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CD19 CAR T Cells drive a remodeling of the Immune Microenvironment associated with T-cell dysfunction in B-Cell Acute Lymphoblastic Leukemia

Category Experimental Hematology / Oncology

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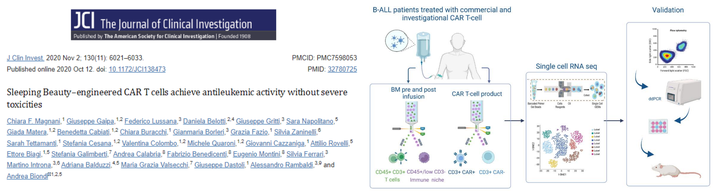
Introduction

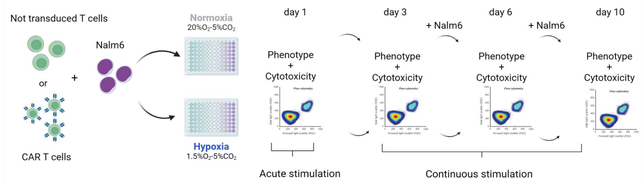
In patients with B-cell Acute Lymphoblastic Leukemia (B-ALL), Chimeric Antigen Receptor (CAR) T cells targeting CD19 have achieved durable responses. However, the contribution of the tumor microenvironment (TME) on CAR T-cell fate and endogenous immunity remains incompletely understood. Trancriptomic data from treated BALL patients' bone marrow (BM)-resident immune cells demonstrated that immunological niche reacts to CAR T cell-mediated inflammation by activation of inhibitory pathways and molecules. Remodelling of the composition of BM after CAR T-cell infusion is observed.
Significant enrichment for gene expression profile associated with Hypoxia was correlated with the expansion of Myeloid Derived Suppressor Cells (MDSC). In parallel, TGFβ signaling and cell exhaustion in endogenous CD8+ T cells and infused CAR T cells were observed.
Aim: Define role of Hypoxia in exacerbating the exhaustion of CAR T cells and endogenous immunity.

Methods

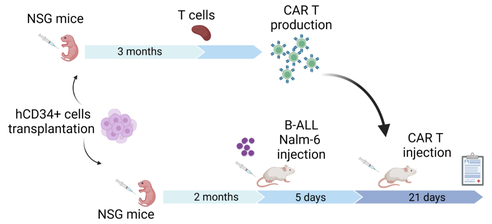
Single cell RNA sequencing in patients' samples



In vitro experiments



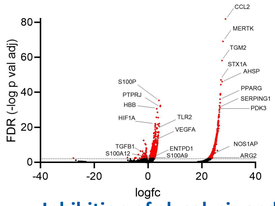
In vivo evaluation



Results

Enrichment in Interferon response, Hypoxia, and TGF-β signaling was associated with the expansion of MDSC, and exhausted T cells

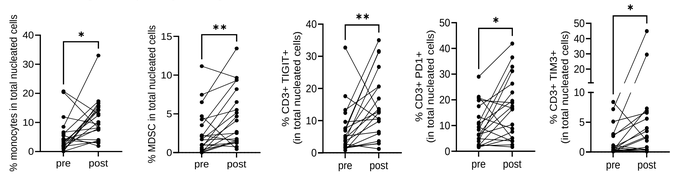
Volcano plot of myeloid cells



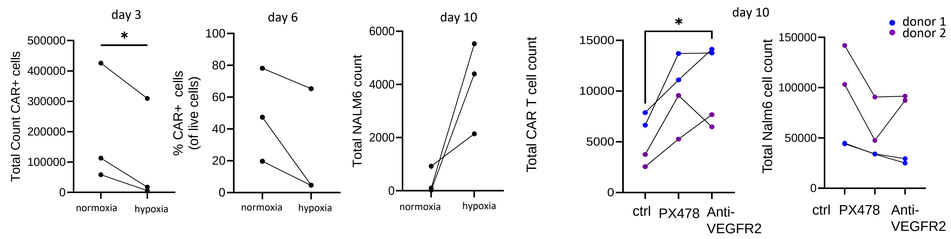
Significantly-enriched Hallmark gene sets in post-treatment versus pre-treatment within CD45+CD3- libraries

