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TITLE
T cell-released IFN-γ drives the generation of intratumoral antigen-presenting cells that promote rejection of malignant gliomas

HYPOTHESIS:
Adoptive T cell immunotherapy drives the differentiation of hematopoietic stem and progenitor cells (HSPCs) into antigen-presenting cells within the tumor microenvironment.

BACKGROUND/AIMS:
Despite treatment with surgical resection, radiation, and chemotherapy, patients with malignant gliomas only achieve a median survival of 18 months. Our group has pioneered an adoptive T cell immunotherapy that utilizes total tumor RNA-pulsed dendritic cells to expand polyclonal tumor-reactive T cells _ex-vivo_. The strongest anti-tumor efficacy of adoptive T cell immunotherapy is realized when combined with syngeneic, lineage-depleted HSPC transplant, leading to a doubling of median survival and 30% long-term cures in treatment-resistant murine malignant glioma. While HSPCs are known to migrate to gliomas, it remains unknown what they differentiate into in the glioma microenvironment and how this impacts anti-tumor immunity.
Aim 1: Evaluate the impact of HSPC transfer on host tumor-infiltrating myeloid cells.
Aim 2: Determine how activated T cells drive the differentiation of HSPCs into antigen-presenting cells.

METHODS:
We evaluated lineage-depleted HSPC differentiation in the context of adoptive T cell immunotherapy _in-vivo_ and HSPC proliferation and differentiation _in-vitro_ using a T cell co-culture supernatant transfer system. Additionally, we FACS-sorted HSPC-derived cells from tumor-bearing mice to examine antigen presentation capability _ex-vivo_ and used an IFN-γ reporter for _in-vivo_ verification. To determine the impact of HSPC differentiation on anti-tumor efficacy, we performed survival experiments with tumor-bearing animals.

RESULTS & CONCLUSIONS
The anti-tumor efficacy and differentiation of HSPCs into antigen-presenting cells in the brain tumor microenvironment depended on IFN-γ released from tumor-reactive T cells. Additionally, HSPC-derived CD11c⁺ MHCII⁺ cells cross presented tumor-derived antigens to tumor-reactive T cells, increasing T cell activation within the tumor. When evaluating the impact of HSPCs on host immunity, we determined that HSPC transfer strongly correlates with a loss of host myeloid-derived suppressor cells. We have made novel observations that HSPCs significantly enhance adoptive immunotherapy in malignant gliomas. This occurs through HSPCs supplanting host immunity and synergizing with T cells in the brain tumor microenvironment. A phase I trial evaluating the impact of HSPC transfer on adoptive immunotherapy in pediatric high-grade gliomas is on schedule to open this year (ACTION—FDA IND#BB-17298). This data will inform this trial and translate into a novel HSPC platform for patients.