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CRISPR screening of CAR T Cells and cancer stem cells reveals critical dependencies for cell-based therapies

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Glioblastoma (GBM) contains self renewing GBM stem cells (GSCs) potentially amenable to immunologic targeting, but chimeric antigen receptor (CAR) T cell therapy has demonstrated limited clinical responses in GBM. Here, we interrogated molecular determinants of CAR-mediated GBM killing through whole-genome CRISPR screens in both CAR T cells and patient-derived GSCs. Screening of CAR T cells identified dependencies for effector functions, including Transducin-like enhancer protein 4 (TLE4) and IKAROS Family Zinc Finger 2 (IKZF2). Targeted knockout of these genes enhanced CAR antitumor efficacy. Bulk and single cell-RNA sequencing of edited CAR T cells revealed transcriptional profiles of superior effector function and inhibited exhaustion responses. Reciprocal screening of GSCs identified genes essential for susceptibility to CAR-mediated killing, including RELA and NPLOC4, the knockout of which altered tumor-immune signaling and increased responsiveness of CAR therapy. Overall, CRISPR screening of CAR T cells and GSCs discovered avenues for enhancing CAR therapeutic efficacy against GBM, with the potential to be extended to other solid tumors.

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