Modulation of immune metabolism enhances the efficacy of PD-1 blockade immunotherapy

Immunotherapy by PD-1 blockade dramatically improved the survival rate of cancer patients, but unfortunately a significant fraction of patients remains less sensitive to this therapy. To overcome this issue, we developed a novel strategy to modulate T cell energy metabolism. We firstly compared the mitochondrial activity of tumor-reactive cytotoxic T lymphocytes (TR CTLs) before and after the PD-1 blockade therapy in mouse model. It was shown that the mitochondria of TR CTLs in draining lymph nodes were activated with increased reactive oxygen species (ROS). Increase of ROS in T cells by ROS precursors treatment synergized the tumoricidal activity of PD-1 blockade. Perturbation of mitochondrial activity by uncouplers enhanced the efficacy of PD-1 blockade therapy in a ROS-dependent manner. This enhancement effect involved mTOR/AMPK-related energy signaling pathway. When PGC-1α, a common downstream signaling factor of mTOR and AMPK, was activated by a PPAR ligand Bezafibrate, the PD-1 blockade efficacy was improved. These findings indicate the importance of PGC-1α-associated pathway in T cells for enhancement effect, which bridge energy metabolism and T cell immunity.