Enhancing Glioblastoma Immunotherapy with Integrated Chimeric Antigen Receptor T Cells through the Re-Education of Tumor-Associated Microglia and Macrophages

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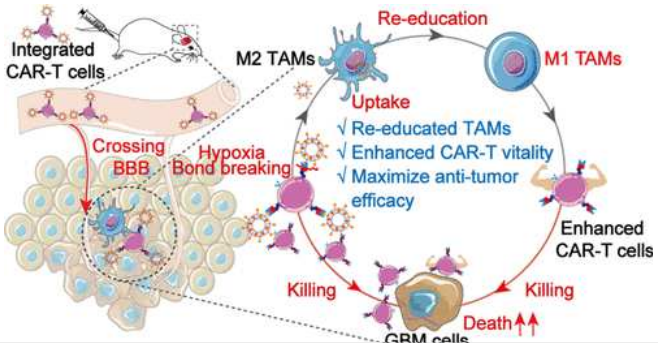
SI Supporting Info (1) »

SUBJECTS: Cells, Central nervous system, Fluorescence, Tumors, Vesicles

Abstract



cells against GBM. Molecularly targeting drug pexidartinib (PLX) has been reported to re-educate TAMs toward the antitumorigenic M1-like phenotype. Here, we developed a cell–drug integrated technology to reversibly conjugate PLX-containing liposomes (PLX-Lip) to CAR-T cells and establish tumor-responsive integrated CAR-T cells (PLX-Lip/AZO-T cells) as a combination therapy for GBM. We used a mouse model of GBM to show that PLX-Lip was stably maintained on the surface of PLX-Lip/AZO-T cells in circulation and these cells could transmigrate across the blood–brain barrier and deposit PLX-Lip at the tumor site. The uptake of PLX-Lip by TAMs effectively re-educated them into the M1-like phenotype, which in turn boosted the antitumor function of CAR-T cells. GBM tumor growth was completely eradicated in 60% of the mice after receiving PLX-Lip/AZO-T cells and extended their overall survival time beyond 50 days; in comparison, the median survival time of mice in other treatment groups did not exceed 35 days. Overall, we demonstrated the successful fusion of CAR-T cells and small-molecule drugs with the cell–drug integrated technology. These integrated CAR-T cells provided a superior combination strategy for GBM treatment and presented a reference for the construction of integrated cell-based drugs.

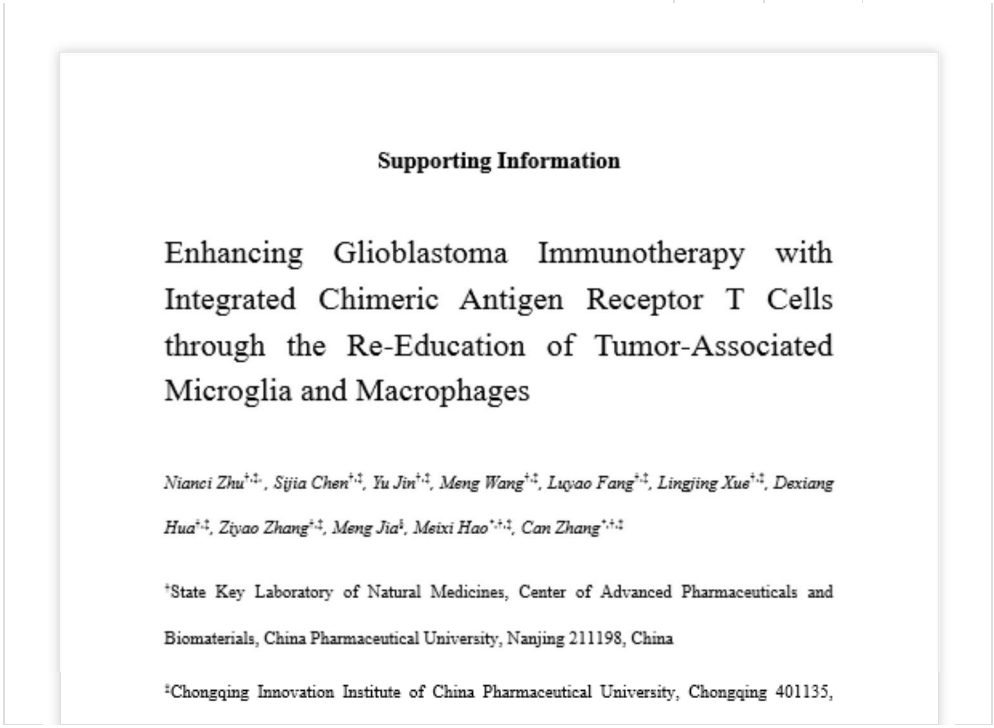
KEYWORDS: glioblastoma, CAR-T cells, re-educated TAMs, blood–brain barrier

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsnano.4c00050.

- Materials and methods including the detailed methods of the synthesis of DSPE-PEG2k-AZO-N_3 and SA_2-DBCO, preparations and characterization of the liposomes, cell culture, and isolation of the primary cells; synthesis of DSPE-PEG2K-AZO-N_3 and SA_2-DBCO; ^{1}H NMR spectra of DSPE-PEG2K-AZO-N_3 and SA_2-DBCO; UV absorbance of azobenzene bone in DSPE-PEG2K-AZO-N_3 at different time under hypoxic conditions; Figures S4−S5, characteristics of the PLX-Lip; characteristics of GD2 CAR-T cells; optimal preparation conditions of PLX-Lip/AZO-T cells; characteristics of PLX-Lip/AZO-T cells; drug-loading stability of PLX-Lip/AZO-T cells in serum-containing medium; construction of orthotopic GBM-bearing mice model; biodistribution of CAR-T cells and PLX-Lip in vivo; characteristics of integrated CAR-T cells not responsive to hypoxia; release of PLX and PLX-Lip from PLX-Lip/AZO-T cells under hypoxic conditions with time; uptake of PLX-Lip released from PLX-Lip/AZO-T cells by TAMs

Associated Microglia and Macrophages



Supporting Information

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