A NOVEL LIOMBLASTOMA MODEL RESISTANT TO BOTH INNATE AND ADAPTIVE IMMUNOTHERAPY

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Background Glioblastoma (GBM) is the most common and aggressive adult primary brain malignancy, with a median overall survival of only 15 months. Clinically, GBM is refractory to T cell immune checkpoint blockade (ICB) likely as a result of its immunosuppressive tumor microenvironment enriched in glioma-associated myeloid cells (GAMs) and lacking in effector T cells.1,2 The Qki-/- Pten-/- P53-/- (QPP8) tumor model reflects this phenotype3 but is highly sensitive to agonists of the innate Stimulator of Interferon Genes (STING) pathway.4,5 Here we report a novel QPP8v GBM tumor model with faster growth kinetics and decreased sensitivity to STING agonists compared to parental QPP8, enabling study of resistance mechanisms to STING activation in GBM.

Methods Orthotopic QPP8 tumors were selected in vivo for growth kinetics, then expanded into stable neurosphere cultures ex vivo for generation of three QPP8v cell lines. These lines were re-implanted in vivo to test penetrance, growth kinetics, and sensitivity to STING agonists and ICB. Using the synthetic cyclic di-nucleotide STING agonist IACS-8803 (8803) we treated orthotopic QPP8 and QPP8v tumors intratumorally.6 We then analyzed survival and performed high parameter flow cytometry profiling of the tumor immune microenvironment following STING agonist treatment.

Results We found that STING agonist therapy cured 100% of murine orthotopic QPP8 tumors versus 40% in the QPP8v model, and that the median survival of QPP8v was half that of parental QPP8. In both models, STING agonist-treated tumors displayed significantly increased infiltration of inflammatory Ly6C+ mononcytic cells and NK cells, as well as increased CD8 T and NK cell Granzyme B. In both models, STING agonist increased CD86 expression across the myeloid infiltrate, and substantially increased both CD80 and CD86 expression on dendritic cells in the cervical lymph nodes. While STING agonist promoted a trend of increased CD8 T cell infiltration in QPP8 tumors, this effect was absent in QPP8v.

Conclusions We report that the novel QPP8v tumor model displays faster growth kinetics and decreased STING agonist sensitivity compared to parental QPP8, while maintaining insensitivity to ICB. Despite the decreased sensitivity to STING agonists, profiling of the tumor immune microenvironment revealed similar proinflammatory conversion of the myeloid infiltrate. Additionally, both models displayed increased NK and CD8 T cell Granzyme B, suggesting that infiltrating effector cells are more cytotoxic following STING agonist treatment. However, the augmented densities of CD8 T cells within QPP8 tumors were not observed in QPP8v, suggesting that suboptimal CD8 T cell infiltration contributes to QPP8v immune escape.

Ethics Approval All mice were housed in accordance with the Association for Assessment and Accreditation of Laboratory Animal Care and NIH standards. All experiments were conducted according to protocols approved by the University of Texas MD Anderson Cancer Center Institutional Animal Care and Use Committee.

REFERENCES

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