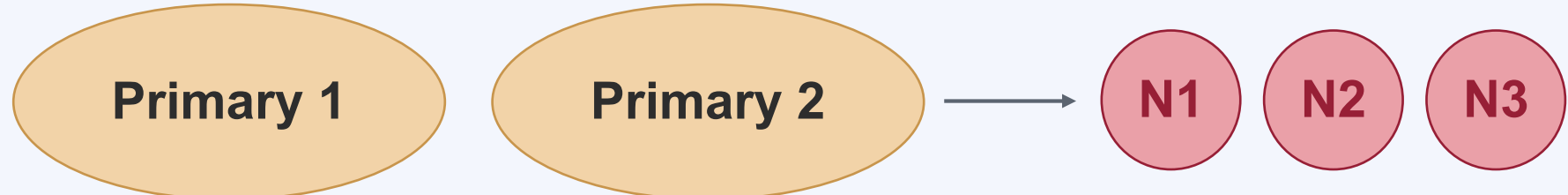
INTRODUCTION

- Small solid-predominant pulmonary nodules may appear radiologically early, yet biologic behavior can be discordant.
- This case showed widespread N1, N2 and N3 lymph-node involvement despite apparently early primary lesions.
- Objective: define the cellular basis of this clinical-radiologic discordance using single-cell RNA sequencing.

INDEX CASE AND SAMPLING

n = 1 patient

Two primary LUAD lesions and matched nodal metastases



Normal lung epithelial cells were incorporated as a reference for trajectory analysis.

ANALYTICAL WORKFLOW

- 1 scRNA-seq and quality control
- 2 Cell-type annotation
- 3 Malignant epithelial subclustering
- 4 Primary-versus-nodal comparison
- 5 Pseudotime trajectory with normal epithelium
- 6 Differential expression and functional enrichment

STUDY SCOPE AND LIMITATIONS

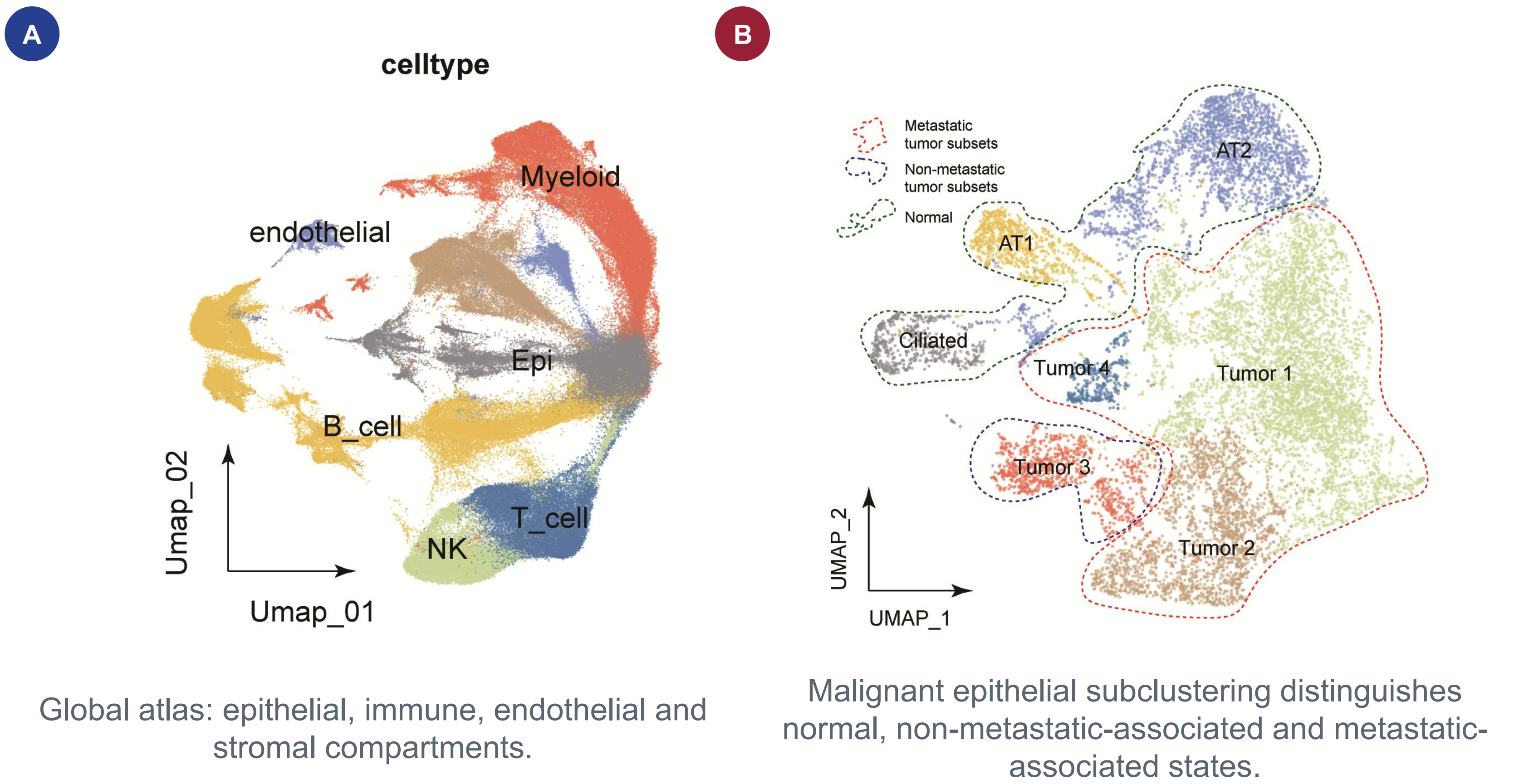
- Single-patient design: no population-level inference.
- Cross-sectional scRNA-seq and pseudotime do not establish clonal ancestry, temporal sequence or causality.
- Cell-level observations are descriptive because the patient is the biological unit.
- Independent cohort, spatial and perturbation validation are required.

