Transcriptional patterns of primary and metastatic SCLC

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INTRODUCTION

Small Cell Lung Cancer (SCLC) is a highly aggressive neuroendocrine tumor characterized by rapid growth, early metastasis, and poor prognosis. Transcription factors (TFs) play pivotal roles in driving SCLC progression, influencing tumor cell plasticity, metastasis, epithelial-mesenchymal transition (EMT), and therapy resistance. Understanding the expression and regulation of these genes is crucial for uncovering the molecular mechanisms underlying SCLC progression and identifying potential targets for novel therapeutic interventions.

GOAL

This study aims to elucidate the transcriptional differences between primary and metastatic SCLC tumors using scRNA-seq to identify key markers and regulatory pathways driving metastasis and tumor-immune interactions, providing novel insights into potential therapeutic targets.

METHODS

For the analyses publicly available scRNA-seq data of primary and metastatic SCLC tumors was used. Data was processed using the Seurat package in R. 13 samples (6 primary, 7 metastatic) were integrated using Seurat's anchor-based method. PCA and UMAP were used for dimensionality reduction and visualization of clusters. Clusters were annotated using known marker genes from public datasets. Differential expression analysis was performed between primary and metastatic cells.

RESULTS

Immune and tumor cells were annotated using known marker genes. Cell counts were assessed to ensure sufficient representation of both cell populations. Tumor cells were then subsetted from the dataset for differential expression (DE) analysis between primary and metastatic samples, revealing key transcriptional differences driving SCLC metastasis.

