



P3.347:Unveiling Oncofetal Reprogramming and Key Biomarkers in SCLC Brain Metastasis via Single-Cell Multi-Omics

Haonan Gu¹, Huiyang Shi², Haohua Zhu³, Xingsheng Hu², Ting Xiao¹

¹National Cancer Center/ National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing/CN, ²National Cancer Center/ National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing/CN, ³Cancer Center, Aerospace Center Hospital, Beijing/CN

Correspondence: xiaot@cicams.ac.cn



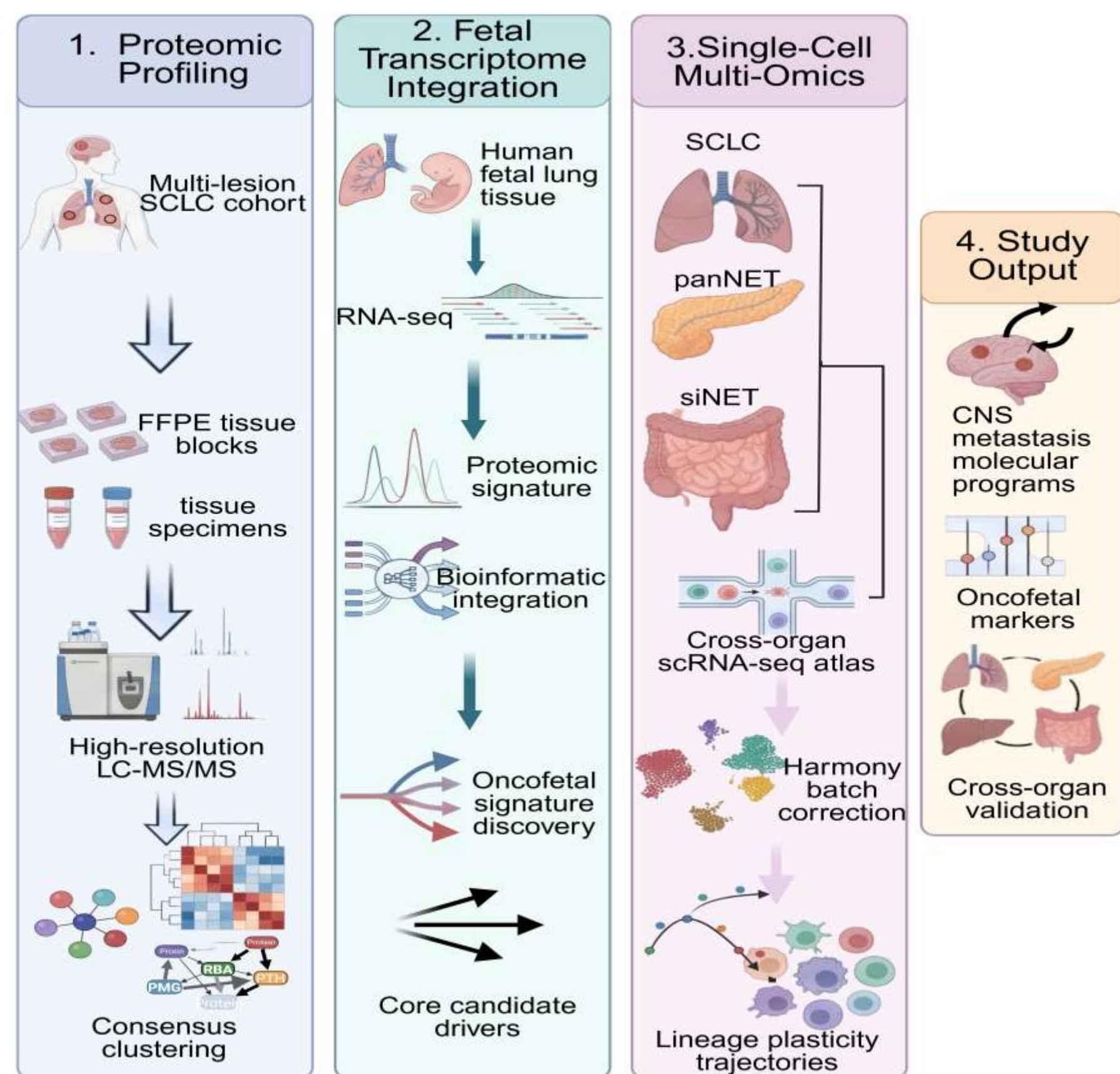
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INTRODUCTION

- Background:** Small cell lung cancer (SCLC) is a highly aggressive neuroendocrine neoplasm (NEN) with a nearly 60% cumulative incidence of brain metastasis (BrM). Emerging evidence suggests that SCLC malignancy is heavily driven by oncofetal reprogramming, wherein embryonic developmental pathways are aberrantly reactivated
- Hypothesis:** We hypothesize that the distinct malignancy gradient across organ-specific NENs is rooted in their embryonic origins, where foregut-derived SCLC possesses a lower threshold for oncofetal reprogramming compared to mid/hindgut-derived NENs like pancreatic or intestinal NENs).