References

- [1] Kim N, Kim HK, Lee K, et al. Single-cell RNA sequencing demonstrates the molecular and cellular reprogramming of metastatic lung adenocarcinoma. Nat Commun. 2020;11(1):2285.
- [2] Lambrechts D, Wauters E, Boeckx B, et al. Phenotype molding of stromal cells in the lung tumor microenvironment. Nat Med. 2018;24(8):1277-1289.

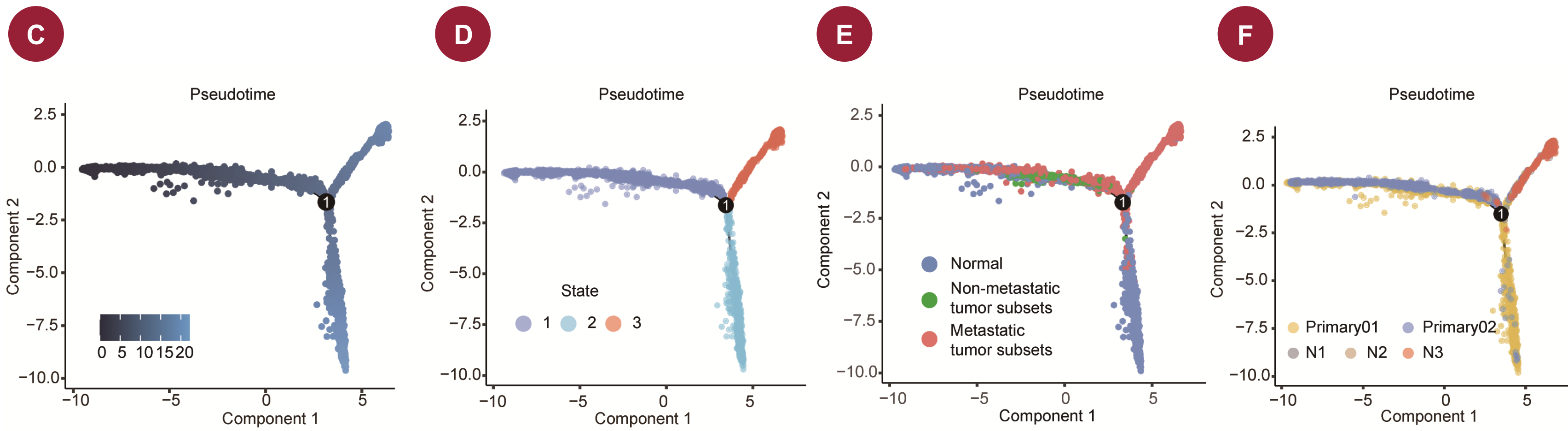
RESULT 1 | MALIGNANT EPITHELIAL HETEROGENEITY

Primary lesions contained biologically distinct malignant epithelial subpopulations.