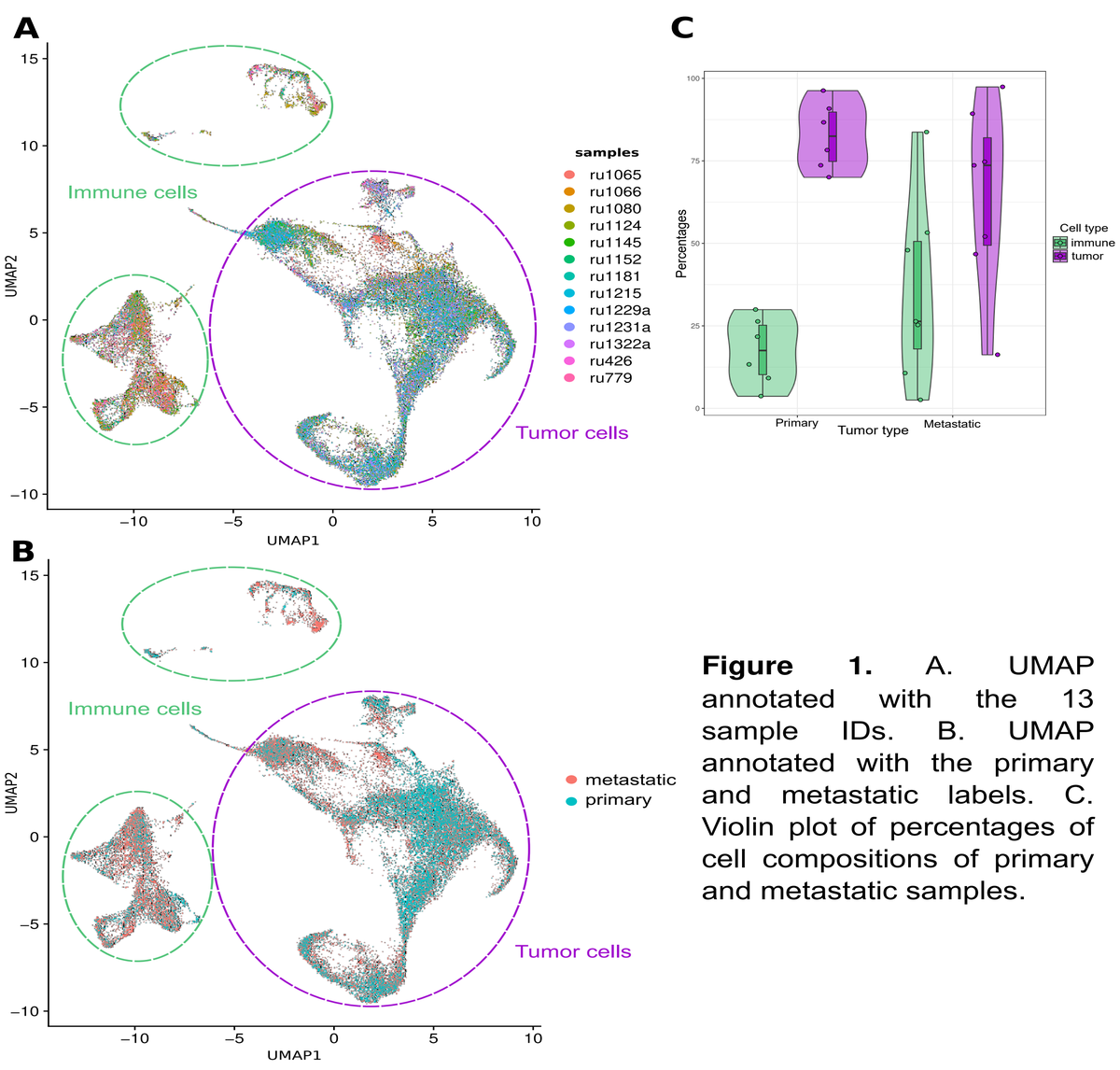

Figure 1. A. UMAP annotated with the 13 sample IDs. B. UMAP annotated with the primary and metastatic labels. C. Violin plot of percentages of cell compositions of primary and metastatic samples.

A broader transcriptional activity difference was observed across both primary and metastatic tumor cells, with distinct upregulation of specific genes in the metastatic samples, and downregulation in primary samples. Notably, certain gene clusters are consistently upregulated in the metastatic group, suggesting potential markers for metastatic progression. Assessing the EMT and immune checkpoint gene expressions, we can see clearer differences between metastatic and primary tumor cells, indicating specific transcriptional changes driving metastasis (Figure 2).

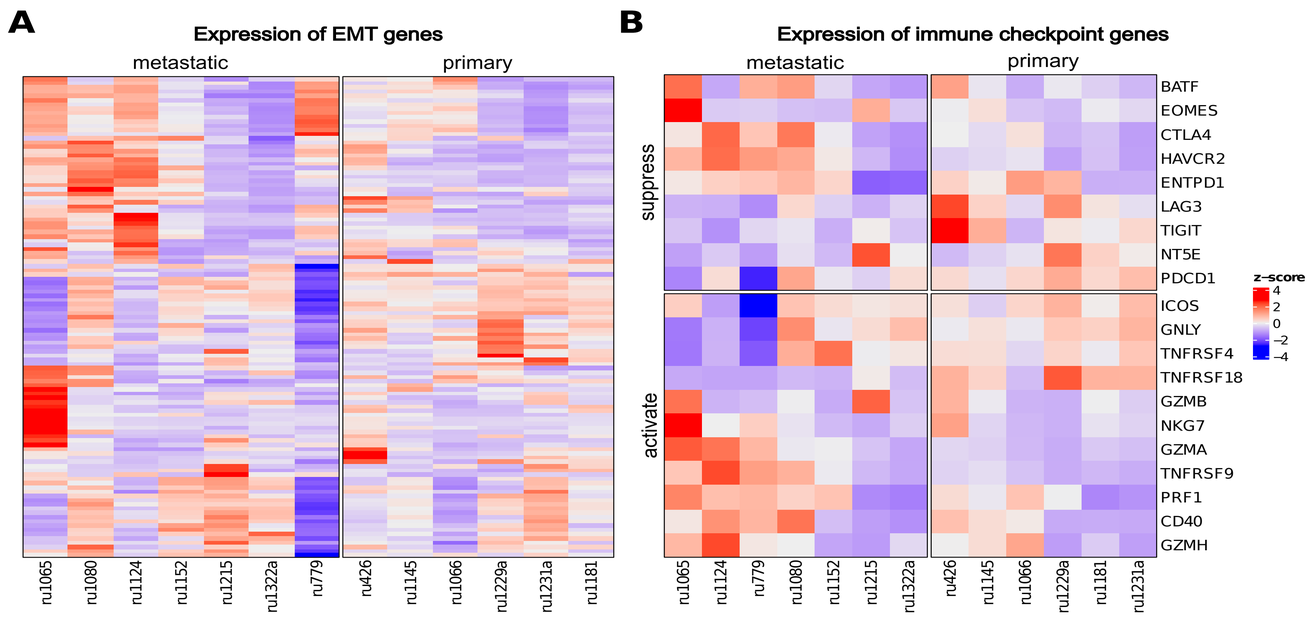

Figure 2. A. Heatmap of EMT gene expressions in primary and metastatic SCLC. B. Heatmap of immune checkpoint gene expressions in primary and metastatic SCLC.

DE between primary and metastatic SCLC tumors reveal distinct transcriptional profiles. To validate our DE genes, we have assessed its expression in the Liu SCLC cohort, revealing four distinct sample clusters (S1-S4) and two main gene clusters (G1 and G2), seen in Figure 3. The gene clusters show significant variation in expression levels across the sample clusters, with G1 characterized by upregulation of genes involved in cell division processes (e.g., chromosome segregation, nuclear division), and G2 enriched for immune-related processes (e.g., cell killing, leukocyte-mediated immunity, and cell activation).

