determine irAE type-specific incidence, the incidence of multiple irAEs in a single patient, and response to corticosteroid therapy.

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254 CTLA-4 BLOCKADE PROMOTES TREG GLUCOSE METABOLISM AND REDUCES TREG FUNCTIONAL STABILITY IN GLYCOLYSIS-DEFECTIVE TUMORS

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Background Durable clinical responses to immune checkpoint blockade (ICB) occur in a limited fraction of patients. We thus hypothesized that the characteristic tumor metabolic switch towards aerobic glycolysis could contribute to ICB resistance. High glucose consumption and lactate production by tumor cells can indeed restrict nutrient availability for tumor-infiltrating T cells, which also rely on glycolysis to proliferate and function. Therefore, we investigated whether targeting tumor glucose metabolism potentiates ICB anti-tumor activity.

Methods We modeled tumor-selective glycolysis inhibition by knocking down the critical glycolytic enzyme lactate dehydrogenase A (LDHA-KD) in the murine metastatic breast carcinoma 4T1 and melanoma B16, which are known immune-refractory tumor models. Anti-CTLA-4 and anti-PD-1 were tested in immunocompetent mice orthotopically implanted with control vs. LDHA-KD tumor cells. Changes in glucose metabolism were assessed by Seahorse and fluorescent-glucose flow-cytometry staining. Changes in immune cells were measured by multiparameter flow cytometry. Glucose-dependent effects of anti-CTLA-4 in regulatory T cells (Tregs) were tested in standard suppression assays with increasing glucose concentration (0.5–10 mM). Pearson correlations between glycolysis and intra-tumor immune-cell infiltration by CIBERSORT immune-deconvolution method were analyzed in bulk RNA-