

P2.175 Tumor micro environment signatures uncovered by Bulk RNA sequencing predict immunotherapy response in NSCLC

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INTRODUCTION

- Non-small cell lung cancer (NSCLC) accounts for ~85% of lung cancer cases, with immune checkpoint inhibitors (ICIs) transforming outcomes, particularly in PD-L1-high tumors. Immune evasion and tumor microenvironment (TME) composition are central determinants of immunotherapy response in lung cancer.
- Neoadjuvant chemo-immunotherapy is standard for resectable stage IB-IIIB NSCLC, boosting pCR rates to 15-25%.
- This study elucidates transcriptomic TME phenotypes in ICI treated NSCLC.

METHODS

- Bulk RNA sequencing was performed on tumor and matched normal adjacent tissue (NAT) from 12 NSCLC patients post-neoadjuvant chemo-immunotherapy, stratified by pathological response (pCR, n=7; non-pCR, n=5). Differential gene expression (DEG) analysis followed by Gene Set Enrichment Analysis (GSEA) applied to characterize the immune landscape across responders and non-responders.

DISCUSSION AND CONCLUSION

- Enrichment of B-cell and TLS-associated signatures in responders suggests a potential role for intratumoral B-cell responses in immunotherapy sensitivity.
- The co-occurrence of B-cell, T-cell, and NK-cell programs indicates a coordinated immune-active TME associated with treatment response.
- The neuro-immunosuppressive axis observed in non-responders may contribute to an immunotherapy-resistant tumor microenvironment.
- These findings provide a rationale for investigating B-cell/TLS biology as a predictive biomarker and the neuro-immunosuppressive axis as a potential therapeutic target.
- Limitation: Small cohort size (n=12) warrants validation in larger, independent cohorts.

RESULTS

- Responders showed strong enrichment of adaptive immune programs, particularly B-cell-associated genes including CD19, CD22, BLK, FCRL2, FCRLA, and MZB1.
- B-cell signatures were accompanied by T-cell activation (CD27, TIGIT, FOXP3, CCR7) and NK-cell effector programs, indicating an immune-inflamed TME.
- GSEA confirmed enrichment of B-cell activation, lymphocyte differentiation, adaptive immunity, and T-cell receptor signaling in responders.
- Non-responders showed enrichment of neuro-immunosuppressive and neuroendocrine/epithelial programs, including GABAergic, glutamatergic, purinergic, and GPCR signaling.
- Immune and inflammatory pathways were relatively preserved in NAT, suggesting an immune-excluded, TGF- β -associated phenotype in non-responders.

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A. Study design and transcriptomic workflow