Increased MDSC and T-cell exhaustion post-treatment

Spectral flow cytometry validation n= 20

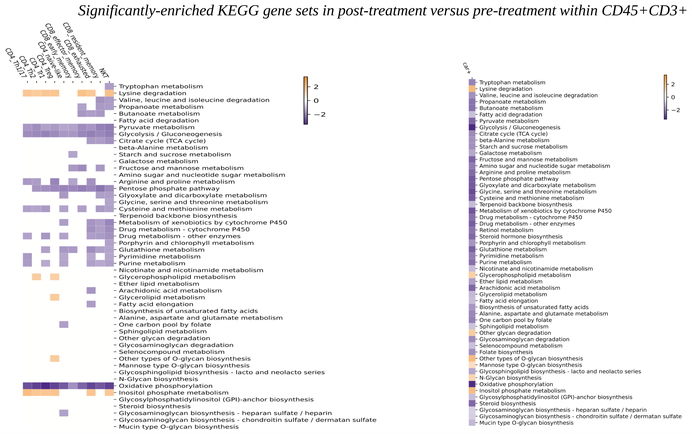


Role of chronic inflammation and Hypoxia in driving T cell dysfunction

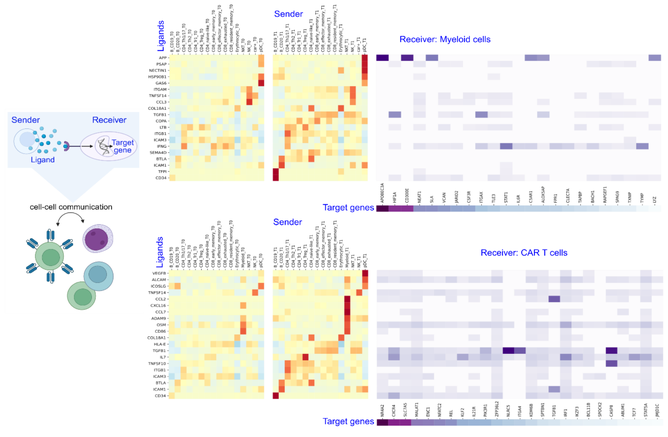


Inhibition of glycolysis and oxidative phosphorylation associated with increased lipid metabolism suggest that endogenous T cells and CAR T cells are facilitated to cell exhaustion

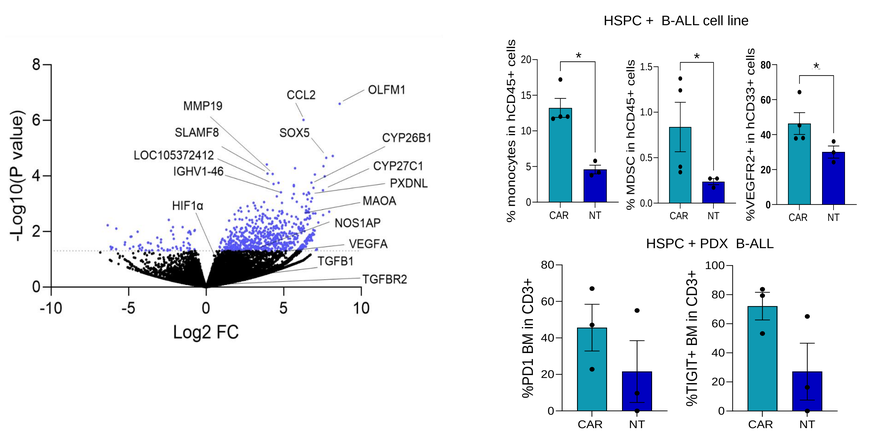
Significantly-enriched KEGG gene sets in post-treatment versus pre-treatment within CD45+CD3+ libraries



HIF1α, VEGF and TGFβR2 are key players in the crosstalk between CAR T cells and the immune niche, leading to general immune suppression



Increased monocytes, MDSCs and myeloid VEGFR2+ cells following CAR T-cell therapy in tumor-bearing HSPC-humanized mice



Conclusions

CAR T cells promote myeloid, and MDSC recruitment in the BM microenvironment in patients with B-ALL, ultimately leading to T cell exhaustion as active feedback of regulation in response to CAR T-cell-mediated inflammation, which may antagonize the effect of CAR T-cell therapy. Hypoxia have a role in exacerbating CAR T cell dysfunction and exhaustion. Mitigation of the pathway of Hypoxia and could restore CAR T cells activity and persistence in vitro
This study provide novel and potential therapeutic targets within the tumor microenvironment that antagonize the effects of CAR T cell therapy.

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