METHODS

- Proteomic Profiling:** High-resolution LC-MS/MS proteomic analysis was conducted on a multi-lesion SCLC clinical cohort (n = 121). Unsupervised consensus clustering defined molecular subtypes and functional signaling networks.
- Fetal Transcriptome Integration:** Proteomic signatures were bioinformatically integrated with human fetal lung bulk RNA-seq datasets to pinpoint core oncofetal drivers.
- Single-Cell Multi-Omics:** Constructed a cross-organ scRNA-seq atlas using Harmony batch correction to resolve tumor heterogeneity, lineage plasticity trajectories, and embrvonic reactivation thresholds.



DISCUSSION AND CONCLUSION

- Master Regulator Identification:** Identified PCID2 as a novel oncofetal driver that dictates lineage infidelity and controls the plasticity threshold in SCLC, driving high-grade neuroendocrine transformation and metastatic seeding.
- Developmental and Embryonic Framework:** Established a unified spatial-embryonic origin model to account for the malignancy gradient across NENs. Foregut-derived SCLC exhibits heightened susceptibility to embryonic pathway reactivation compared to mid/hindgut-derived pancreatic or intestinal NENs.
- Mechanism of Brain Metastasis:** Demonstrated that PCID2-mediated reprogramming endows primary SCLC cells with enhanced invasive capacity and neuro-tropism, directly accounting for the high cumulative incidence (~60%) of brain metastasis.

REFERENCES & ACKNOWLEDGEMENTS

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RESULTS

- PCID2-mediated reprogramming is uniquely heightened in foregut-derived SCLC compared to mid/hindgut NENs.
- PCID2 expression strongly correlated with SOX2 and significantly predicted shortened overall.

