Tumor Microenvironment Sugar Fighting: Metabolic Competition Can Determine Cancer Progression

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**Abstract**

Properly functioning T cells are critical for effective tumor immunity. Upon activation, T cells engage aerobic 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. Using a mouse sarcoma model, we show that glucose consumption by tumors metabolically restricts T cells in the tumor microenvironment, which dampens their mTOR activity and glycolytic capacity, limits their IFN-γ production, and leads to tumor progression. We demonstrate that enhancing glycolysis in an antigenic ‘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 therapy is used clinically to promote immune rejection of progressing tumors. We show that checkpoint blockade (anti-CTLA-4, anti-PD-1, and anti-PD-L1) monoclonal antibodies restore glucose in the microenvironment of progressing tumors, permitting T cell glycolysis and IFN-γ production. Together our results show that metabolic competition in the tumor microenvironment dictates effector T cell function and that 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.

**Selected Publications for Reference**