Presurgical Anti-PD-1 Immunotherapy Expands and Reinvigorates Tumor- Reactive T Cells in Recurrent Glioblastoma

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Background
• Glioblastoma (GBM) is the most common and lethal brain tumor.1
• Standard of care has not changed in 20+ years, and median patient survival is only 14 months1.
• Immunotherapies have revolutionized the treatment of other cancers but are less effective against GBM2.
• Tumor-specific T cells are present at low frequencies in GBM and express inhibitory molecules such as PD-1, rendering them dysfunctional2,3.
• Presurgical anti-PD-1 (aPD1) has been shown to improve clinical outcomes and promote T cell infiltration2,3.

Objective
• To identify and quantify a population of potentially tumor-reactive T cells within the local GBM microenvironment.
• To characterize phenotypic changes in these T cells associated with favorable therapeutic response to aPD1.

Methodology
Figure 2: Experimental Design. Single-cell RNA and TCR sequencing were performed on the tumor-infiltrating immune cells from 42 recurrent GBM patients treated with and without aPD1.

Figure 3: Clustering and Differential Expression Analysis. UMAP of 35,248 lymphoid cells, capturing 8 T cell phenotypes (labeled). The color of each cluster corresponds to its gene expression box plot.

Figure 4: Tumor-Reactive T Cell Frequencies. Bar plots indicating the proportion of tumor-reactive T cells in untreated (blue) and aPD1-treated (red) patients. P-values were calculated using a Welch’s t-test.

Figure 5: Clonal Distribution. T cell clone sizes estimated by TCRβ sequencing.

Figure 6: Clonal Overlap. Treatment-associated differences in transitional TCRs shared between phenotypes.

Transcriptional Analysis

Conclusions
• CXCL13+ T cells with a unique antitumor expression signature4 are rare in GBM but are increased by aPD1.
• High TCR overlap with the progenitor exhausted population implies that aPD1 prolongs the functionality of these cells.
• Future studies will seek to verify tumor-reactivity by examining TCR specificity against patient-derived GBM samples.

References

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