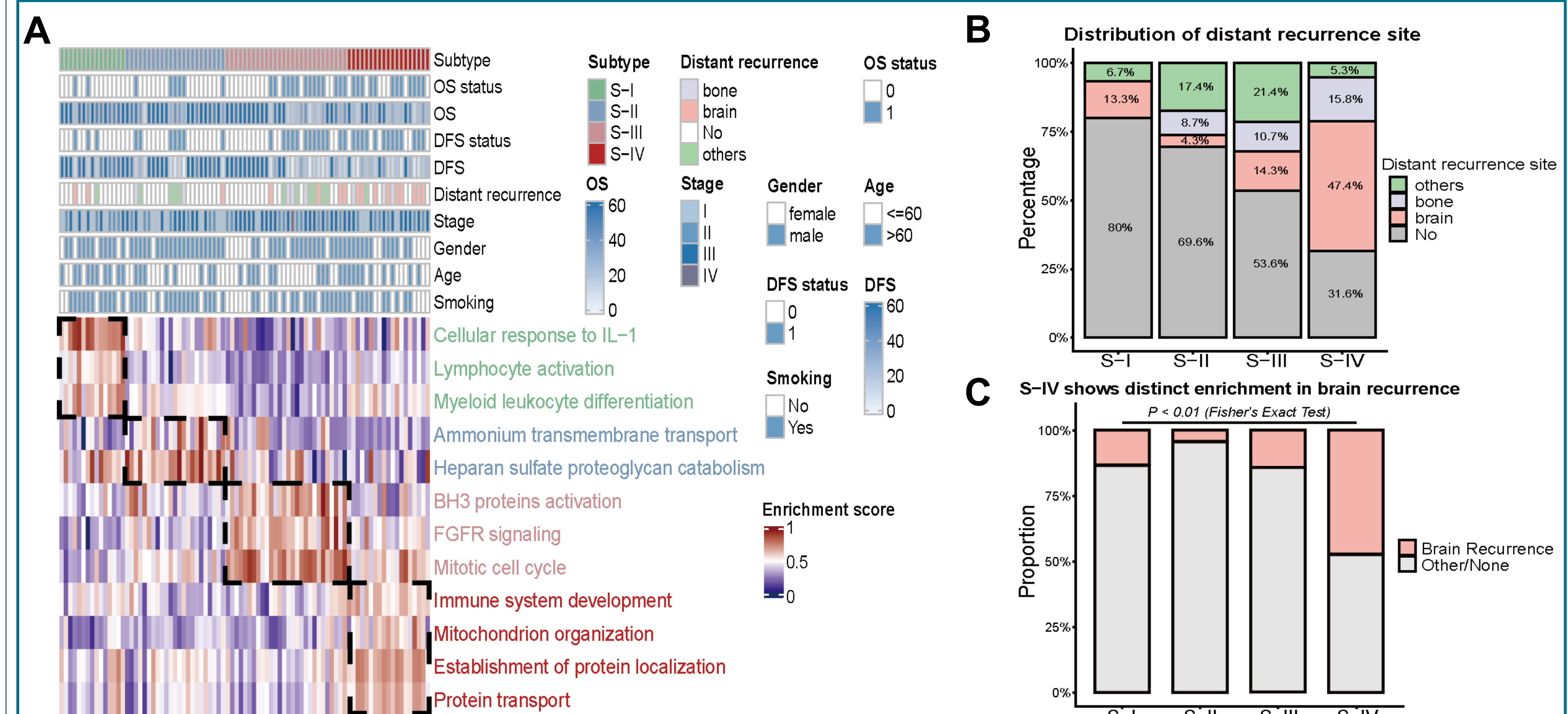


Figure 1. Clinicopathological Characteristics and Brain Metastasis Preference across Molecular Subtypes. (A) Subtype Clinical Features and Pathway Enrichment Heatmap. (B) Distribution of Distant Metastatic Sites across Subtypes. (C) Subtype S-IV Exhibits Significant Tropism for Brain Metastasis.

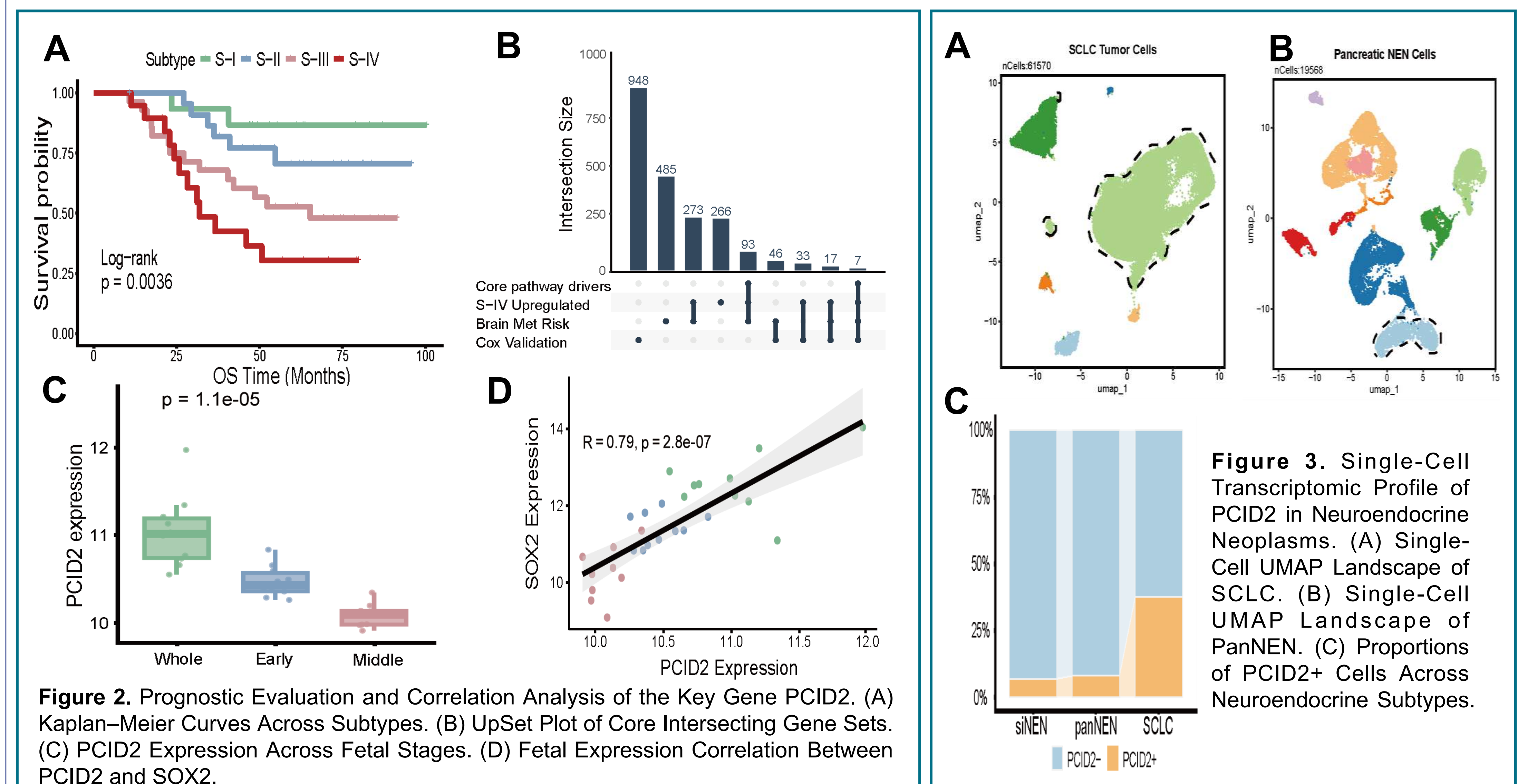


Figure 2. Prognostic Evaluation and Correlation Analysis of the Key Gene PCID2. (A) Kaplan-Meier Curves Across Subtypes. (B) UpSet Plot of Core Intersecting Gene Sets. (C) PCID2 Expression Across Fetal Stages. (D) Fetal Expression Correlation Between PCID2 and SOX2.

