

Integrated Tumor Transcriptomic and Methyloomic Profiling Reveals Biomarkers Associated With Occult Lymph Node Metastasis in Resectable NSCLC

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INTRODUCTION

Lymph-node involvement is a major determinant of staging, treatment and prognosis in resectable non-small cell lung cancer (NSCLC), yet occult nodal disease may remain undetected before surgery.

- Transcriptomic programs can reveal tumor proliferation, immune context and metastatic potential.
- DNA methylation is stable, measurable in tissue and potentially transferable to circulating cell-free DNA.
- Integrating both layers may improve the biological and predictive characterization of nodal metastasis.

Objective: identify tumor transcriptomic and methyloomic biomarkers associated with pN1/pN2 disease and evaluate their potential for pre-operative plasma-based prediction.

Primary comparison

Node-positive (pN1/pN2) versus pN0 tumors.

Working hypothesis

Coordinated transcriptional and epigenetic signals identify occult nodal metastasis.

METHODS

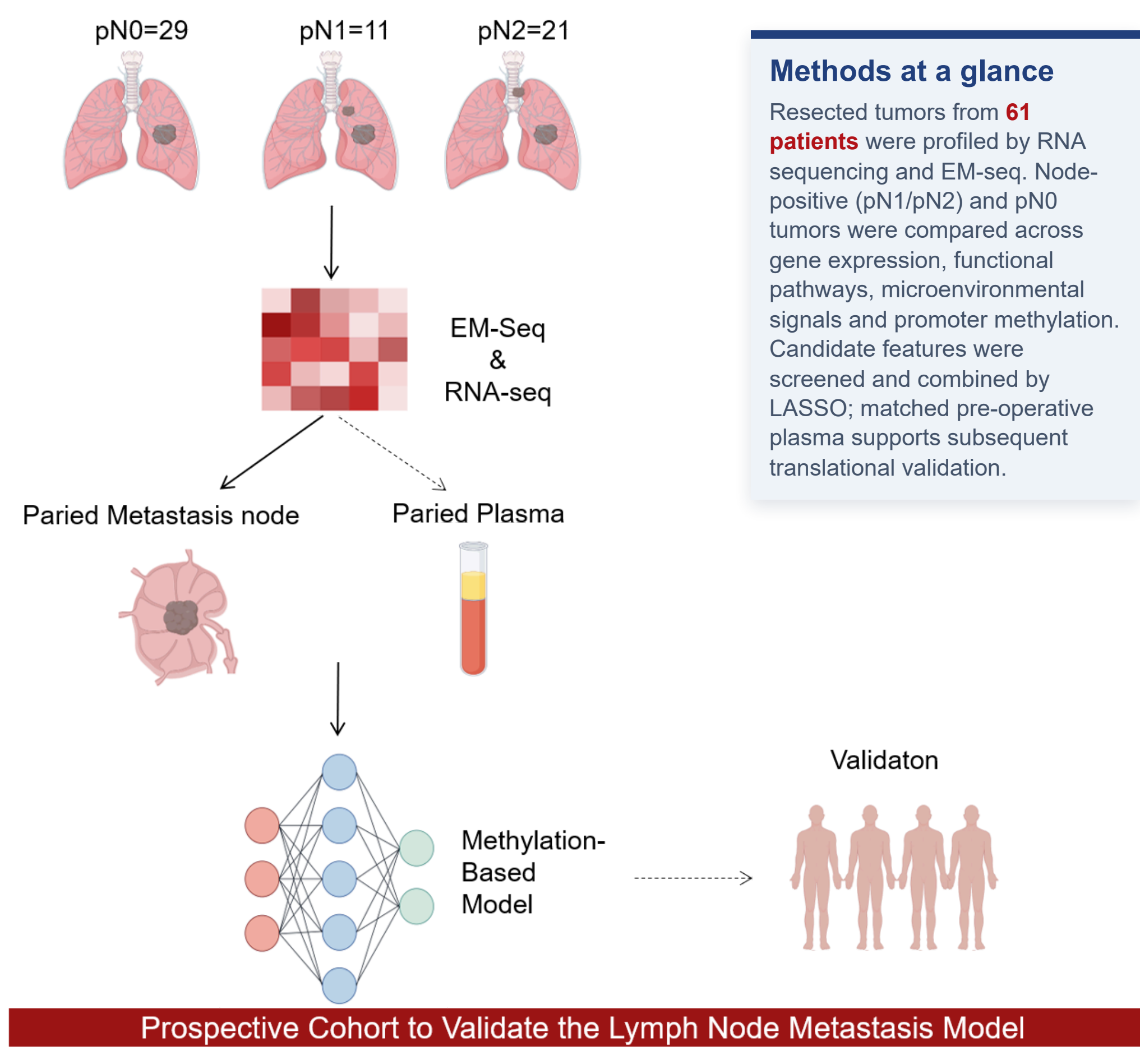


Figure 1. Study design. Tumor multi-omics discovery followed by paired nodal/plasma assessment and prospective validation.

Study cohort

61 resectable NSCLC patients: pN0, n=29; pN1, n=11; pN2, n=21. All pN2 cases involved mediastinal nodes.

Multi-omics assays

Tumor mRNA sequencing plus enzymatic methyl-seq (EM-seq), with matched pre-operative plasma for translational evaluation.

Primary comparison

Node-positive disease (pN1/pN2) versus pN0. Differential expression threshold: $|\log_2FC| > 1$ and $p < 0.05$.

Prediction strategy

Feature-level AUC analysis, univariable regression screening and LASSO classification for nodal-metastasis prediction.