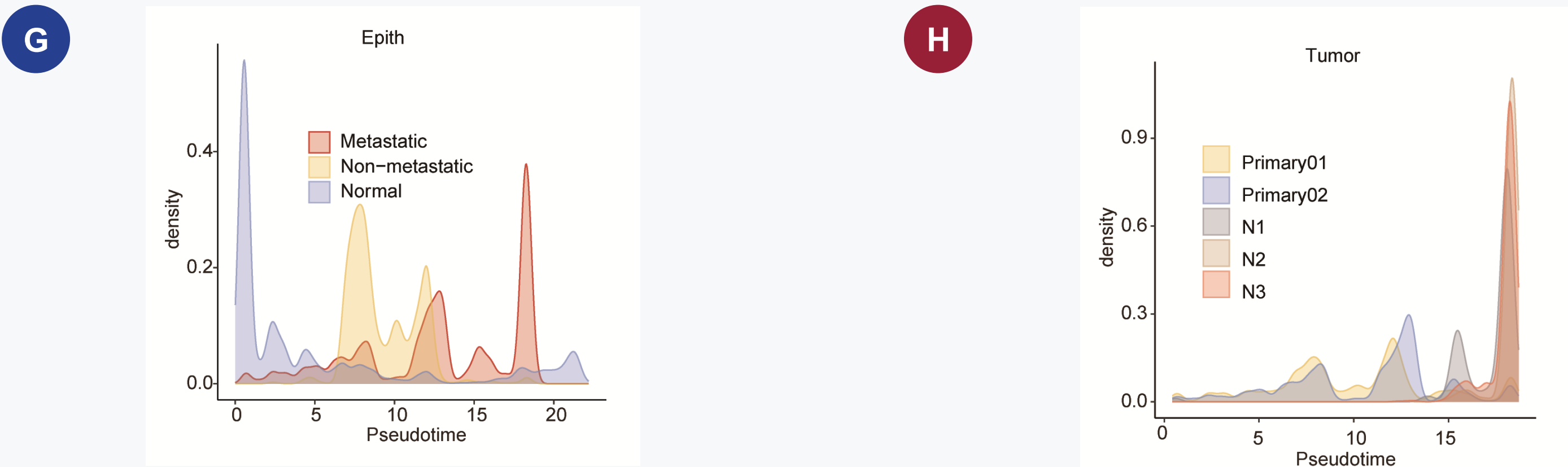


RESULT 2 | DIVERGENT TRANSCRIPTIONAL TRAJECTORIES

Pseudotime analysis suggested a divergent branch toward the metastatic-associated tumor state.



Normal epithelium, non-metastatic-associated states and metastatic-associated states occupied distinct positions along the inferred trajectory.