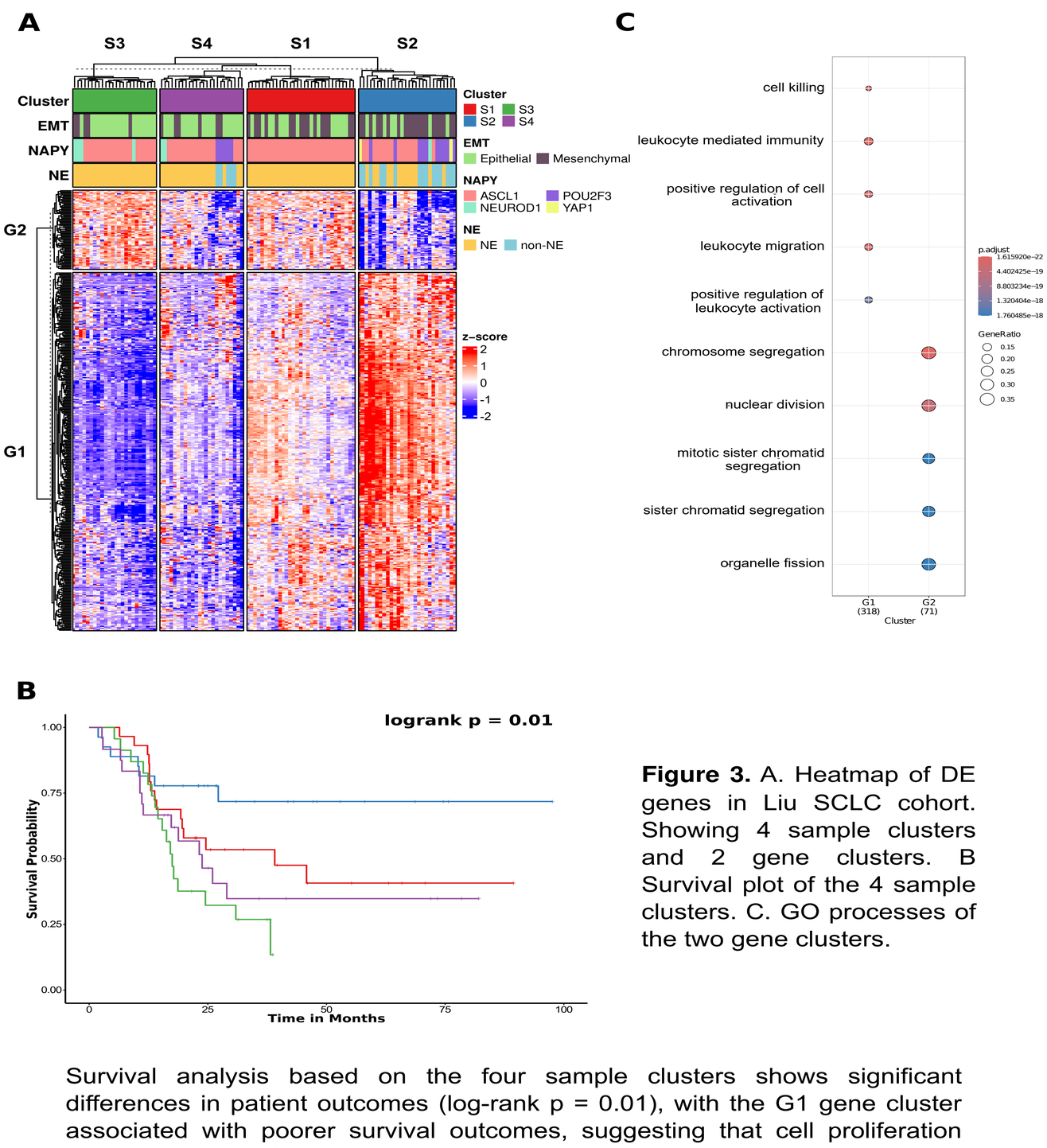

Figure 3. A. Heatmap of DE genes in Liu SCLC cohort. Showing 4 sample clusters and 2 gene clusters. B Survival plot of the 4 sample clusters. C. GO processes of the two gene clusters.

Survival analysis based on the four sample clusters shows significant differences in patient outcomes (log-rank p = 0.01), with the G1 gene cluster associated with poorer survival outcomes, suggesting that cell proliferation pathways may be linked to aggressive tumor behavior.

DISCUSSION

By integrating comprehensive analyses, we aimed to uncover the transcriptional drivers of SCLC metastasis, the heterogeneity within metastatic tumors, the EMT process, and mechanisms of immune evasion. Our findings could contribute to a deeper understanding of SCLC biology and may inform the development of novel therapeutic strategies targeting metastatic disease.

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