Inhibition of AKT Signaling During Expansion of TCR-Engineered T-Cells from Patient Leukocyte Material Generates SPEAR T-Cells with Enhanced Functional Potential In Vitro

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Introduction

- T-cell attributes for adoptive cell therapy for patients with advanced cancer can be optimized during ex-vivo expansion culture.
- Inhibition of AKT signaling, driven by TCR receptor (TCR) activation and cytokine stimulation during ex-vivo expansion, has been hypothesized to uncouple TCR activation-induced proliferation and terminal differentiation programs, leading to generation of less differentiated T-cells with increased functional potential.
- AKT inhibition during T-cell expansion has been previously shown to generate T-cells with enhanced anti-tumor effector function and tumor cell-killing properties, resulting in increased persistence in vivo during adoptive T-cell transfer.
- Both TCR and cytokine growth factor signals used for ex-vivo T-cell expansion promote rapid activation of AKT (protein kinase B) signaling, which drives T-cell activation, proliferation, and terminal differentiation.

Objective

- To determine the effect of an AKT inhibitor (AKTi) on the generation of a SPEAR T-cell product with improved ex-vivo expansion and memory phenotypes.

Mechanism of Action

- Both TCR and cytokine growth factor signals used for ex-vivo T-cell expansion promote rapid activation of AKT (protein kinase B) signaling, which drives T-cell activation, proliferation, and terminal differentiation.

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- At the end of the assay, the numbers of CD8+ and CD4+ cells (transduced TCR+, and non-transduced TCR-) remaining in each well were counted by flow cytometry.
- ADP-A2M4 T-cells was monitored in 384-well format IncuCyte assay by quantifying GFP+ target cell numbers over 7 days. Data show mean values of 4 replicate wells per time point +/-SD.
- Non-specific cytokine secretion was not detected in corresponding non-transduced T-cell controls (data not shown). Secretion of IFNγ and IL-2 levels was measured by enzyme-linked immunosorbent assay.

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References


www.cellreports.org

https://youtu.be/zdI8IGXoQd0

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