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Spatial Profiling Identifies PDZK1IP1 as a Driver of Brain Metastasis in EGFR-Mutant NSCLC

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INTRODUCTION

- Brain metastasis (BM) and histological transformation are key resistance mechanisms in EGFR-mutant non-small cell lung cancer (NSCLC).
- The spatial heterogeneity underlying these trajectories remains poorly understood. We utilized spatial transcriptomics (ST) to identify molecular mediators of BM colonization.

METHODS

- ST was applied to six longitudinal FFPE specimens from a patient with EGFR 19del-mutant adenocarcinoma, spanning baseline primary tumor, lymph node metastasis, post-targeted therapy small cell lung cancer (SCLC) transformation, and BM. ST data were integrated with public single-cell RNA sequencing (scRNA-seq) to deconvolute cellular compartments. Pseudotime trajectory analysis mapped developmental origins.
- Findings were validated via an independent scRNA-seq cohort and immunohistochemistry (IHC) on paired primary and BM clinical samples. Functional roles were assessed via siRNA_x0002_mediated knockdown in neurotropic A549-BrM cells.

RESULTS

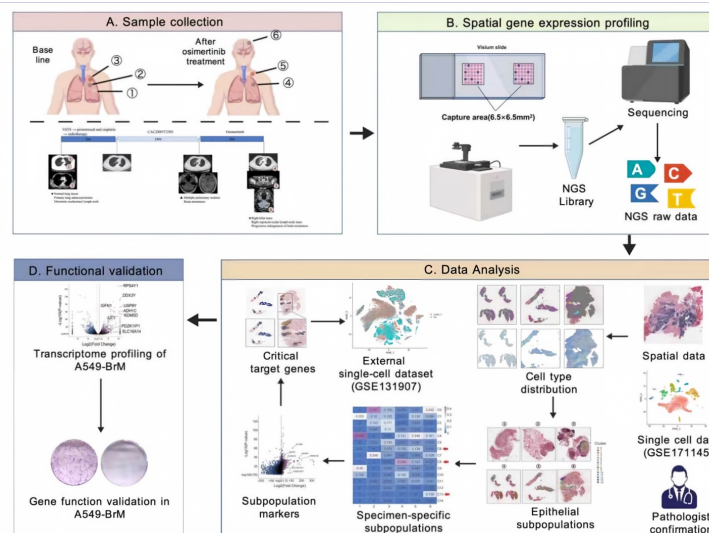


Figure 1. Overall study design and integrative analytical workflow.

(A) Clinical timeline and longitudinal sample collection. The disease trajectory of a 31-year-old male patient with EGFR exon 19 deletion lung adenocarcinoma is shown, spanning surgery, adjuvant chemoradiotherapy, canakinumab trial (CACZ885T2301), and subsequent osimertinib treatment. Six matched formalin-fixed paraffin-embedded (FFPE) specimens were collected at baseline and post-treatment progression: ① baseline normal lung tissue, ② baseline primary lung adenocarcinoma, ③ baseline mediastinal lymph node metastasis, ④ post-treatment lung tumor tissue with small cell lung cancer (SCLC) transformation, ⑤ post-treatment supraclavicular lymph node metastasis, and ⑥ post-treatment brain metastasis. Representative CT and MRI scans illustrate the clinical progression. (B) Spatial transcriptomic (ST) profiling. The six FFPE tissues were processed using the Visium platform for spatial gene expression mapping, followed by next-generation sequencing (NGS) library preparation. (C) Integrative bioinformatics pipeline. ST data were integrated with an external single-cell RNA sequencing (scRNA-seq) dataset (GSE171145) and confirmed by pathologist annotations to deconvolute epithelial and microenvironmental cell distributions. Downstream analyses focused on identifying specimen-specific subpopulations and critical brain metastasis-associated target genes, which were further cross-validated using an independent scRNA-seq brain metastasis cohort (GSE131907). (D) Functional validation. Transcriptome profiling and in vitro phenotypic assays were performed using the neurotropic A549-BrM cell line model to validate the biological functions of the identified target genes (e.g., PDZK1IP1).

Integration mapped five functional compartments. A neuroendocrine-like subcluster (C8) was exclusively enriched in post-treatment SCLC tissues, marking lineage plasticity. Conversely, subcluster C13 was spatially restricted to the BM niche at the terminal differentiation trajectory. Cross-cohort validation identified PDZK1IP1 as upregulated in BM. IHC confirmed significantly elevated PDZK1IP1 protein in clinical BM lesions versus paired primary tumors ($P < 0.0001$). In vitro, PDZK1IP1 was highly expressed in A549-BrM cells. Its knockdown significantly impaired cell viability, colony formation, invasion, and migration, while simultaneously inducing E-cadherin downregulation and Vimentin upregulation.

DISCUSSION AND CONCLUSION

Our spatial atlas of EGFR-mutant lung cancer identifies PDZK1IP1 as a clinically relevant marker of the brain-tropic niche. PDZK1IP1 maintains epithelial competence, preventing epithelial-to-mesenchymal transition (EMT) and facilitating BM colonization, highlighting it as a promising therapeutic target.