330 REDIRECTING GLUCOSE USAGE DURING IN VITRO EXPANSION IMPROVES THE IN VIVO PERSISTENCE AND FUNCTION OF ADOPTIVE T CELL THERAPIES FOR CANCER

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Background While adoptive T cell therapies have shown impressive results in cancer therapy, persistence of cells remains a key feature of therapeutic efficacy. In all forms of cellular therapies, large numbers of cells are transferred to the patient, yet comparatively few can be detected within the body. We hypothesize this lack of survival and persistence is in part due to the hypermetabolic conditions, especially hyperglycemia, used to generate large numbers of T cells in vitro. Within this study, we aim to preserve a more in vivo-like metabolic state during T cell expansion so that upon transfer they may more easily re-enter the immune system and persist as a living drug.

Methods T cells were activated in culture with cognate peptide or *in vivo* with cognate antigen. The pyruvate dehydrogenase kinase (PDHK1) inhibitor dichloroacetate (DCA) was used to redirect glucose flux in vitro. Mouse tumor experiments were performed with gp100-specific pmel-1 TCR-Tg T cells transferred into B16-F10 -bearing mice. Mouse co-transfer experiments were performed with pmel-1 T cells on a congenically mismatched background. Human CAR-T experiments were performed using anti-hCD19 CAR-T cells transferred into immunodeficient mice bearing hCD19-A549 lung cancer cells.

Results Identical T cells stimulated in vitro or in vivo do not differ in effector function but differ heavily in their glycolytic metabolism. As direct inhibition of glycolysis severely hinders T cell expansion, the PDHK1 inhibitor DCA redirects glucose away from lactate production into mitochondrial metabolism, maintaining a robust expansion rate. Expansion under DCA improves cytokine production and promotes features of stemness. However, the most striking effect of expansion under DCA is evident after cells are transferred: improved immediate and long term survival of the transferred T cell product. These immediate changes in survival result in striking therapeutic efficacy, including increased tumor clearance, immunologic memory, and long-term cellular persistence in both mouse and human tumor models.

Conclusions We demonstrate that by redirecting glucose into mitochondria using DCA, T cells experience vastly reduced metabolic stress during expansion. This relatively simple energetic shift in vitro drastically improves the immediate survival and engraftment of T cells after infusion, resulting in enhanced anti-tumor efficacy and long-term memory. Our study not only suggests the current manufacturing process for cell therapies, utilizing hypermetabolic media, may hinder their ultimate therapeutic success, but provides potential solutions to bring the promise of cellular therapies to additional patients.

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