Spatial Analytics of HCC Response to Anti-PD1 Therapy:
A Two by Two Case Study

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Abstract

This study aimed to better understand the differential immune landscape in HCC patients who responded, or didn't respond to Anti-PD1 therapy in hopes of identifying key agents in driving immune response. For this, a spatial transcriptomics analysis was adopted, and key results were chosen for demonstration.

Introduction

Hepatocellular carcinoma (HCC) is a major public health burden, and the most common primary liver cancer in adults around the world. A therapy for HCC patients is anti-PD1. However, in recent years, the efficacy of anti-PD1 therapy on HCC has observed varying results.

In this two by two case study, anti-PD1 therapy responding [R] and non-responding [NR] HCC patient studies were evaluated using spatial transcriptomics analytics. This study aims to identify changes in the immune microenvironment, and find key agents in the immune system that confer better response to anti-PD1 treatment.

Methodology

Sample information:
4 liver cancer biopsy samples from the Fudan University Shanghai Cancer Center*
- 2 responders to anti-PD1 immunotherapy
- 2 non-responders to anti-PD1 immunotherapy

Spatial transcriptomics analytics (10X Genomics)
Chemistry: Visium V4 slide- FFPE v2
Probe set name: Visium Human Transcriptome Probe v2.0
Transcriptome: GRCh38-2020-A
Pipeline version: spaceranger-2.0.1

* Ethics approval documents have been obtained by the research group

Results

Fig 1.

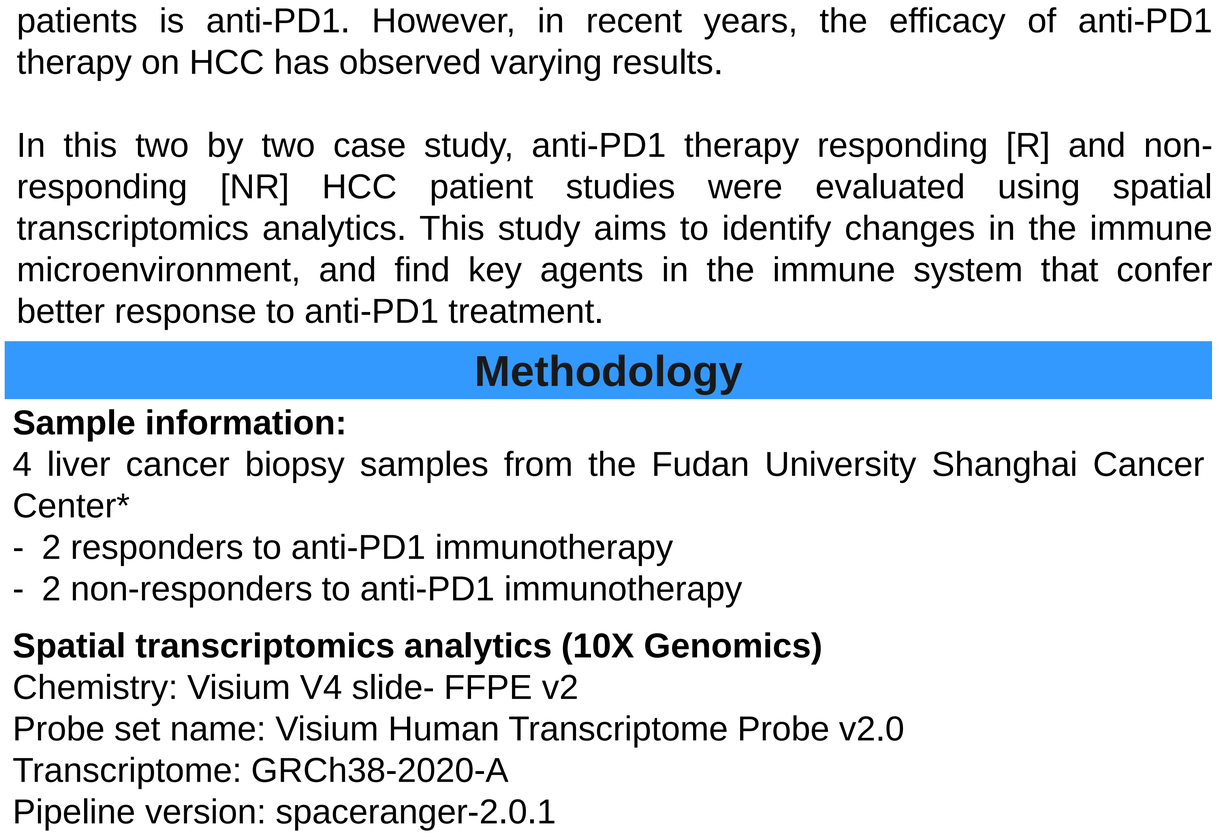
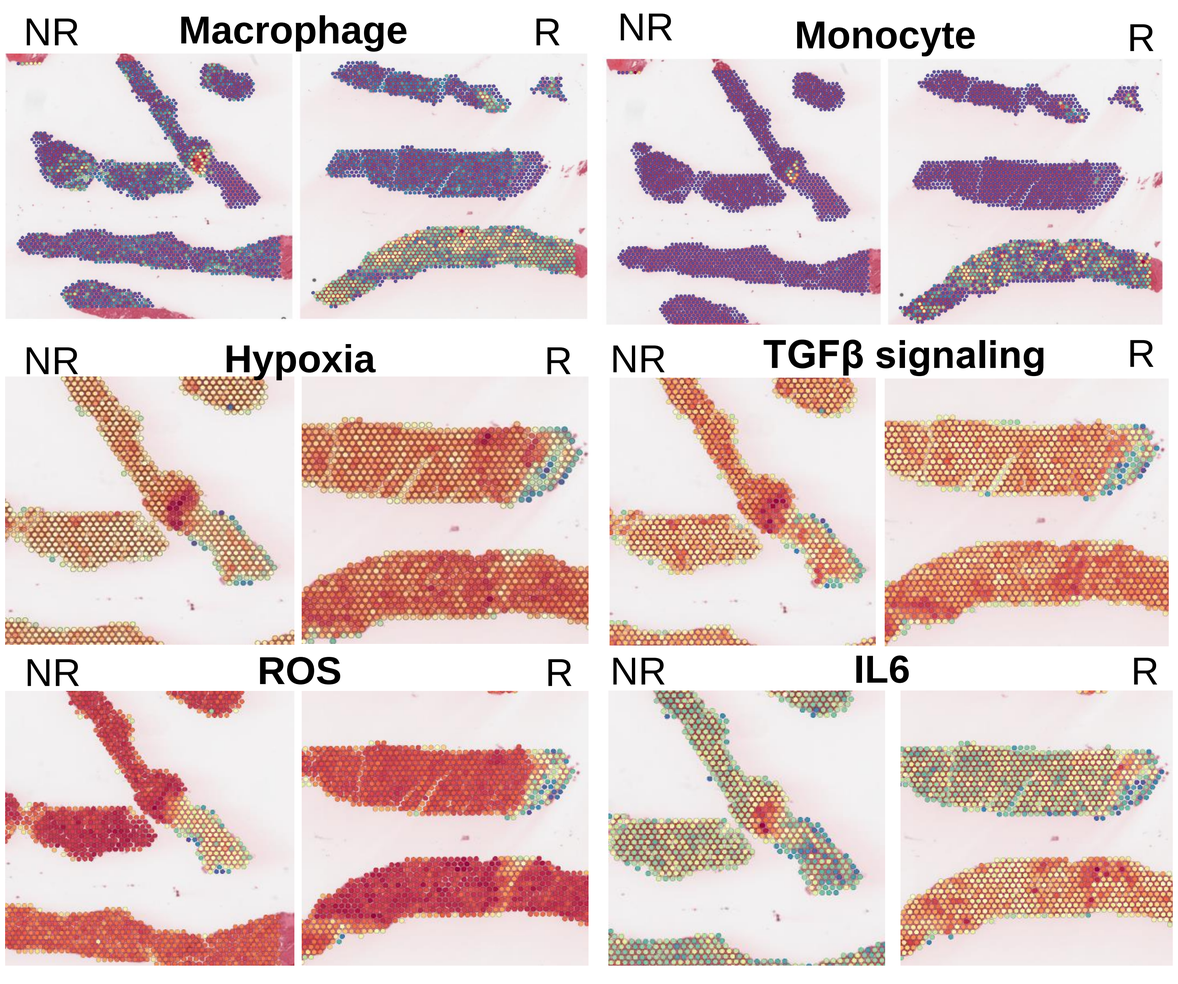


