Spatial architecture of neoadjuvant immunochemotherapy response in pleural mesothelioma

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AACR 2026

Poster # 6194

INTRODUCTION

BACKGROUND

Pleural mesothelioma (PM) is a rare and aggressive malignancy originating from the mesothelial cells of the pleural lining, with a well-established etiological association with asbestos exposure. Although **immunochemotherapy is being applied as a first-line treatment**, most patients fail to respond to the therapy.

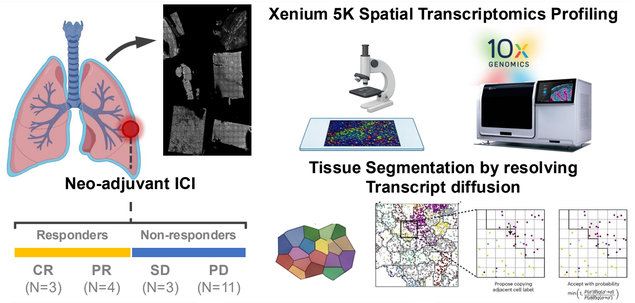
Previous single-cell RNA sequencing studies on PM have revealed cellular heterogeneity but **lack spatial resolution and comparative analyses of immune checkpoint inhibitor (ICI)** responses, limiting understanding of tumor microenvironment (TME)-mediated resistance mechanisms.

This study aims to comprehensively identify the **cellular composition and spatial architecture of the TME**, as well as mechanisms responsible for ICI resistance in PM.

OBJECTIVE

Comprehensively characterize the **spatial tumor microenvironment** of pleural mesothelioma in the context of neoadjuvant immunochemotherapy response using **Xenium Prime 5K spatial transcriptomics**, to identify cellular composition, spatial niche architecture, mesothelial cell functional states, and cell-cell interaction networks that distinguish responders from non-responders.

STUDY DESIGN & METHODS



RESULTS

1. Distinct Cell Type Composition Between Responders and Non-Responders

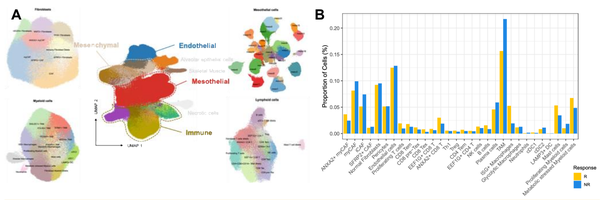


Figure 1. (A) 36 distinct cell clusters were identified, including mesothelial, immune, stromal, and normal alveolar cells **(B)** TAM proportion is significantly higher in **non-responders**. B cells, CD8 Tem, and CD8 Tex are enriched in **responders**.

2. Mesothelial Cell Functional States and CNV

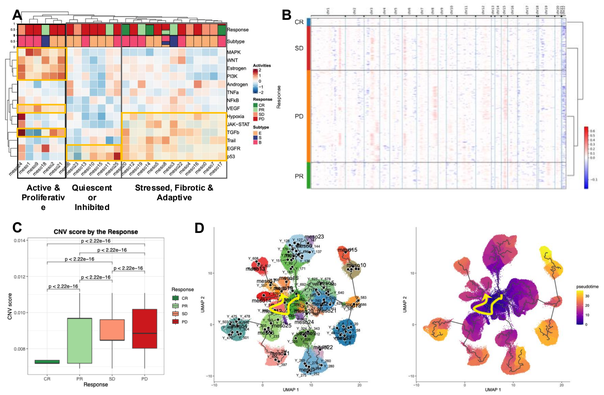
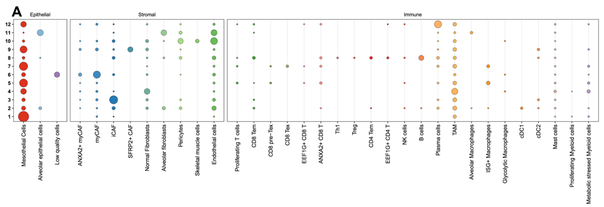


Figure 2. (A) Functional annotation of mesothelial cells revealed three distinct functional groups: **Active & Proliferative** (MAPK/PI3K/VEGF), **Quiescent or Inhibited**, and **Stressed & Adaptive** (p53/TRAIL). **Non-responders** displayed an "Active & Proliferative" phenotype, whereas **responders** demonstrated a "Stressed & Adaptive" state. **(B, C)** Mesothelial cells exhibited chromosome 22 deletions, with CNV scores inversely correlating with treatment response. **(D)** Meso8 cluster represents a progenitor-like central population that differentiates outward into multiple states

