Identification of gene that drives T cells to exhaustion may lead to more effective immunotherapies

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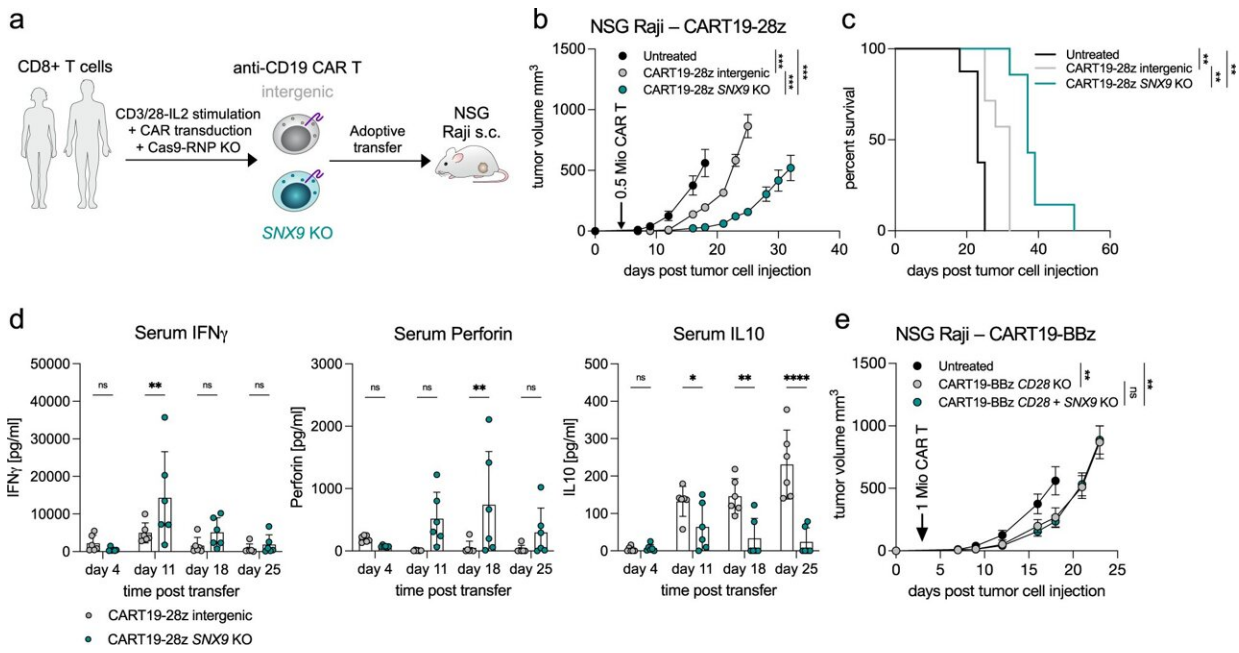

Deletion of SNX9 improves CAR T cell anti-tumor efficacy. a Schematic representation of the CAR T cell transfer experiments. Healthy donor human CD8 T cells are stimulated ex vivo and lentivirally transduced with an anti-human-CD19(FMC63vH)-CD28-CD3zeta-T2A-copGFP CAR construct and electroporated with Cas9-crRNA-tracrRNA complexes to generate SNX9 KO cells and intergenic controls. These cells are then transferred to NSG mice with subcutaneous Raji tumors (CD19+). b Tumor volume in mm^3 of NSG mice treated 3 days post Raji tumor injection by i.v. transfer of 0.5 Mio human CD8 anti-CD19-28z CAR T cells with or without SNX9 KO (mean and SEM). Statistics are pairwise 2-way ANOVAs followed by Bonferroni correction. n = 8

animals for untreated of n = 2 experiments. n = 7 mice for CART-treated mice of n = 1 experiment. Experiment was replicated with similar results with higher CART numbers. c Survival of the NSG mice in 5b until humane endpoint of 1500mm^3 tumor size. Statistics are log-rank Mantel-Cox tests followed by Bonferroni correction. (b and c): n = 8 for untreated, n = 7 for intergenic and SNX9 KO CAR T conditions. d Human cytokines measured by Legendplex (Biolegend) in the serum of Raji-bearing NSG mice treated with anti-CD19-28z CAR T cells with and without SNX9 KO. Statistics are paired-2-way ANOVA with Holm-Sidak correction. n = 6 mice per condition. Mean and SD are shown. e Tumor volume in mm^3 (mean and SEM) of NSG mice treated 3 days post Raji tumor injection by i.v. transfer of 1 Mio human CD8+ CD28 KO anti-CD19-BBz CAR T cells with or without SNX9 KO. n = 6 for intergenic and SNX9 KO, n = 8 for untreated. Statistics are 2-way ANOVAs followed by Bonferroni correction. * p

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