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PI3Kδ/γ inhibition promotes human CART cell epigenetic and metabolic reprogramming to enhance antitumor cytotoxicity.

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Current limitations in using chimeric antigen receptor T(CART) cells to treat patients with hematological cancers include limited expansion and persistence in vivo that contribute to cancer relapse. Patients with chronic lymphocytic leukemia (CLL) have terminally differentiated T cells with an exhausted phenotype and experience low complete response rates after autologous CART therapy. Because PI3K inhibitor therapy is associated with the development of T-cell-mediated autoimmunity, we studied the effects of inhibiting the PI3Kδ and PI3Kγ isoforms during the manufacture of CART cells prepared from patients with CLL. Dual PI3Kδ/γ inhibition normalized CD4/CD8 ratios and maximized the number of CD8+ T-stem cell memory, naive, and central memory T-cells with dose-dependent decreases in expression of the TIM-3 exhaustion marker. CART cells manufactured with duvelisib (Duv-CART cells) showed significantly increased in vitro cytotoxicity against CD19+ CLL targets caused by increased frequencies of CD8+ CART cells. Duv-CART cells had increased expression of the mitochondrial fusion protein MFN2, with an associated increase in the relative content of mitochondria. Duv-CART cells exhibited increased SIRT1 and TCF1/7 expression, which correlated with epigenetic reprograming of Duv-CART cells toward stem-like properties. After transfer to NOG mice engrafted with a human CLL cell line, Duv-CART cells expressing either a CD28 or 41BB costimulatory domain demonstrated significantly increased in vivo expansion of CD8+ CART cells, faster elimination of CLL, and longer persistence. Duv-CART cells significantly enhanced survival of CLL-bearing mice compared with conventionally manufactured CART cells. In summary, exposure of CART to a PI3Kδ/γ inhibitor during manufacturing enriched the CART product for CD8+ CART cells with stem-like qualities and enhanced efficacy in eliminating CLL in vivo.

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