Spatial transcriptomics identifies unique pharmacodynamic effects of checkpoint inhibitor treatment on the tumor microenvironment in NSCLC

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Introduction

Immune checkpoint inhibitor (ICI) therapies have improved outcomes in non-small cell lung cancer (NSCLC). However, the long-term benefit of ICI therapy is only realized in a subset of patients and why this occurs remains elusive. Examining how patients respond to ICI treatment is critical to developing personalized treatments for each tumor and improving patient outcomes. Spatial transcriptomics platforms, like spatial transcriptomics, have enabled the characterization of molecular changes with high resolution in the tumor microenvironment (TME). By leveraging the spatial transcriptomics platform, the Cell Atlas (CTA) platform, we aimed to identify unique pharmacodynamic effects of combination ICI treatment on the tumor microenvironment (TME) in NSCLC.

Methods

All patients had surgical resection of tumors then adjuvant gemcitabine, or vinorelbine; patients were followed until progression and/or death. In our cohort, patients who may derive additional benefit from combination ICI treatment were selected to be included in this study. We hypothesized that pretreatment with neoadjuvant chemo before resection may drive an initial immune response and a compensatory Treg expansion.

Results

Patients who experienced progressive disease had higher CD8 activity before treatment, but this increased over time, consistent with known mechanism of PD1 blockade. CD8+ T cell increases over time, consistent with known mechanism of PD1 blockade. CCR5 and B2M were among the top upregulated genes in the TME post-ICI treatment. Pathway enrichment was performed using mSigDB Hallmark Pathways to summarize broad molecular changes. Pathways upregulated post-ICI suggested a strong immune response consistent with T-cell activation including IL2, TNFα, and IFNγ. Immune cell signatures showed significant changes during ICI treatment. Macrophages (Figure 4B,C).

Conclusions

- Pathway enrichment suggested an improved immune response consistent with T-cell activation including IL2, TNFα, and IFNγ.
- Immune cell signatures showed significant changes during ICI treatment. Macrophages showed the most heterogeneity (Figure 4A).
- We observed an increase in T-cell expression after long term checkpoint inhibitor treatment, evidenced by increased cytotoxic T populations and pro-inflammatory pathways (IFNγ, IL12). Figure 4E).
- In our cohort, patients who may derive additional benefit from combination ICI treatment were selected to be included in this study.

References


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