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IMMUNOPHENOTYPING OF BRAIN TUMORS IDENTIFIES INTERFERON ENRICHED PHAGOCYTES IN HUMAN GLIOMAS

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Background Gliomas are recalcitrant brain tumors. Anti-glioma immunity and immunopathogenic responses are critical contributors for better survival of isocitrate dehydrogenase-mutant (IDH^{mut}) over wild-type (IDH^{wt}) gliomas. Despite this correlative pattern of immunity and survival, an unbiased understanding of cell-type specific transcriptomic and epigenomic states of glioma-derived myeloid cells beyond immunosuppressive paradigms remains elusive.

Methods To this end, we performed single-cell RNA-sequencing (scRNA-seq) on 140,000 tumor-associated immune cells from eighteen IDH mutation classified primary (N=8) and recurrent (N=10) human gliomas and three non-glioma brains (NGBs). We performed unsupervised clustering and cell annotation based on overlapping canonical lineage and signal dependent transcription factors. Gene ontology and gene set enrichment analyses were performed to define functional states of glioma associated myeloid cells.

Results Our analyses revealed twelve myeloid cell types across glioma subgroups. We noted abundant microglial cells in IDH^{mut} than IDH^{wt} gliomas. Concomitantly, continuum of microglia and macrophage phenotypes were observed in IDH^{wt} glioma, which exhibit more severe tumor pathologies. Strikingly, we identified a hybrid microglia/macrophage cell subset with enriched interferon module inferred from our gene ontology analyses. These hybrid phagocytes were significantly increased in recurrent IDH^{wt} gliomas. As tissue macrophages exhibit multifaceted polarization in response to microenvironmental cues, we clarify the existence of microglia/macrophage functional states beyond M1/M2 paradigms exemplified by the presence of palmitic-, oleic- acid, and glucocorticoid responsive polarized states. Specifically, certain microglia and monocyte-derived subpopulations were associated with antigen presentation gene modules, akin to cross-presenting dendritic cells. Furthermore, immune related gene ontology analysis identified enriched antigen presentation and phagocytosis gene modules in distinct microglia-like clusters. Importantly, the phagocytic immunomodulator; Triggering Receptor Expressed on Myeloid Cells 2 (TREM2) was upregulated in these microglia-like cells. Contrary to tumor promoting role of TREM2 myeloid cells in non-brain cancers, we identify TREM2 axis as a regulator of antigen presentation. Additionally, single cell- Assay for Transposase-Accessible Chromatin using sequencing (sc-ATAC-seq) on ~40,000 tumor-associated microglia revealed genes associated with IFN-gamma/IL-12/IL-10 pathway were negatively regulated in IDH^{mut}/IDH^{wt} microglia compared to homeostatic microglia in NGBs.

Conclusions In summary, our study sculpts transcriptional and epigenomic details and re-defines glioma-specific immune contexture for downstream immunogenomics applications. We specifically reveal interferon and TREM2 nodes on microglia-

like phagocytic cells as clinically tractable anti-glioma immunotherapy target.

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