TARGETING A NOVEL MYELOID CHECKPOINT SIGLEC-15 IN GBM GENERATES AN EXTREMELY DURABLE RESPONSE WITH ZIKA VIRUS ONCOLOYTIC THERAPY

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Background Glioblastoma (GBM) is a highly aggressive and malignant brain tumor. Despite aggressive treatment, GBM has a poor prognosis, and it is difficult to eliminate using current treatment strategy. Moreover, recurrence is a major challenge.

Methods To develop glioma model, we performed intracranial injection of CT2A and SB28 mouse glioma cells. ZIKV injection was given intratumorally 7 days post tumor implantation. Four doses of anti-siglec-15 and anti-PD1 injection were given intraperitonially.

Results We are developing Zika virus as a therapy for GBM. Previously we showed ZIKV significantly increases survival in multiple syngeneic glioma mouse models. Like other oncolytic therapies, it generates a potent, anti-tumor CD8+ T-cell response. Post-ZIKV, we observe a 32-fold increase in myeloid cells in the GBM microenvironment. Siglec-15 is a novel myeloid immune checkpoint in cancer, which suppresses T-cell activation; an antibody targeting Siglec-15 is currently in clinical trial for lung cancer. Using immunostaining, we report for the first time that Siglec-15 is expressed on myeloid cells in human GBM specimens. Using syngeneic murine models, we observed that anti-Siglec-15 alone does not improve survival. However, in combination with ZIKV, anti-Siglec-15 significantly improves survival in the CT2A, SB28, and GL261 glioma models. Elaborating CT2A model, the combination treatment increased long-term survivors (at least 90 days) to 60%, compared to 20% with ZIKV alone and 0% with no treatment. To further confirm the role of Siglec-15, we used Siglec-15 knockout (KO) mice and observed 70% long-term survivor rate in Siglec-15 KO mice treated with ZIKV, compared to 40% in wild-type mice (C57BL/6J) with ZIKV. ZIKV treatment in Siglec-15 KO mice led to activation of CD8+ T-cells and increased expression of cytotoxic molecules granzyme B and perforin, indicating enhanced anti-tumor activity. Additionally, we detected high levels of IFN-gamma and TNF-alpha, further supporting the anti-tumor response. We further improved efficacy by targeting T-cells checkpoint marker PD-1. This combination resulted in 90% long-term survivors in Siglec-15 KO mice following ZIKV treatment. Moreover, in a model for recurrence, upon contralateral rechallenge with CT2A in long-term survivors, we observed long-term memory T-cell responses, with increased numbers of CD8+ T-cells displaying effector and resident memory cell phenotypes, compared to age-matched controls. We obtained similar results with immune-resistant SB28 model.

Conclusions This work suggests that ZIKV oncolytic therapy combined with blocking myeloid checkpoint Siglec-15, using an agent already in humans, and blocking CD8+ T cell checkpoint with anti-PD1, is worthy of study in humans.

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