ANTI-VEGF THERAPY IMPROVES EGFR-VII-CAR-T CELL DELIVERY AND EFFICACY IN SYNGENEIC Glioblastoma Models IN MICE

Xinjue Dong, Jun Ren, Zhrah Amoogzar*, Menal Datta, Somin Lee, Sylvie Roberge, Mark Duquette, Dai Furukuma, Rakesh Jain. MGH, Harvard Medical School, Boston, MA, United States

Abstract

Background Chimeric antigen receptor (CAR)-T cells have revolutionized treatment of multiple types of hematological malignancies, but have shown limited efficacy in patients with glioblastoma (GBM) or other solid tumors. This may be largely due to the immunosuppressive tumor microenvironment (TME) that compromises the delivery and anti-tumor activity of CAR-T cells. We previously showed that blocking VEGF (vascular endothelial growth factor) signaling can normalize tumor vessels in murine and human tumors, including GBM, breast, liver, and rectal carcinomas. Moreover, we demonstrated that vascular normalization can improve the delivery of CD8+ T cells and efficacy of immunotherapy in breast cancer models in mice. In fact, the US FDA has approved 7 different combinations of anti-VEGF drugs and immune-checkpoint blockers for liver, kidney, lung and endometrial cancers in the past 3 years.1-7 Here we tested the hypothesis that anti-VEGF therapy can improve the delivery and efficacy of CAR-T cells in immunocompetent mice bearing orthotopic GBM tumors.

Methods We engineered two syngeneic mouse GBM cell lines (CT2A and GSC005) to express EGFRVIII – one of the most common neoantigens in human GBM – and CAR-T cells to recognize EGFRVIII. We tested our CAR-T cells in orthotopic GBMs for their efficacy in recognizing, and killing tumor cells, and the survival advantage when tumor vessels are normalized.

Results We found that treatment with the anti-mouse VEGF antibody (B20) improved CAR-T cell infiltration and distribution throughout the GBM TME, delayed tumor growth, and prolonged survival of GBM-bearing mice compared to EGFRVIII-CAR-T cell therapy alone (figure 1).

Conclusions Our study provides a strategy to overcome major challenges in CAR-T cell therapy in GBM by: (i) increasing the CAR-T cell infiltration, intratumoral distribution, and activation in murine GBM models, and (ii) reprogramming TME by increasing the number and activation of endothelial effector T cells, resulting in improved anti-tumor efficacy of CAR-T therapy in two GBM mouse models. Given that anti-VEGF therapies have been approved for a number of solid tumors, including GBM, our study provides mechanistic insights and compelling preclinical data in support of testing the combination of vascular normalizing agents and CAR-T therapies in GBM patients. Furthermore, this approach may also improve CAR-T therapy of other solid tumors that share similar TME features as well as for other cell-based therapies using autologous or allogeneic immune cells (e.g., NK cells, macrophages).

References

25. Martinez Bedoya D, Dutiot V & Migliorini D. Allogeneic CAR T Cells: An Alterna-
Abstract 911 Figure 1  Anti-VEGF treatment improves the efficacy of EGFRvIII-CAR-T
(A) Schematic representation of experimental setup to evaluate the effect of PBS, CAR-T, B20, IgG + CAR-T and B20 + CAR-T on the survival of GSC005 and C2TA GBM-bearing mice. (B) and (C) Median survival and tumor growth kinetics for C2TA tumors [PBS (n=22, 15.5 days), CAR-T (n=14, 20.5 days), B20 (n=8, 24.5 days), B20 + CAR-T (n=19, 32 days)]. (D) and (E) Median survival and tumor growth kinetics for GSC005 tumors [PBS (n=12, 13.5 days), CAR-T (n=17, 18.5 days), B20 (n=10, 24 days), IgG + CAR-T (n=13, 18 days), B20 + CAR-T (n=21, 37 days)]. Error bars show median ± SEM. Statistical analysis was performed using one-way ANOVA test. *p <0.05, ****p < 0.001