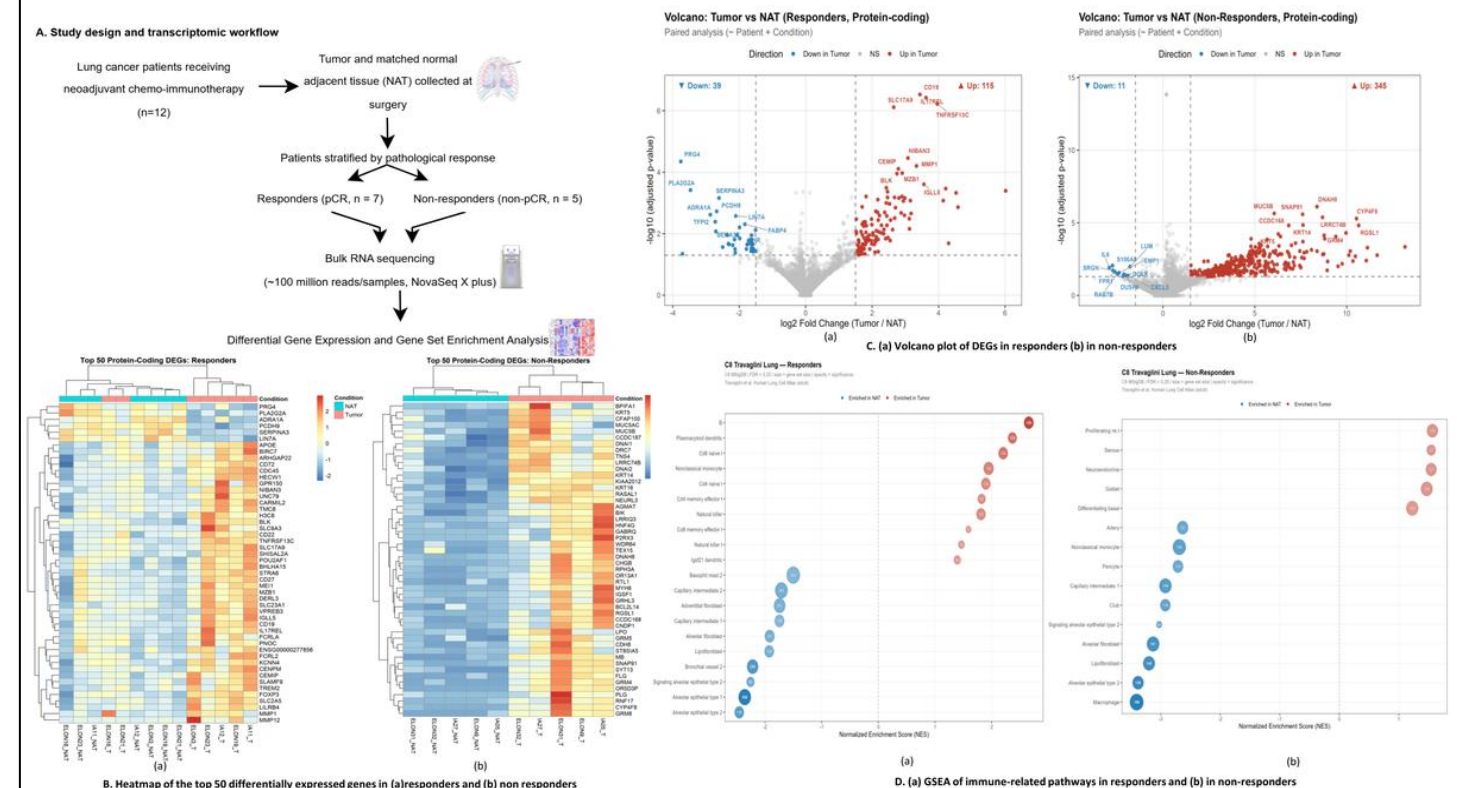
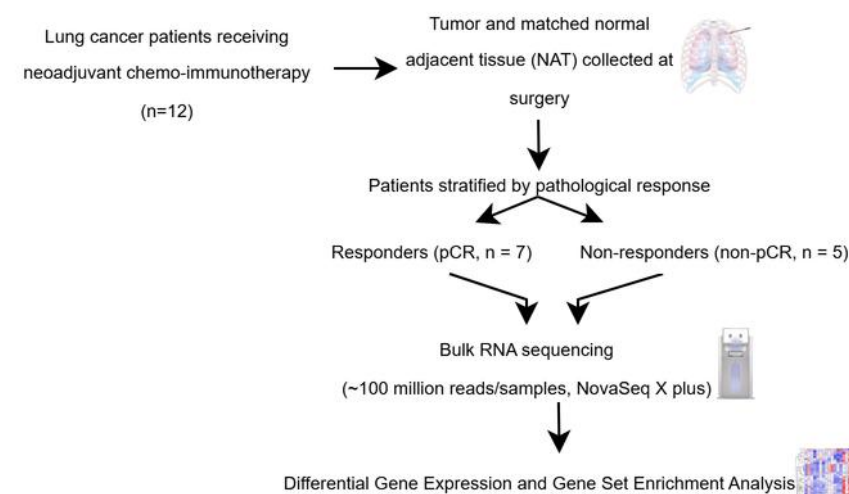


Figure 1: (A) Study design and bulk RNA-seq workflow of 12 lung cancer patients treated with neoadjuvant chemo-immunotherapy, stratified into responders (pCR, n=7) and non-responders (non-pCR, n=5), followed by differential expression and pathway analyses. (B) Heatmaps of the top 50 DEGs in responders and non-responders. (C) Volcano plots showing significantly up- and downregulated genes in each group. (D) GSEA showing enrichment of B-cell, T-cell, and other immune programs in responders, while non-responders showed epithelial and neuroendocrine-related signatures.