

P2.234 : Lineage Plasticity and Histological Transformation in Pulmonary Pleomorphic Carcinoma: A Multi-region, Multi-Omics Study

Likun Hou^{1,2}, Quan Li², Ming Li², Nhu-An Pham², Ming-Sound Tsao²



IALSC 2026 World
Conference on Lung Cancer
SEPTEMBER 12 - 15, 2026
SEOUL, REPUBLIC OF KOREA

¹Department of Pathology, Shanghai Pulmonary Hospital, Tongji University, Shanghai, China; ²Princess Margaret Cancer Centre, University Health Network and University of Toronto, Toronto, Ontario, Canada;

INTRODUCTION

Pulmonary pleomorphic carcinoma (PPC) is a rare and highly aggressive subtype of non-small cell lung cancer (NSCLC), characterized by the coexistence of epithelial and sarcomatoid components. While histological transformation from conventional NSCLC to PPC is a known mechanism of acquired drug resistance, the molecular drivers underlying this lineage plasticity during natural tumor progression remain elusive. This study employs multi-omics analysis on patient tumors and patient-derived xenograft (PDX) models to investigate the evolutionary trajectory and key signaling pathways governing the transition from the squamous cell carcinoma (SCC) component to the sarcomatoid component.

METHOTHS

We analyzed four resected PPCs containing SCC components. Epithelial (EPI), transitional (MED), and sarcomatoid (SAR) components were microdissected for multi-region whole-exome sequencing (WES) to assess clonality and phylogenetic evolution. Additionally, three treatment-naïve PPC biopsies and one PPC-derived PDX model (established in NOD SCID mice) were subjected to single-cell RNA sequencing (scRNA-seq). Differential gene expression (DEG) analysis and Gene Set Enrichment Analysis (GSEA) were performed to characterize the transcriptional plasticity.

	Gender	Age	Smoking	Sample types
Case1	Male	77	Heavy	Resection
Case2	Male	76	Heavy	Resection
Case3	Male	78	NA	Resection
Case4	Male	68	Heavy	Resection
Case5	Male	78	Heavy	Biopsy
Case6	Male	62	Heavy	Biopsy
Case7	Female	52	No	Biopsy

RESULTS

Multi-regional WES identified shared driver mutations across EPI, MED, and SAR regions, supporting a common clonal origin. Phylogenetic reconstruction in three cases placed the SCC branch at the root, with MED and SAR diverging at the tips, directly supporting a linear EPI-to-SAR transformation; the remaining case exhibited tight clustering, indicating late divergence. scRNA-seq resolved a dynamic continuum of EPI, MED, and SAR transcriptional states, characterized by progressive upregulation of EMT transcription factors and significant ECM remodeling. GSEA confirmed EMT as the top enriched pathway in the SAR compartment; Beyond EMT, it also revealed significant activation of ECM-receptor interaction and TNF α /NF- κ B signaling. The identified EMT signature was recapitulated in the PDX model (clusters 0-5), validating the in vivo histologic conversion.

