

Conference Abstracts

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Germline Predisposition to Immune Effector Cell-Associated Hemophagocytic Lymphohistiocytosis-like Syndrome (IEC-HS) after CAR T Cell Therapy for Lymphoma and Myeloma

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Abstract

Background

IEC-HS is a rare but potentially fatal adverse event following chimeric-antigen-receptor T-cell (CART) therapy. Clinically, IEC-HS resembles primary/familial hemophagocytic lymphohistiocytosis (HLH), which is caused by homozygous mutations in genes regulating cytotoxic and phagocytic immune cells. Here, we investigated germline predisposition to risk for IEC-HS in lymphoma and myeloma patients.

Methods

We performed whole-exome-sequencing on blood samples from 18 cases with IEC-HS (12 lymphoma/6 myeloma) and 59 controls (41 lymphoma/18 myeloma) without IEC-HS after standard-of-care CART therapy.

Results

The frequency of protein-truncating variants (PTVs) and pathogenic variants (as per ClinVar) in 587 genes associated with inherited disorders of the immune system was significantly more common in the cases vs. the controls (median 10/pt vs. 3/pt; $p < 0.001$) and greater proportion of IEC-HS cases than controls (9/18 vs. 12/59; $p < 0.05$) had such mutations affecting 51 genes implicated in primary HLH. The IEC-HS cases had nonsense mutations in UNC13D and HAVCR2, frameshift mutations causing premature truncation in UNC13D, CYBC1, STXBP2, WAS, LAMP1, NLRP3, ADA and CDC42, and a pathogenic missense variant in TNFRSF1A; none of these genes were altered in the controls. To elucidate potential mechanisms, UNC13D- and STXBP2-knockout (KO) CD19 CART were generated from healthy-donor-derived T-cells. In co-culture with B-cell lymphoma cell-lines, both KO CART showed

A

Immune genes

p = 0.0019

No. of variants per variant

Case Control

B

HLH genes

p = 0.011

Proportion

Case Control

Variants

0
1
2
≥

C

Case

Control

Tumor type

Lymphoma Myeloma

Variant type

Synonymous Frame shift Stop_gained Missense Nucleotide

D

UNC13D

EXON13 GXXT

STXBP2

Y1918A/E

0 100 200 300 400 500 600 700 800 900 1000 aa

0 50 100 150 200 250 300 350 400 450 500 550 600 aa

E

Genomic Variants in Immune-Related and Primary/Familial HLH Genes in EBV+ Cases and Controls.

Panel A shows the number of genomic variants in immune-related genes among cases and controls. The P value was calculated with the Wilcoxon rank-sum test. **Panel B** shows the proportion of variants in each group according to the number of genomic variants in HLH-related genes. The P value was calculated with Fisher's exact test. **Panel C** shows the landscape of genomic variants in HLH-related genes in all other immune-related genes (bottom) among cases and controls. For HLH-related genes, only genes with a variant frequency of 1% or higher in either group are shown; for other immune-related genes, only genes with a variant frequency of 10% or higher in either group are shown. **Panel D** shows the protein domain distribution of genomic variants in UNC13D and STXBP2.

Figure 1. Germline Variants in Immune-Related and Primary/Familial HLH Genes in IEC/HS Cases and Controls.

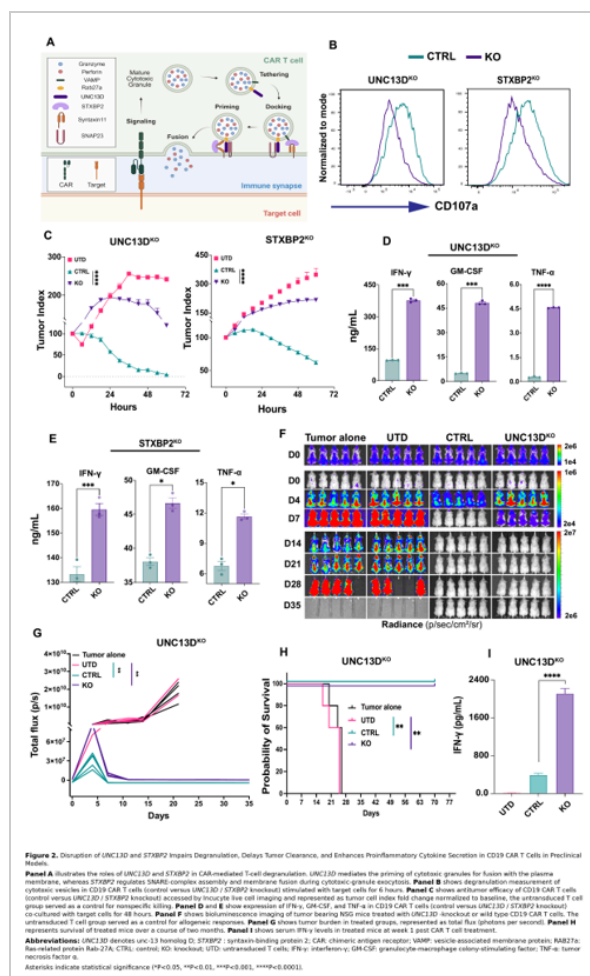


Figure 2. Disruption of UNC13D and STXBP2 Impairs Degranulation, Delays Tumor Clearance, and Enhances Proinflammatory Cytokine Secretion in CD19 CAR T Cells in Preclinical Models.

Conclusion

Heterozygous germline variants in primary HLH genes may predispose patients to IEC-HS after CART therapy, with CART activation triggering excessive IFN- γ and pro-inflammatory cytokine production. These findings improve understanding of IEC-HS pathophysiology, potentially guiding risk stratification, and improved prophylactic/therapeutic strategies.