REDIRECTING GLUCOSE FLUX DURING IN VITRO EXPANSION IMPROVES THE IN VIVO PERFORMANCE OF ADOPTIVE T CELL THERAPIES FOR CANCER

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Background Adoptive cell therapy (ACT) has shown great promise as a cancer therapeutic in some hematologic malignancies. However, several barriers prevent widespread use of cellular therapies in other cancers, including the need for T cells to perform and persist within the nutrient-poor tumor microenvironment (TME). Extensive in vitro culture is required for all current forms of ACT, but current culture strategies favor the energetic needs of T cells for rapid and robust expansion while ignoring their metabolic requirements within the TME. Here we demonstrate that the deleterious effects of in vitro culture can be mitigated by redirecting T cell glycolysis away from terminal lactate production to more energetically efficient OXPHOS during initial expansion. This in vitro metabolic shift drastically improves anti-tumor efficacy in vivo and establishes long-term memory without any further modifications, thus demonstrating an easily applied improvement for all forms of ACT.

Methods Antigen-specific T cells were activated in culture with their cognate peptide or in vivo in response to cognate antigen. The pyruvate dehydrogenase kinase (PDHK1) inhibitor dichloroacetate (DCA) was used to redirect glucose flux during cell expansion. Mouse experiments were performed with gp100-specific pmel-1 TCR-Tg T cells transferred into B16 melanoma-bearing mice. Human experiments were performed with anti-hCD19 CAR-T cells transferred into NSG mice bearing hCD19-A549 lung cancer cells.

Results Identical, antigen-specific T cells stimulated with typical in vitro culture conditions or responding to cognate antigen in vivo differ not in effector function but heavily in their metabolism: typical T cell activation and culture heavily favors aerobic glycolysis. The PDHK1 inhibitor DCA allows for glucose uptake and metabolism but shunts glucose into the mitochondria, maintaining mitochondrial health. In vitro expansion of T cells in the presence of DCA improves their pre-infusion metabolic profile, cytokine production, and survival in low nutrient culture media. Expansion in the presence of DCA results in striking improvements in ACT in both murine TCR-Tg and human CAR-T cells.

Conclusions Current culture strategies do not prepare T cells for performance within the TME. DCA shunts glycolysis in a manner that re-directs metabolism to a more oxidative state. This small redirection improves the phenotype of T cells pre-infusion and better prepares them for the lack of nutrients in vivo. By generating more functional T cells for infusion, we are able to metabolically enhance their in vivo performance in a manner potentially synergistic with other more engineered improvements.

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