Identification of genomic determinants contributing to cytokine release in immunotherapies and human diseases

Background

Cytokine release syndrome (CRS) can result from immune therapies such as CAR T-cell treatment, triggering a powerful immune response that often leads to severe inflammation. Identifying the genomic factors that contribute to CRS is essential for developing therapies to prevent or mitigate its effects. This study focused on the identification and characterization of PFKFB4, a gene linked to glycolytic activity, as a potential driver of cytokine release during CAR T-cell therapy and other diseases related to CRS.

Research Questions

- Which genomic factors are responsible for driving CRS in CAR T-cell therapies?
- How does PFKFB4 regulate cytokine release through its influence on the glycolytic pathway?
- Can targeting PFKFB4 provide an actionable approach for managing CRS and related diseases?

Results & Conclusions

- Expression of gene PFKFB4, a regulator of fructose-2,6-bisphosphate levels, was progressively higher in CAR T-cells from people who developed severe CRS.
- Additional genes involved in glycolysis were also upregulated in severe CRS samples.
- These findings were consistent with other disease cohorts (COVID-19, influenza, autoimmune diseases, and multiple different types of cancer) where elevated PFKFB4 expression was linked to more severe cytokine responses.
- The data strongly supports PFKFB4 as a key factor in CRS
- The nCounter analysis system was able to measure key targets to quickly understand the implications of a therapy on pathway biology.
- The findings suggests that drugs targeting PFKFB4 and the glycolytic pathway could effectively manage CRS in immunotherapy patients.

Experimental Design

Sample Type	CD22 CAR T-cell products from clinical trial participants
Tissue Type	Suspension cells
Assay	nCounter® CAR-T Characterization Panel
Analyte	RNA
Instrument	nCounter® Analysis System

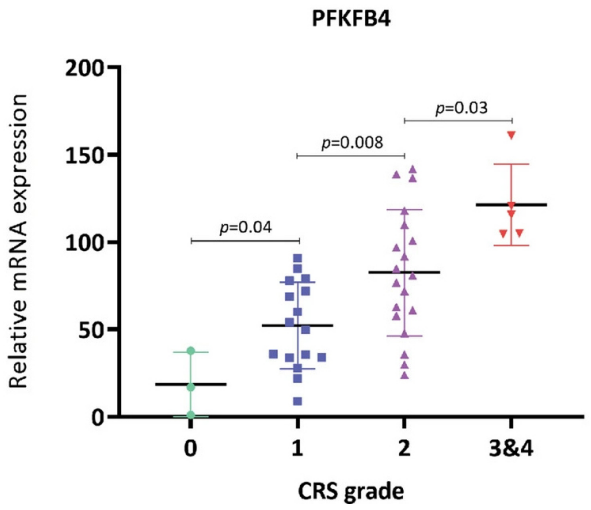

Figure 1: Differential gene expression of PFKFB4. The PFKFB4 gene was differentially up-regulated with increasing CRS severity.

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"[nCounter] has proven to be simpler and more effective compared to real-time qPCR, and time-saving and easier to analyze compared to RNA-seq." -Shao et al.

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