Background Properly functioning T-cells are critical for effective immunity. Upon activation, T-cells engage glycolysis and this metabolic adaptation is required for the optimal production of effector cytokines that mediate tumor clearance. However, during cancer T-cells often experience a progressive decline in effector functions, preventing tumor regression. Failure of T-cells to protect against cancer is thought to result from lack of antigen recognition, chronic activation, and/or suppression by other cells. Whether other mechanisms exist, or precisely how T-cell hypersponsiveness in tumors is established, remains unclear.

Methods We used an established mouse sarcoma model of regressing and progressing tumors to compare the metabolic parameters between T-cells and tumor cells. By genetically-engineering the glucose metabolism of regressing sarcoma cells, we were able to compare between groups based on tumor growth at the same background of antigenicity. Checkpoint blockade therapy (e.g. anti-PD-1, and anti-PD-L1 antibodies) were used to determine if the treatment can correct nutrient restriction experienced by T cells in a progressing tumor.

Results Glucose consumption by tumors metabolically restricts T-cells in the tumor microenvironment, which dampens their mTOR activity and glycolytic capacity, limits their interferon-gamma (IFN-γ) production, and leads to tumor progression. Enhancing glycolysis in an antigen ‘regressor’ tumor is sufficient to override the ability of T-cells to respond to a major tumor rejection antigen, allowing progression of tumors that are normally rejected. Checkpoint blockade increases the metabolic fitness of T-cells and restore glucose in the microenvironment of progressing tumors, permitting T-cell glycolysis and IFN-γ production.

Conclusions Metabolic competition in the tumor microenvironment dictates effector T-cell function and this influences cancer progression. Combining therapies that blunt tumor metabolism with those that promote glycolysis in T cells could provide new effective treatments for cancer. In lupus, research looking into metabolic requirement for immune cells and other modulators may provide novel insight to the nature of lupus development.