(PF1221) OVERCOMING LACTATE-MEDIATED T CELL SUPPRESSION VIA PTPN1 INHIBITION: A NOVEL STRATEGY TO ENHANCE CAR-T CELL EFFICACY IN MULTIPLE MYELOMA

Topic: 25. Gene therapy, cellular immunotherapy and vaccination - Biology & translational research

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Background

Background: In multiple myeloma, tumor cell metabolism and hypoxia lead to lactate accumulation and an acidic microenvironment. Lactate suppresses T cell anti-tumor capabilities, including those of CAR-T cells. The limited clinical efficacy of CAR-T in multiple myeloma pressing for the need to uncover mechanisms that sustain T cell activity under lactate conditions.Identifying mechanisms that sustain T cell function under lactate conditions is therefore crucial for improving CAR-T cell efficacy in hematological cancers. This study identified genetic regulators that preserve T cell function under

Aims

Aims: This study aims to identify key regulators that maintain T cell function under the immunosuppressive conditions of the multiple myeloma tumor microenvironment, specifically focusing on overcoming lactate-induced suppression. We will investigate the role of PTPN1 in T cell activation and effector function in the presence of lactate and evaluate its potential as a therapeutic target to enhance CAR-T cell efficacy.

Methods

Methods: We performed a genome-wide CRISPR knockout (KO) screen in human Jurkat T cells to identify genes critical for maintaining CD25 expression under lactate stress. Cells were stimulated with anti-CD3 and anti-CD28 antibodies in the presence of 15 mM lactate, followed by sorting of $CD25^+$ and $CD25^-$ populations and next-generation sequencing (NGS). Candidate genes were validated through in vitro assays in primary T cells and, crucially, in ex vivo expanded T cells representative of those used in adoptive cell therapy.

Results

Results: The CRISPR screen identified Protein Tyrosine Phosphatase Non-receptor type 1 (PTPN1) as a crucial regulator of T cell activation in the presence of lactate. Mechanistically, lactate suppressed $CD8^+$ T cell activation and cytotoxic function by reducing oxidative modification of PTPN1 at cysteine 215 (Cys215). This redox shift impaired TCR/IL-2/STAT5 signaling and effector cytokine production. Crucially, both genetic ablation of *PTPN1* and pharmacological inhibition using AC484 significantly rescued T cell signaling and restored the anti-tumor function of ex vivo expanded $CD8^+$ T cells, including their cytotoxic capacity, under lactate-rich conditions. These findings demonstrate that PTPN1 plays a critical role in mediating lactate-induced suppression of T cell effector function relevant to adoptive cell therapy.

Summary/Conclusion

Conclusions: Lactate suppresses T cell function, including that of CAR-T cells, by shifting the redox state of PTPN1 towards a less oxidized conformation, thereby impairing T cell signaling. Targeting PTPN1 restores T cell activation and effector functions under lactate stress, highlighting PTPN1 as a potential therapeutic target to enhance CAR-T cell persistence and efficacy in the acidic TME of hematological malignancies. These findings offer a novel strategy to overcome metabolic barriers and improve the clinical success of CAR-T cell immunotherapy.