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Optimizing clonal expansion of CD8 T cells by using silent mutations

Stanford scientists have discovered that using silent mutations to alter codon:anticodon affinity can be used to tune clonal expansion in CD8 T cells. Optimizing the differentiation and expansion of CD8 T cells can be a transformative method that increases the efficacy of CAR T-cell therapies.

Synonymous single nucleotide variants (sSNVs), or silent mutations, are genetic variations that occur in protein-coding regions of the genome but do not change the amino acid sequence of the encoded protein. While sSNVs were initially thought to be functionally neutral, they have recently been shown to effect gene expression, translation, and protein function. For example, the codon:anticodon specificity between a tRNA and an mRNA can affect the timing of translation and the co-translational folding of the protein. Despite their potential impact and prevalence, sSNVs are often overlooked in genome-wide association studies. Understanding the effects of sSNVs can gain insights into disease mechanisms and methods for optimizing precision medicine approaches.

An sSNV that increases codon:anticodon affinity was found to be enriched in effector memory CD8 T cells (CD8 TEMs). Importantly, this sSNV was expanded specifically in CD8 TEMs with minimal enrichment in other cell types. Consequently, this establishes proof-of-concept that a more favorable codon can be utilized to facilitate increased and specific clonal expansion of CD8 T cells *in vivo*.

Stage of Development:
Proof of concept

Applications

- Optimization of CD8 T cell differentiation and expansion
- Development of more efficacious CAR T-cell therapies

Advantages

- Enhancement of CD8 T cell activity by introducing silent mutations
- High potential for novel enhancement mechanisms from previously overlooked sSNVs

Publications

- Caleb A. Lareau, Ansuman T. Satpathy, et al. "Codon affinity in mitochondrial DNA shapes evolutionary and somatic fitness." bioRxiv 2023.04.23.537997

Patents

- Published Application: WO2023249934

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