Fig 2.



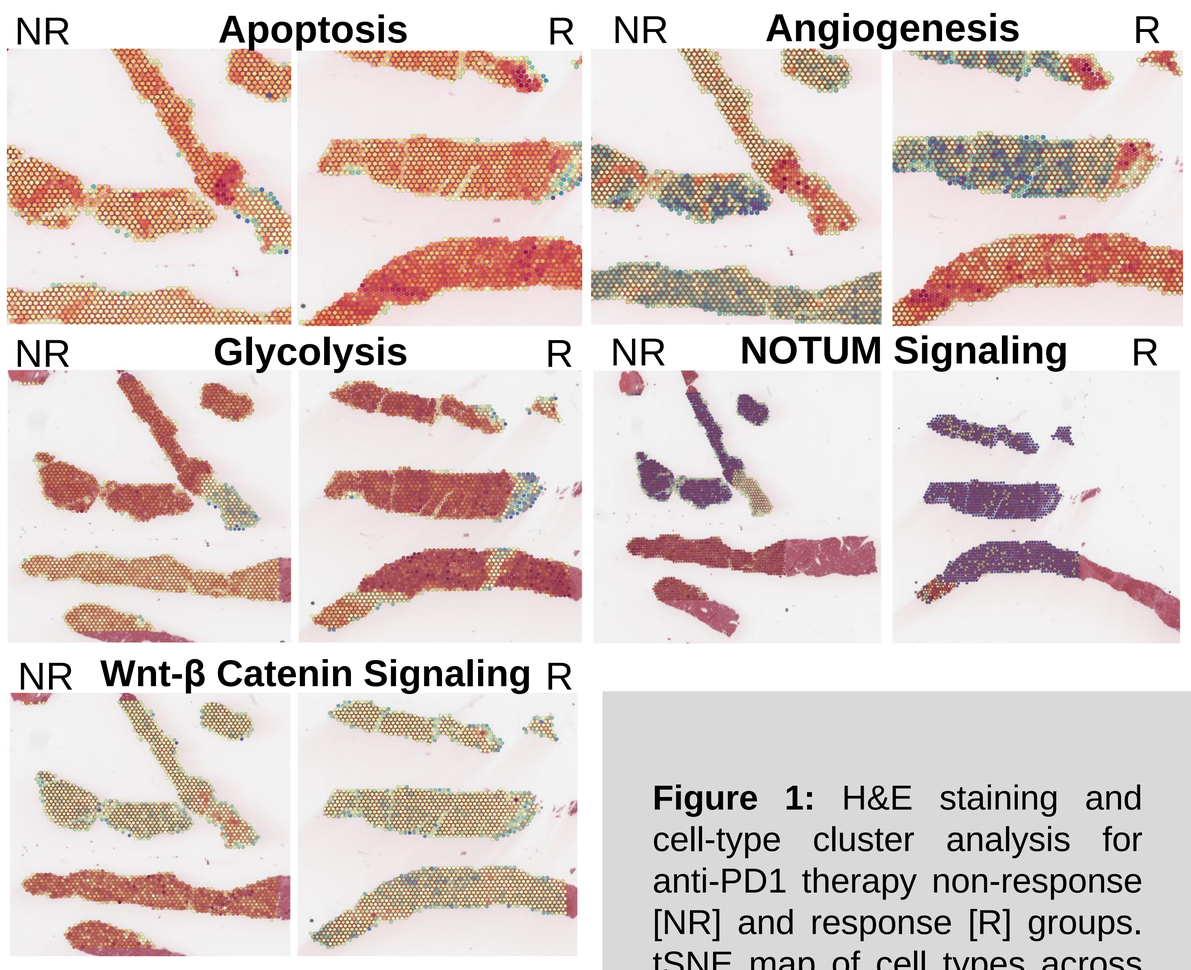


Fig 3.

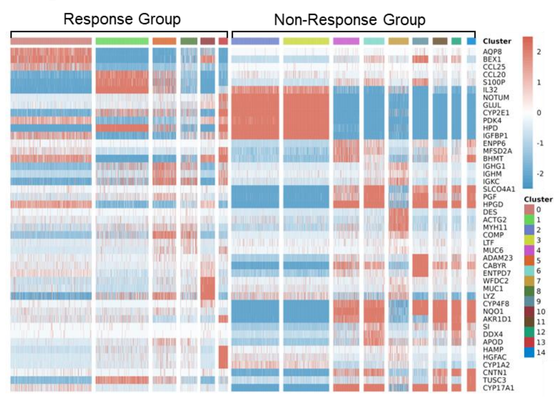


Figure 1: H&E staining and cell-type cluster analysis for anti-PD1 therapy non-response [NR] and response [R] groups. tSNE map of cell types across all samples.

Figure 2: Gene signature markers enrichment patterns in NR [left] and R [right] tissue

Figure 3: Heatmap of top GSEA markers enriched across cell types for R and NR group.

The hypoxia hallmarks are highly enriched in the both groups. At the more hypoxic regions, denser macrophage and monocyte populations are observed, especially at the boundary between fibrotic and carcinoma tissues.

From the NR group, the tissues with stronger hypoxic patterns are also correlate with TGFβ signaling, ROS, IL6, apoptosis, and angiogenesis expression. The remaining regions have high expression of glycolysis hallmark. Similar correlations are not observed in R group.

At the highly proliferative cancerous tissues, Wnt-β catenin signaling, including the NOTUM, gene, is highly expressed. Glycolytic and lipid-related metabolism and T-cell receptor signaling pathway differentiated expressed in the immunosuppressive regions.

Summary

In our results, the macrophage and monocyte populations seemed to cluster around the tumor boundary in the immunotherapy non-responder patients. Immunosuppressive signaling pathways were more enriched in those regions, and the cancerous tissues appeared to be more proliferative.

An aspect of further study is the influence of the Wnt-β catenin pathway in anti-PD1 resistance. From the differential expression of Wnt-β catenin signaling and NOTUM in non-responders, one stemming hypothesis is that increased activity of Wnt-β catenin could be a method to bypass the ICI therapy and reduce its efficacy. Another aspect this can impact is cancer metabolism and its relationship with T-cell receptor signaling, which were among some of the top enriched marker genes expressed in the immunosuppressive regions.

This study is largely preliminary, with a small dataset and limited tests conducted on the samples. For further studies, in vitro and in vivo models realizing the above mentioned microenvironmental conditions will be useful to illustrate the complex immune response in the HCC tissues.

Reference

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