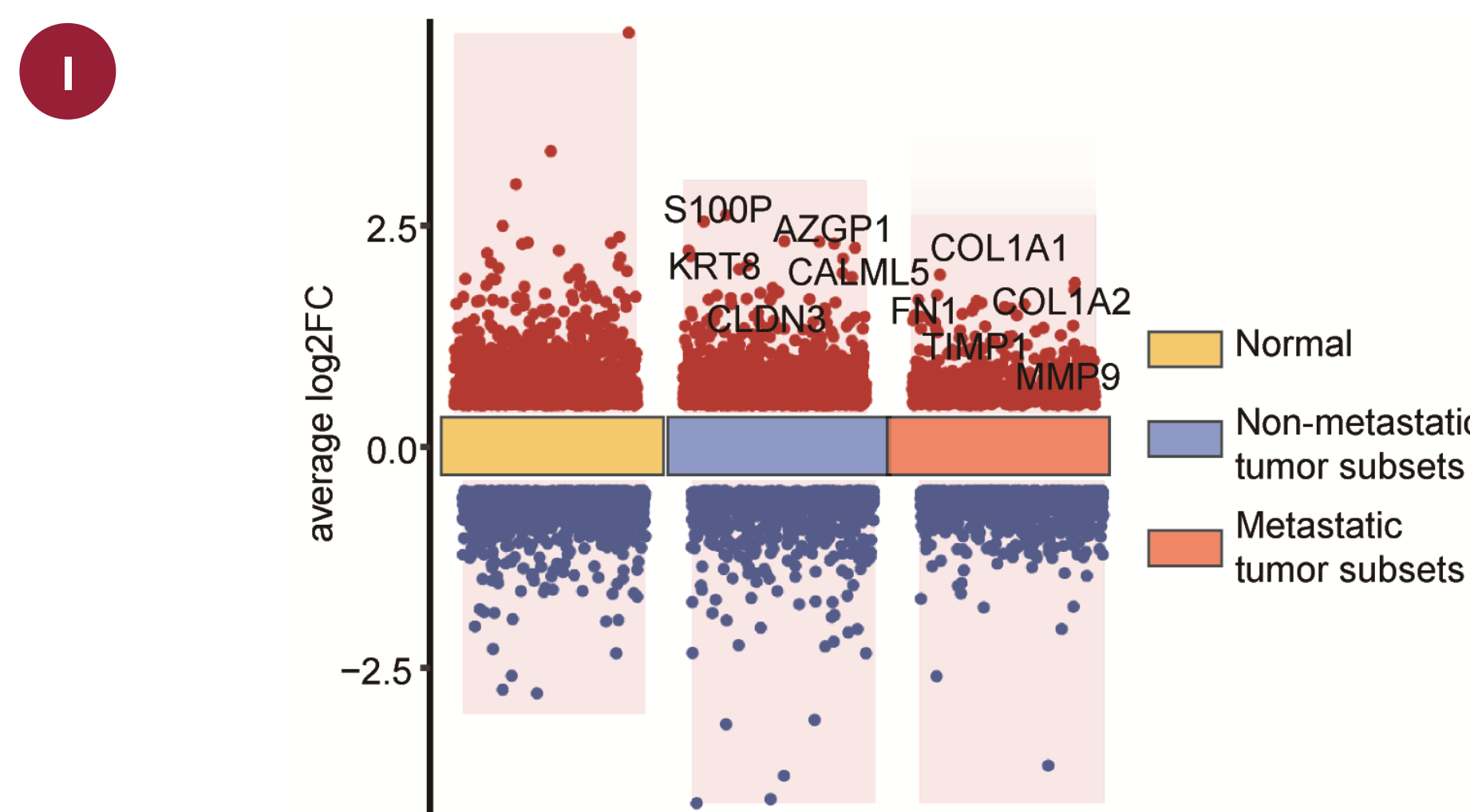


Epithelial states along pseudotime

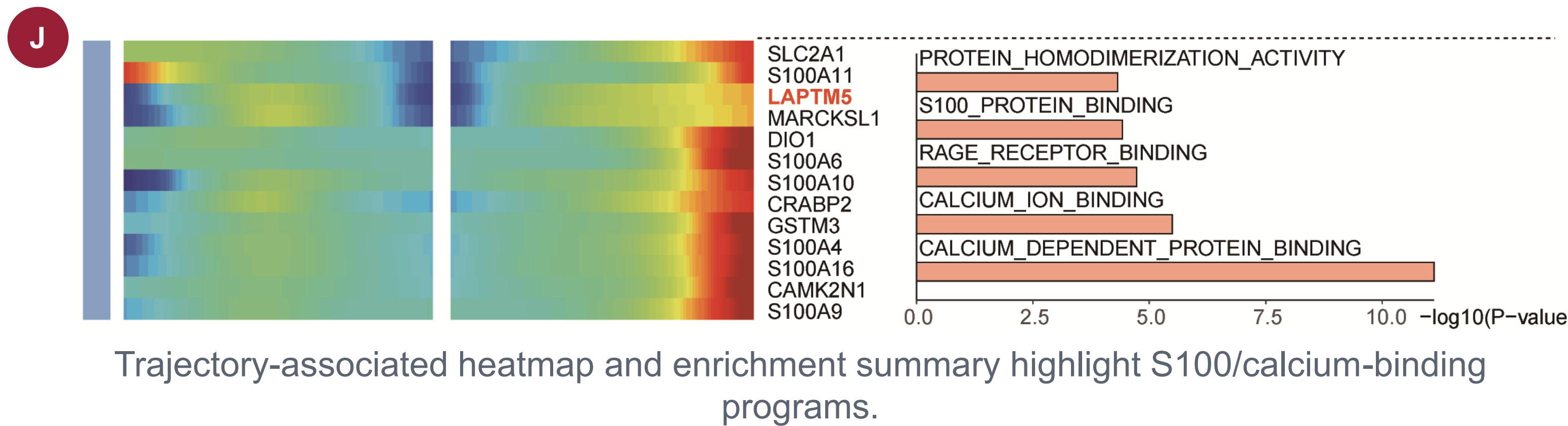
Primary and N1/N2/N3 site distribution

RESULT 3 | METASTASIS-ASSOCIATED TRANSCRIPTIONAL PROGRAM

The nodal-enriched state was associated with S100-family and calcium-binding programs.



Metastatic-associated tumor states showed increased S100-family and matrix-related signals.



UPREGULATED ALONG THE TRAJECTORY

S100A4
S100A6
S100A9
S100A10
S100A11
S100A16

ENRICHED FUNCTIONS

- Calcium ion binding
- S100 protein binding
- Calcium-dependent protein binding

DISCUSSION AND CONCLUSION

Core finding

Single-patient, multi-site scRNA-seq identified a malignant epithelial state present in the primary lesions and markedly enriched across N1, N2 and N3 nodal metastases.

Interpretation

This state was linked to S100-family and calcium-binding transcriptional programs; the data support association, not causal metastatic function.

Take-away: this case illustrates that radiologic earliness may not guarantee biologic indolence. Findings are hypothesis-generating and require independent validation.