SELECTIVE EXPANSION OF ANTI-TUMOR CD4 T-CELL SUBSETS CONTRIBUTES TO ONCOLOYTIC VIROTHERAPEUTIC EFFICACY IN MALIGNANT GLIOMA
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Background Malignant glioma, an aggressive type of brain tumor, remains an intractable problem with uniformly fatal outcomes in patients. We engineered herpes simplex virus (HSV)-1 and developed oncolytic HSV (oHSV) to treat brain tumors, given its capacity to selectively kill tumor cells while sparing normal cells, and to boost anti-tumor immunity. Both of our phase I trial and preclinical studies have demonstrated the safety and efficacy of this oHSV-based therapy. However, the nature of anti-tumor immune responses to such therapy remains largely unclear.

Methods An oHSV expressing murine IL-12 (M002) and vehicle control were used to treat immunocompetent mice bearing intracranial glioma. The in vitro cell culture assays, in vivo adoptive transfer approaches and single-cell RNA sequencing coupled with T-cell receptor (TCR) repertoire analysis of intratumoral CD4+ T-cells were performed.

Results We revealed that M002 treatment preferentially induced unique CD4+ T-cell populations in the tumor that were distinct from conventional T helper subsets and displayed less exhausted phenotype but increased effector activity. CD4+ T-cells isolated from M002-treated tumors prolonged mice survival and had better tumor-killing ability than CD4+ T-cells from vehicle-treated control tumors in an MHCII-dependent manner. Notably, M002 treatment reduced the CD4+ T-cell clonal diversity but expanded certain clones.

Conclusions These results suggest that the capacity of oncolytic virotherapy to reshape the CD4+ T-cell repertoire and to enhance their anti-tumor functionality contributes to its improved efficacy. This study has provided insights into the immune-based mechanistic actions of oHSV therapy and has suggested the strategies for the development of better treatments for brain tumor patients.

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Ethics Approval All animal experiments were performed in compliance with federal laws and institutional guidelines as approved by the UAB IACUC.

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