

1040-D IDENTIFICATION OF FOUR CLINICALLY-RELEVANT IMMUNOMODULATORY PROGRAMS SHARED ACROSS NEARLY ALL GLIOMA-ASSOCIATED MYELOID CELLS

¹Tyler E Miller*, ²Chadi El Farran, ³Charles Couturier, ²Zeyu Chen, ²Joshua D'Antonio, ⁴Alex Shalek, ⁵Kevin Petrecca, ¹Mario Suva, ²Bradley Bernstein. ¹Massachusetts General Hospital, Boston, MA, USA; ²Dana Farber Cancer Institute, Boston, MA, USA; ³Broad Institute of MIT and Harvard, Cambridge, MA, USA; ⁴Massachusetts Institute of Technology, Cambridge, MA, USA; ⁵McGill University, Montreal, QC, Canada

Background Gliomas are incurable malignancies notable for an immunosuppressive microenvironment with abundant myeloid cells whose immunomodulatory properties remain poorly defined.

Methods We utilize scRNA-seq data for 183,062 myeloid cells from 85 human tumors and integrate mitochondrial DNA-based lineage tracing, spatial transcriptomics, and functional organoid models.

Results We discover that nearly all glioma-associated myeloid cells express at least one of four immunomodulatory activity programs. These include a Scavenger Immunosuppressive program, a C1Q Immunosuppressive program, a CXCR4 Inflammatory program, and an IL1B inflammatory program. We reveal that these programs are driven by microenvironmental cues and therapies rather than myeloid cell type or origin. All four programs are present in lower-grade and high-grade gliomas and expressed in multiple myeloid cell types derived from blood or resident myeloid cell origins. The Scavenger Immunosuppressive program is induced in hypoxic regions, while the C1Q Immunosuppressive program is driven by dexamethasone. Both immunosuppressive programs are less prevalent in lower-grade gliomas, which are instead enriched for the CXCR4 Inflammatory program. We validated this striking myeloid cell plasticity by demonstrating that application of peripheral blood monocytes to glioma organoid models leads to de novo induction of microglia, macrophage and dendritic cell identities, and all four immunomodulatory programs.

Conclusions Our study provides a resource and new framework to understand immunomodulatory myeloid cells in glioma, and a foundation to develop effective immunotherapy strategies for glioma patients.

Ethics Approval All work with human subjects was approved by the Dana Farber Cancer Institute's Institutional Review Board under the protocol 10-417.

<http://dx.doi.org/10.1136/jitc-2023-SITC2023.1040-D>