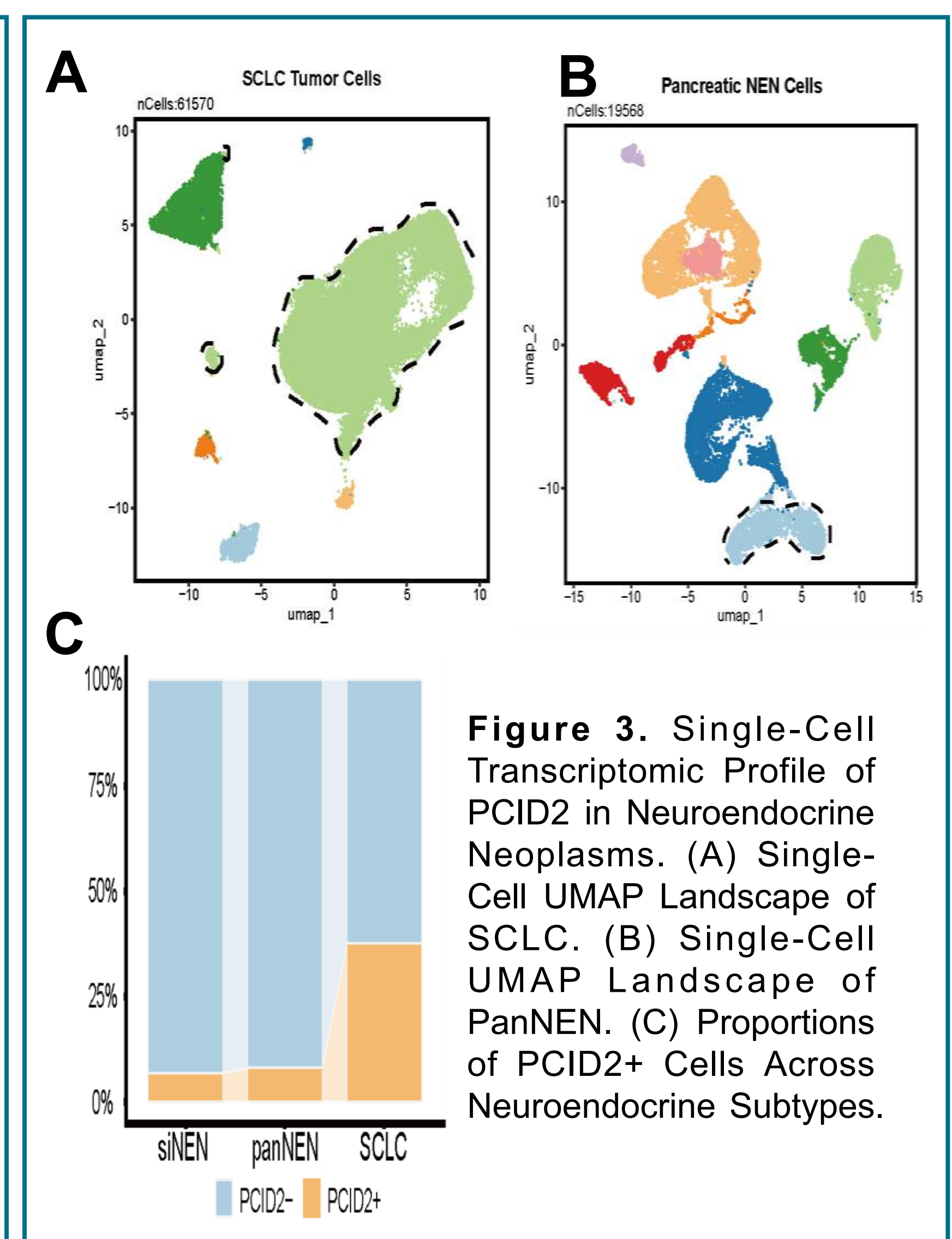


Figure 3. Single-Cell Transcriptomic Profile of PCID2 in Neuroendocrine Neoplasms. (A) Single-Cell UMAP Landscape of SCLC. (B) Single-Cell UMAP Landscape of PanNEN. (C) Proportions of PCID2+ Cells Across Neuroendocrine Subtypes.