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 months[1].
- Immunotherapies have revolutionized the treatment of other cancers but are less effective against GBM[2].
- Tumor-specific T cells are present at low frequencies in GBM and express inhibitory molecules such as PD-1, rendering them dysfunctional[2,3].
- Presurgical anti-PD-1 (aPD1) has been shown to improve clinical outcomes and promote T cell infiltration[2,3].

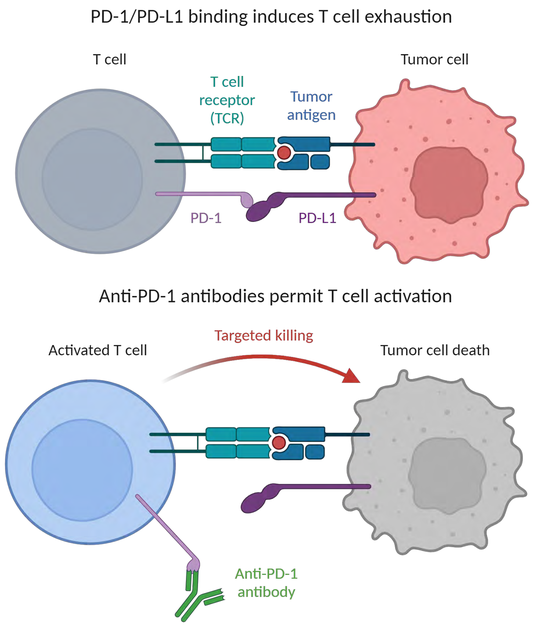

Figure 1: Mechanism of PD-1 Blockade

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

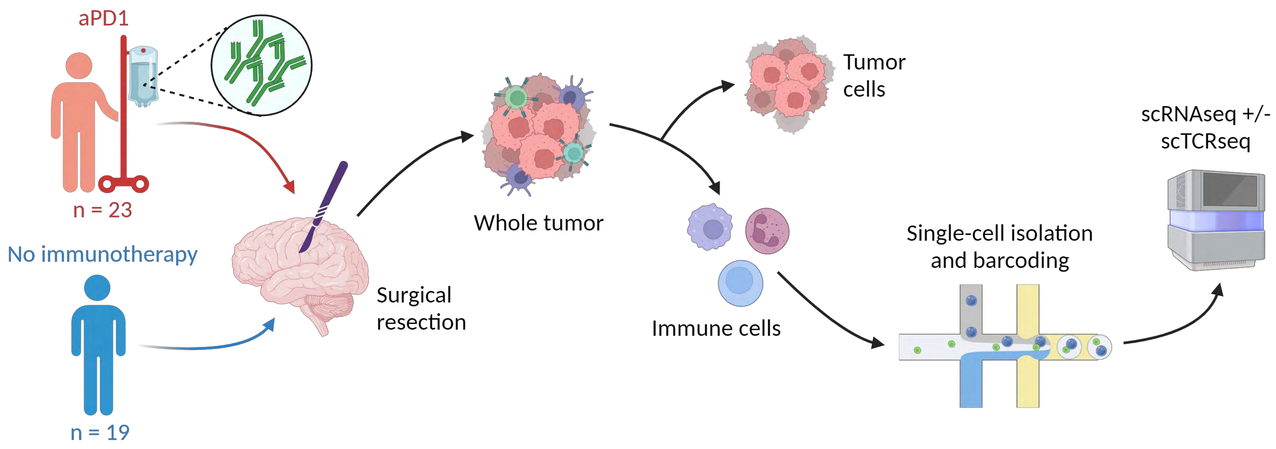

Figure 2: Experimental Design. Single-cell RNA and TCR sequencing were performed on the tumor-infiltrating immune cells from 42 recurrent GBM patients treated with and without aPD1.