3. Spatial Niche Architecture: Tumor-Reactive vs. Immunosuppressive Niches



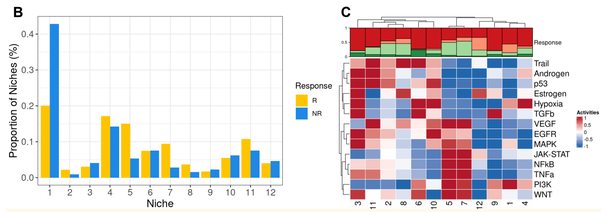


Figure 3. (A, B) Among 12 conserved spatial niches, Niche 5 (CD8 pre-Tex, ISG+ macrophage), Niche 7 (CD8 Tex), and Niche 8 (B cell-enriched TLS-like) were prominent in **responders** with JAK-STAT, NFkB, and TNFa activation. Immunosuppressive niches (Niche 1: mesothelial cells, Niche 9: *SFRP2*+ CAF) with active TGFβ pathways predominated in **non-responders**

4. Niche 8 is a TLS-like immune hub

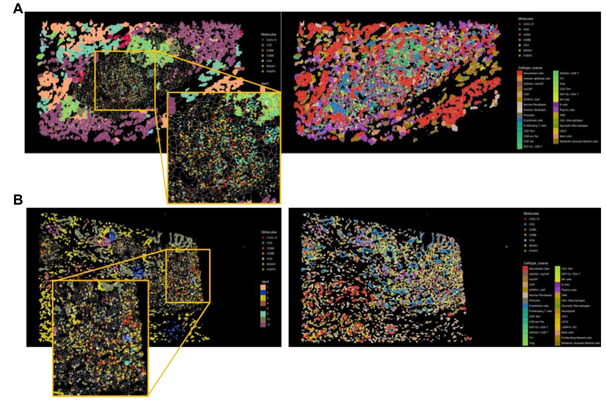


Figure 4. In Niche 8, **(A-C)** *CXCL13* and *CR2* are co-localized in B cells of niche 8 only from responders. **(D)** Mesothelial cell-driven chemokine (CXCL13-CXCR5) and complement (C4A-CR2) signaling orchestrates B cell recruitment and TLS organization. Functional TLS markers (*CR2*, *TNFRSF9*, plasma differentiation) in **responders** and dysfunctional TLS markers (*NR4A3*, *CDKN1A*, hypoxia) in **non-responders**.

5. Niche 8 Islands with CXCL13–CR2 Enrichment

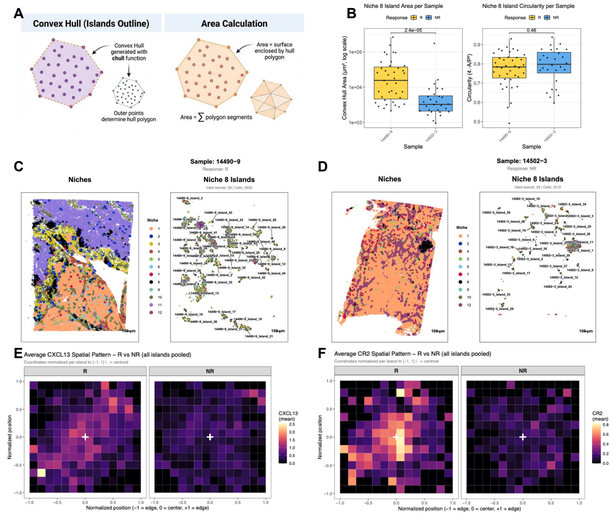


Figure 5. (A) Convex hull-based island detection was applied to define discrete Niche 8 clusters. **(B-D)** Responder contained more numerous and larger Niche 8 islands (39 islands) compared to non-responders (28 islands). **(E, F)** Spatially normalized expression patterns revealed centroid-enriched *CXCL13* and *CR2* signals within Niche 8 islands in **responders** compared to **non-responders**.

CONCLUSION

Our integrative single-cell and spatial analysis of PM identifies distinct programs associated with therapeutic response.

Non-responders showed proliferative mesothelial states (MAPK/PI3K/VEGF), higher CNV burden, and immunosuppressive features, including TAM enrichment and TGFβ-driven niches. In contrast, **responders** exhibited stressed/adaptive mesothelial states (p53/TRAIL), lower CNV levels, and immune-activated niches with CD8$^+$ T cells and TLS-like B cell structures.

Mesothelial CXCL13–CXCR5 and C4A–CR2 signaling supported functional TLS formation in **responders**.

These results highlight spatially organized anti-tumor immunity as a key determinant of response and a potential therapeutic target.

REFERENCES

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