Poster #: 1203

XXI IWCLL International Workshop on CLL

SF3B1 K700E Mutation Promotes SAT1-Mediated Metabolic Reprogramming and Suppresses T-cell Immune Response in Chronic Lymphocytic Leukemia

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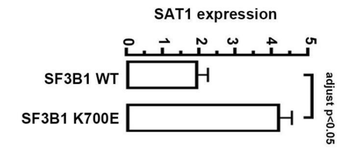
OBJECTIVES

- To explore how SF3B1 K700E mutation influences metabolic reprogramming in CLL cells.
- To investigate the impact of the SF3B1 K700E mutation in regulation of SAT1 expression in CLL cells.
- To examine the role of SAT1 in regulating immune evasion within the context of CLL.

INTRODUCTION

- **CLL** : incurable leukemia with metabolic reprogramming and immune evasion
- SF3B1 mutations (observed in 10–15% cases) : poor prognosis related to RNA splicing dysregulation
- SAT1 :a key polyamine metabolism enzyme, essential for CLL cell growth
- Aim: to explore how SF3B1 K700E mutation regulates SAT1-driven metabolic & immune changes in CLL

Figure 1



METHODS AND RESULTS

- SF3B1 K700E mutation induces SAT1 upregulation, exon 4 skipping, and increased mRNA stability. LC-MS/MS analysis showed SAT1 overexpression significantly elevated N1-acetylspermidine levels and enriched glutamine metabolism and oxidative phosphorylation (OXPHOS), promoting cell proliferation. Functional assays indicated that SAT1 overexpression enhanced CLL cell proliferation and clonogenic potential, while SAT1 silencing suppressed these effects. In vivo, SAT1 overexpression led to increased leukemia infiltration and progression, whereas knockdown reduced tumor growth. Co-transplantation with CD8+ T-cells revealed that SAT1 overexpression induced immune suppression. ChIP-seq analysis demonstrated SAT1's regulation of IL18BP, suggesting the IL18-IL18BP axis as a conserved mechanism of immune evasion in CLL.

Figure 2

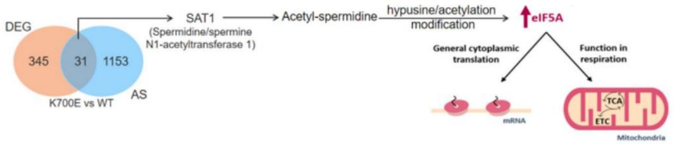


Figure 3

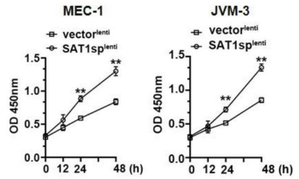


Figure 4

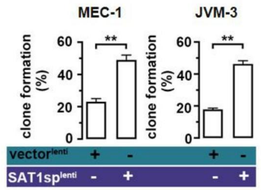


Figure 5

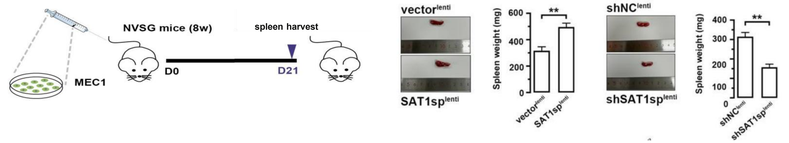


Figure 6

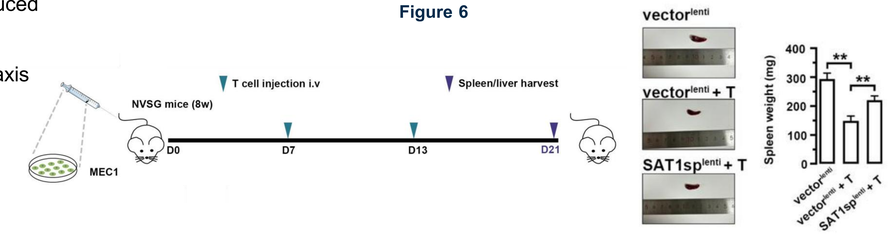
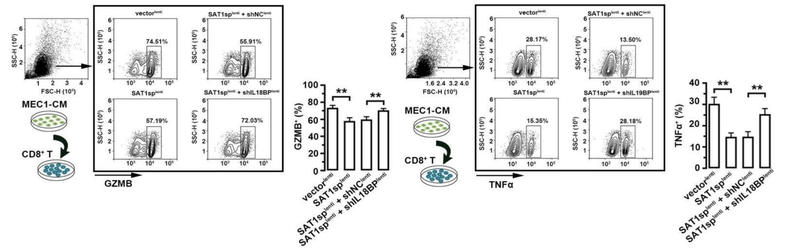


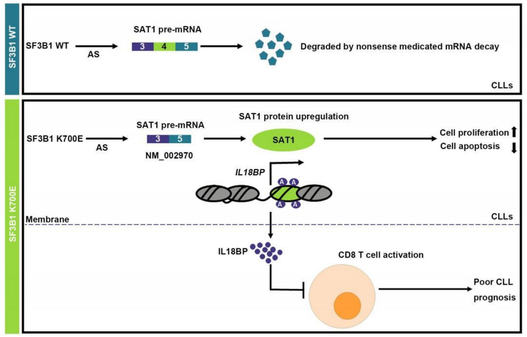
Figure 7



CONCLUSION

- This study shows SAT1 regulates polyamine metabolism and immune suppression in SF3B1-mutated CLL. SAT1 promotes leukemia survival through metabolic reprogramming and acetylates H3K27 at the IL18BP promoter, inhibiting CD8+ T-cell activation. Targeting SAT1 could enhance T-cell immunity and improve outcomes in SF3B1-mutated CLL.

Figure 8



FUNDINGS:

National Natural Science Foundation of China (82301964, 82570242); China Postdoctoral Science Foundation (2023M741075); Natural Science Foundation of Henan (232300421280); Henan Provincial Medical Science Building Key Program (SBGJ202303020)

DISCLOSURES

No relevant conflicts of interest to declare.