Transcriptional Analysis

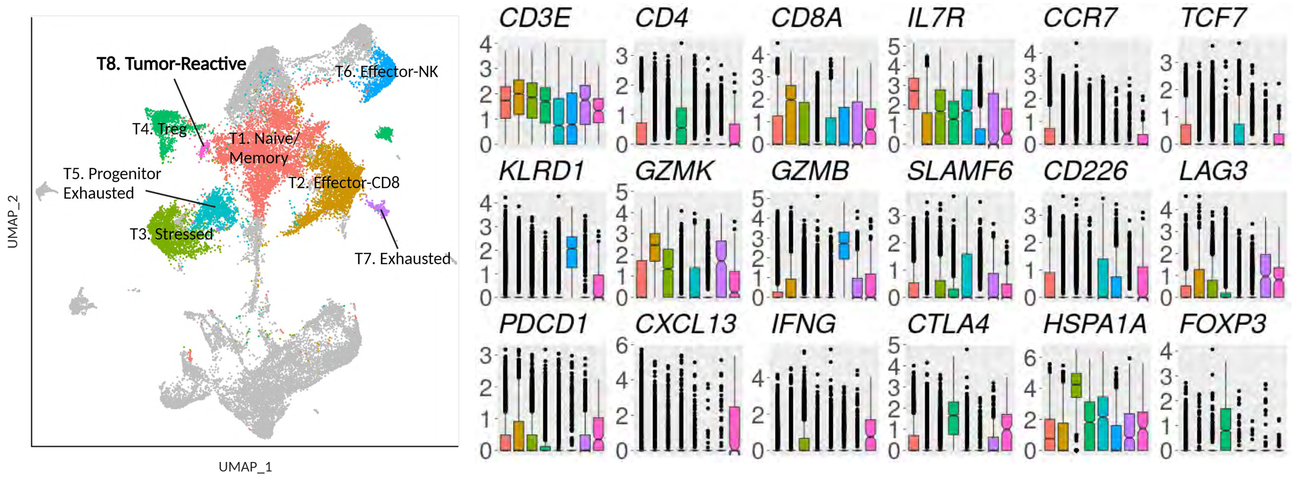

Figure 3: Clustering and Differential Expression Analysis. UMAP of 35,248 lymphoid cells, capturing 8 T cell phenotypes (labeled). The color of each cluster corresponds to its gene expression box plot.

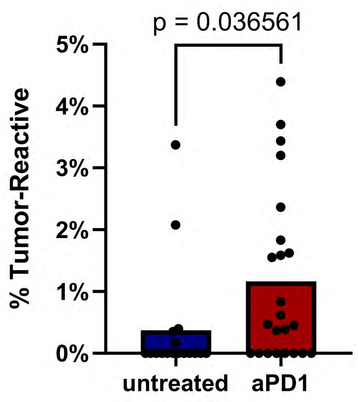

Figure 4: Tumor-Reactive T Cell Frequencies. Bar plots indicating the proportion of tumor-reactive T cells in untreated (blue) and aPD1-treated (red) patients. P-values were calculated using a Welch's *t*-test.

Conclusions

- *CXCL13*+ T cells with a unique antitumor expression signature[4] 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.

Clonotype Analysis

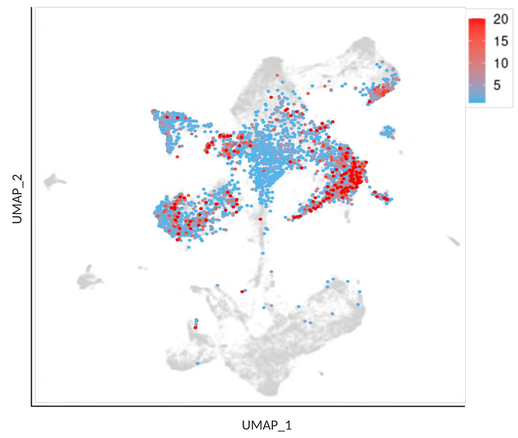

Figure 5: Clonal Distribution. T cell clone sizes estimated by TCRβ sequencing.

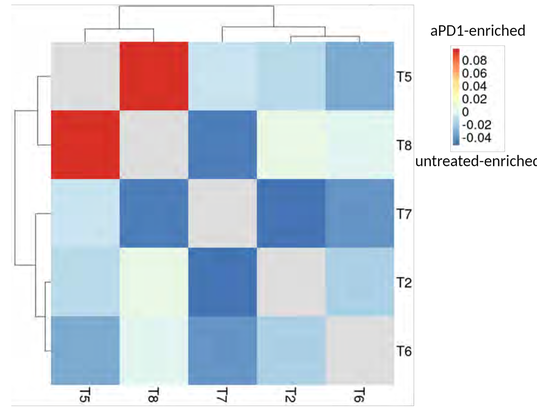

Figure 6: Clonal Overlap. Treatment-associated differences in transitional TCRs shared between phenotypes.

References

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3. Lee, A.H., Sun, L., Mochizuki, A.Y. et al. Neoadjuvant PD-1 blockade induces T cell and cDC1 activation but fails to overcome the immunosuppressive tumor associated macrophages in recurrent glioblastoma. *Nat Commun* 12, 6938 (2021). https://doi.org/10.1038/s41467-021-26940-2
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Acknowledgements

Financial support was provided by the National Institutes of Health, grant number 5R25DE030117-03.