

Who Your Neighbors Are Matter: Spatially Resolved Cell-cell Communication In Small Cell Lung Cancer Reveals Macrophage-driven Immune Evasion Programs

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INTRODUCTION

Background

- SCLC is a highly aggressive lung cancer with a ~7% 5-year survival rate and limited treatment options.(1)
- Anti-PD-1/PD-L1 immunotherapy offers only modest benefit; better understanding of the tumor immune microenvironment is needed.(2)
- Spatial organization of immune cells and cell-to-cell communication (CCC) between tumor and immune cells have been shown to contribute to immune evasion and T cell dysfunction.(3)

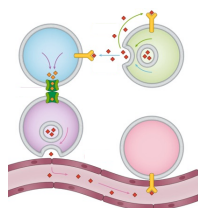


Fig 1. Cell-to-cell communication collectively describes intermolecular interactions.

HYPOTHESIS

Macrophages located within the tumor epithelium engage in spatially constrained immunosuppressive cell-to-cell communication that limits T cell infiltration and anti-tumor immunity in SCLC.

METHODS

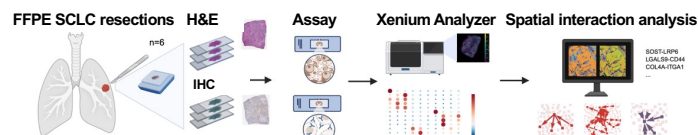


Fig 2. Analytical workflow for spatial transcriptomic profiling of SCLC. Six FFPE primary tumor resections underwent H&E and IHC staining, followed by Xenium Prime profiling, cell type annotation and spatially resolved cell-cell communication analysis.(4)

RESULTS

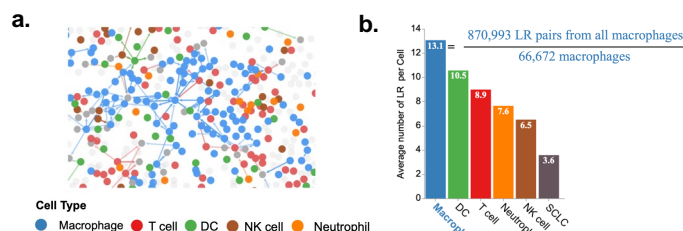


Fig 3. Spatial cell-cell communication. a, Spatial network of CCC in the SCLC TME. Edges connect interacting cell pairs. b, Macrophages exhibit the highest average LR/cell among immune cells in SCLC TME.

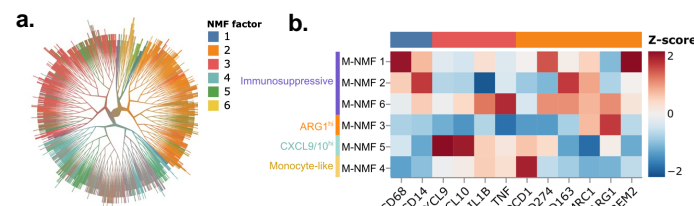


Fig 4. Macrophage heterogeneity. a, Hierarchical clustering of macrophage NMF factors (TooManyCells). b, Heatmap of z-score normalized marker gene expression across macrophage NMF factors.

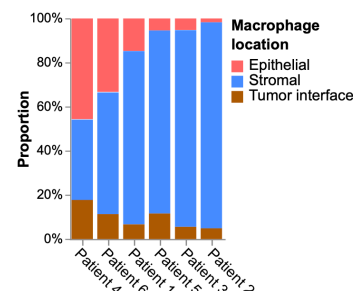


Fig 5. Macrophage compartment proportions across patients. Stacked bar chart showing the proportional distribution of macrophages across the three spatial compartments for each patient.

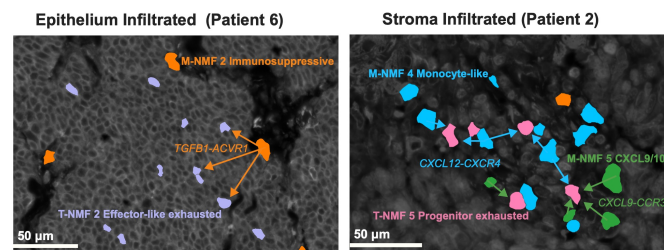


Fig 6. Spatial co-localization of macrophage and T cell NMF subsets. Representative Xenium images from epithelium- and stroma-infiltrated archetypes, highlighting NMF-defined cell subsets and key ligand-receptor interactions.

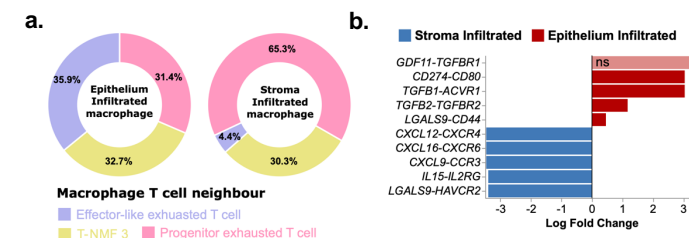


Fig 7. a, Proportional distribution of T cell NMF subsets neighboring different macrophages. b, Differential LR interactions between macrophages and T cells across archetypes.

SIGNIFICANCE

We define spatially resolved macrophage heterogeneity in SCLC and identify compartment-specific macrophage-to-T cell interactions as potential drivers of immunotherapy resistance.

REFERENCES

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