1 Expression

Differential genes and pathway enrichment

2 Microenvironment

Immune, myeloid and stromal enrichment scores

3 Methylation

Regional beta values and gene-expression correlation

4 Modeling

Screened features followed by LASSO and ROC analysis

RESULTS

Transcriptomic differences (Figs. A–B)

Node-positive tumors showed 91 increased genes, including SPP1 and COL11A1, whereas 156 genes were higher in pN0 tumors; SUSD2 was a representative pN0-associated signal.

Functional and microenvironmental context (Figs. A, C)

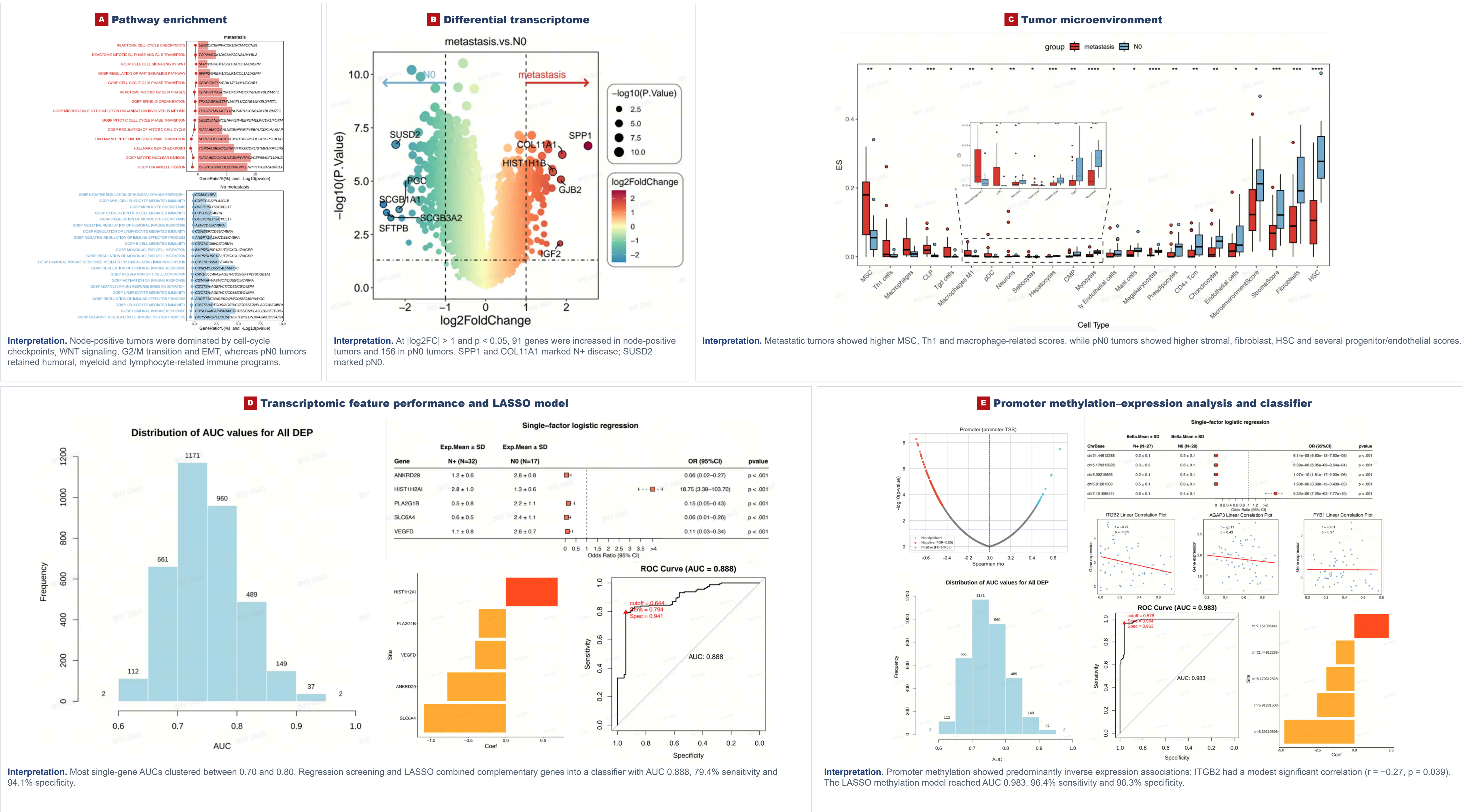
Nodal disease was associated with cell-cycle, WNT, G2/M and EMT programs and higher MSC, Th1 and macrophage-related scores. pN0 tumors retained broader immune, stromal and progenitor/endothelial features.

Methylation findings (Fig. E)

A total of 4,804 CpGs differed by nodal status. Promoter methylation was predominantly inversely related to gene expression, supporting an epigenetic contribution to metastatic biology.

Predictive modeling (Figs. D–E)

LASSO integrated complementary signals: the transcriptomic classifier achieved AUC 0.888, while the methylation classifier reached AUC 0.983 with balanced sensitivity and specificity.



DISCUSSION AND CONCLUSION

Biological interpretation

Node-positive tumors combined proliferative, WNT and EMT programs with broad remodeling of the immune and stromal microenvironment. The metastatic phenotype therefore reflects coordinated tumor-intrinsic and microenvironmental biology.

Predictive performance

- Transcriptomic model: AUC 0.888.
- Methylation model: AUC 0.983.
- Methylation provided the strongest tissue-level discrimination.
- Cross-omics correlations were informative but heterogeneous.

Validation priorities

- Confirm modality-specific sample counts.
- Lock features, thresholds and analysis plan.
- Report calibration and confidence intervals.
- Validate the plasma assay prospectively and independently.

Conclusion Integrated transcriptomic and methyloomic profiling identifies complementary biomarkers of lymph-node metastasis in resectable NSCLC. Methylation markers are especially promising for pre-operative risk stratification, but prospective plasma validation is required before clinical implementation.