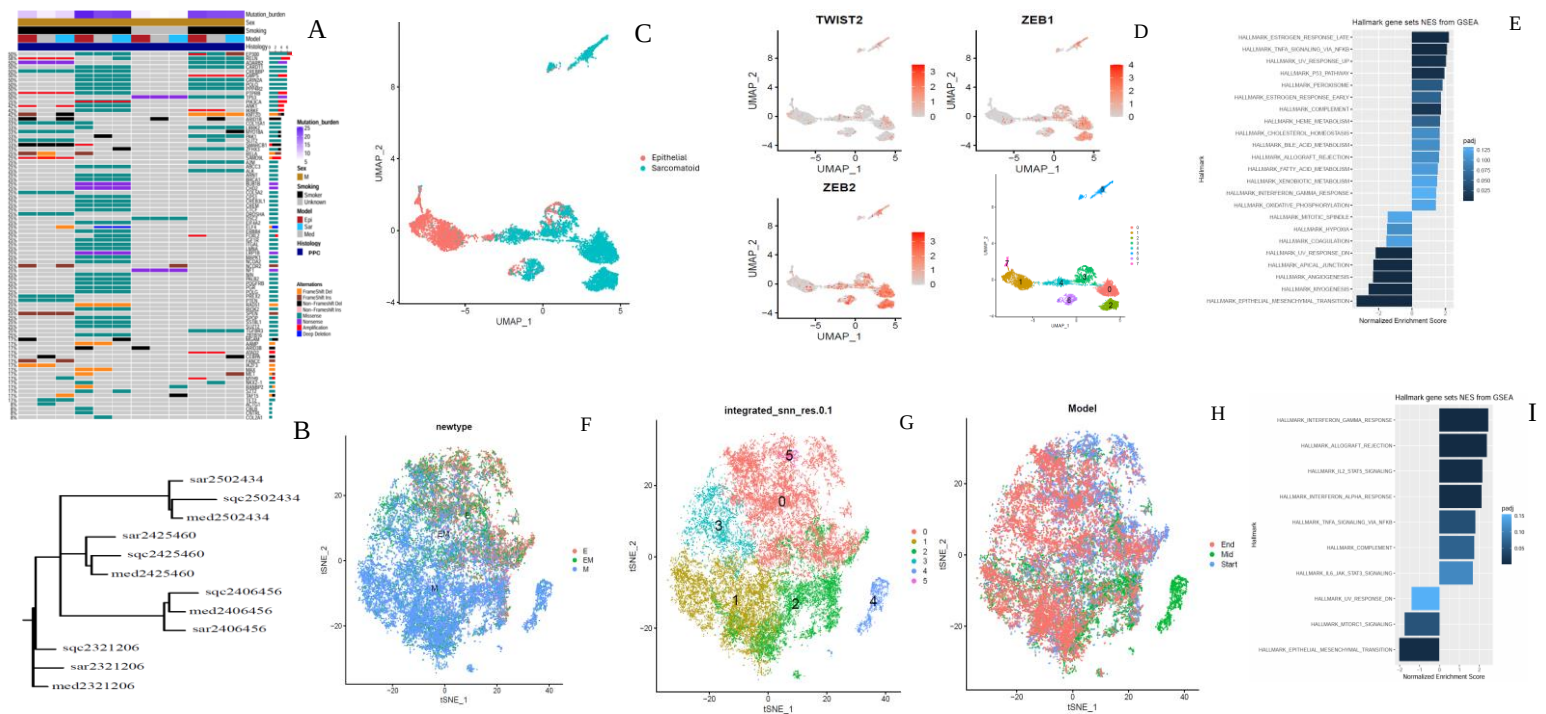


Figure: Multi-omics analysis reveals clonal origin and stepwise EMT-driven evolution in Pulmonary Pleomorphic Carcinoma (PPC)
A: Shared key driver mutations across EPI/MED/SAR confirm a common clonal origin; B: Phylogenetic trees support linear transformation from SCC to SAR; C: UMAP plot reveals a dynamic continuum of EPI (red) and Stroma (green) states in biopsies; D: Progressive upregulation of EMT-TFs (*TWIST2*, *ZEB1*, *ZEB2*) drives the EPI-to-SAR transition; E: GSEA confirms EMT as the top enriched pathway, along with ECM-receptor interaction; F: scRNA-seq clustering identifies distinct EPI, MED, and SAR subpopulations in PDX models; G: Unsupervised clustering (clusters 0-5) in the PDX model recapitulates the EPI, MED, and SAR subpopulations in vivo; H: PDX model recapitulates EPI (Start), MED, and SAR subpopulations in vivo; I: GSEA confirms EMT as the top enriched pathway in PDX transition models;

CONCLUSIONS

Integrated genomic and single-cell analyses provide evidence for the clonal origin and sequential SCC-to-SAR evolution of PPC. scRNA-seq and PDX validation reveal that this transformation is driven by a stepwise EMT, further fueled by ECM remodeling and microenvironmental signaling. These findings underscore the multi-layered mechanisms driving PPC lineage plasticity and highlight potential therapeutic targets.

References: 1. Roma L, et al. Tracing Tumor Heterogeneity of Pleomorphic Carcinoma of the Lung. J Thorac Oncol. 2024 Sep;19(9):1284-1296.
2. Hu L, et al. Histological transformation in lung cancer: a single-arm meta-analysis and systematic review. BMC Cancer. 2026 May 21;26(1):840.