



P2.077: Small Invasive Lung Adenocarcinoma: a Distinct "Born-to-be Malignant" Branch Driven by Genomic Alterations and Immune Remodeling

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INTRODUCTION

Background:

- Lung adenocarcinoma (LUAD) is generally thought to follow a linear progression from pre-invasive lesions to invasive adenocarcinoma^{1,2}.
- However, clinical observations of ≤ 1 cm invasive adenocarcinomas frequently exhibit aggressive behavior, challenging this gradual model.

Hypothesis:

- Small invasive adenocarcinomas (sIACs, ≤ 1 cm) may represent an independent "born-to-be malignant" trajectory rather than a late stage of stepwise progression.

METHODS

Cohort 1 (n=700): targeted sequencing (68-gene panel) for genomic characterization.

sIAC (≤ 1 cm)
(small invasive
adenocarcinomas)
n = 149

VS

sPM (≤ 1 cm)
(small pre-
invasive/minimally
invasive lesions)
n = 551

Cohort 2 (n=28): RNA-seq for transcriptomic profiling.

sIAC (≤ 1 cm)
n = 13

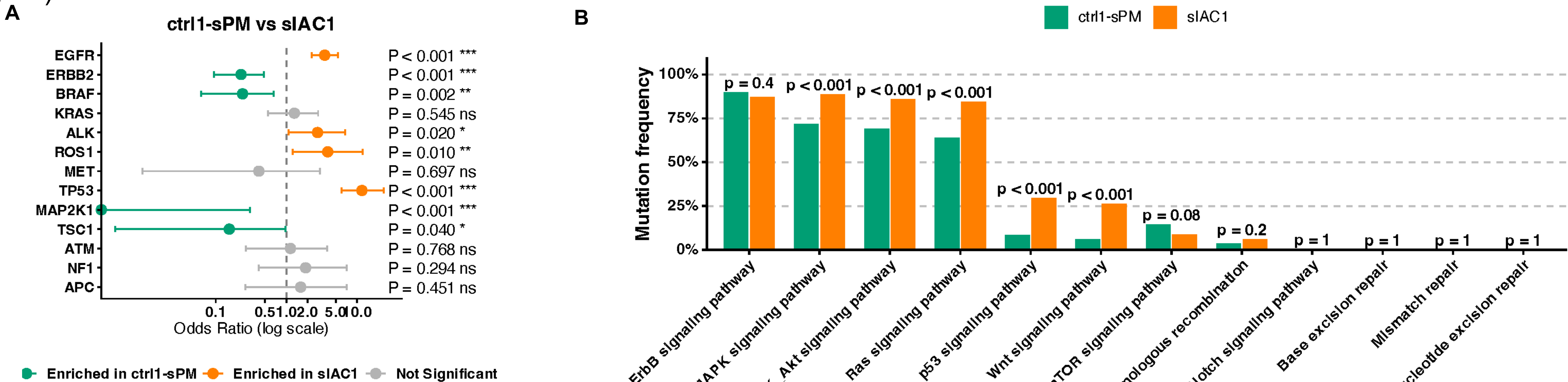
VS

PM (≤ 3 cm)
(pre-
invasive/minimally
invasive lesions)
n = 15

RESULTS

Figure 1. sIACs harbor a distinct and aggressive genomic landscape (Cohort1)

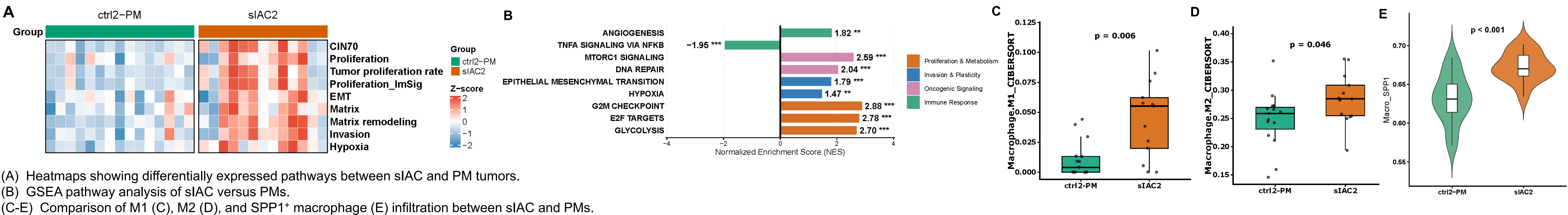
- Visceral pleural invasion and N1/N2 lymph node metastasis occurred exclusively in sIACs.
- sIAC and sPM showed distinct driver alteration patterns:
 - sIACs were enriched for strong oncogenic drivers, including *EGFR* (75.2% vs. 46.5%), *ALK* (6.7% vs. 2.4%), and *ROS1* (5.4% vs. 1.5%), along with increased *TP53* mutations (24.8% vs. 2.7%) and *EGFR/TP53* co-alterations (24.1% vs. 5.1%).
 - Conversely, sPMs were enriched for milder oncogenic drivers, including *ERBB2* (20.0% vs. 5.3%), *BRAF* (10.3% vs. 2.7%), *MAP2K1* (8.0% vs. 0.0%), and *TSC1* (4.2% vs. 0.7%) (Fig 1A).
- sIACs exhibited broader oncogenic pathway involvement, with significantly higher mutation frequencies in the PI3K-AKT, MAPK, RAS, p53, and Wnt pathways compared with sPMs (Fig 1B).



(A) Forest plots comparing the genomic features between sIAC and sPM tumors.
(B) Bar plots illustrating the differential mutation frequencies detected in various signaling pathways of sIAC and sPM tumors.

Figure 2. sIACs exhibit activated malignant programs and immune remodeling (Cohort2)

- sIACs displayed elevated chromosomal instability 70 (CIN70) scores, proliferation, and EMT signatures relative to PM lesions (Fig 2A).
- Cell-cycle progression (E2F targets, G2M checkpoint), metabolic reprogramming (glycolysis, mTORC1), and stress adaptation (DNA repair, hypoxia, angiogenesis) were upregulated in sIACs, whereas $\text{TNF}\alpha$ - $\text{NF}\kappa\text{B}$ signaling was suppressed (Fig 2B).
- sIACs showed increased M1 and M2 macrophage infiltration ($P=0.006$ and $P=0.046$, respectively), along with a markedly higher pro-fibrotic SPP1^+ macrophage signature ($P<0.001$) (Fig 2C-E).



CONCLUSION AND DISCUSSION

- sIACs represent a distinct "born-to-be-malignant" evolutionary trajectory, independent of conventional linear progression.
- Co-occurring oncogenic drivers and *TP53* alterations may trigger intrinsic metabolic and invasive programs.
- Along with immune niche remodeling (e.g., SPP1^+ macrophage enrichment³), these changes may enable tumor progression even at a minimal tumor size.

REFERENCES & DISCLOSURE

Reference

- Liang P, et al. MedComm 2024;5:e644.
- Karasaki T, et al. Nat Med 2023;29:833-45.
- Zheng H, et al. Mol Cancer 2025;24:298.

Disclosure

The authors declare no potential conflicts of interest.