Poster #: 1802

XXI IWCLL International Workshop on CLL

Targeting SF3B1 Disrupts Chronic Lymphocytic Leukemia Survival via PFKFB-mediated Glycolytic Dependency

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OBJECTIVES

- To investigate the role of wild-type SF3B1 as a key metabolic regulator in CLL through modulation of the PFKFB1/PFKFB3 balance.
- To evaluate the therapeutic potential of the splicing modulator H3B-8800 in disrupting glycolytic metabolism in CLL cells.
- To assess the efficacy of combining SF3B1 modulation with BTK inhibition as a strong synergistic therapy for CLL.

INTRODUCTION

- CLL is challenging, especially in relapsed or refractory cases. While SF3B1 mutations occur in 10-15% of cases, the role of wild-type SF3B1 is unclear. This study investigates targeting wild-type SF3B1 with H3B-8800, focusing on its impact on glycolysis and its combination with BTK inhibitors.

Figure 1

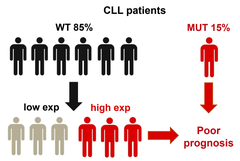
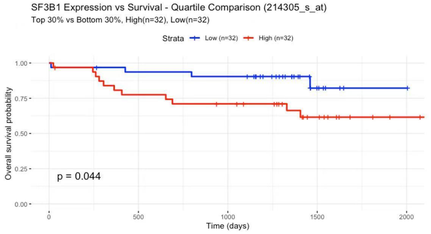


Figure 2



METHODS

- CLL cell lines (MEC-1, JVM-3) and primary CLL cells from treatment-naïve patients were treated with H3B-8800 (0-10 μM) and BTKi (zanubrutinib/ibrutinib) (0-100 μM) for 48 hours. Cell viability was assessed using the CCK-8 assay, and RNA-seq analyzed splicing events and gene expression. Metabolic genes and BCR signaling regulators were validated by qRT-PCR and Western blot. Metabolic phenotypes were evaluated with glucose and lactate assays. Synergy between H3B-8800 and BTKi was assessed using the ZIP model, and apoptosis was quantified by Annexin V/PI staining.

RESULTS

- Knockdown of wild-type SF3B1 inhibited CLL cell growth, emphasizing its crucial role. Pharmacological inhibition with H3B-8800 showed potent cytotoxic effects and altered glycolytic metabolism by modulating PFKFB1 and PFKFB3 expression. H3B-8800 reduced glucose uptake and lactate secretion. Additionally, it upregulated BCR signaling regulators, increasing sensitivity to BTK inhibitors. Combination treatment with H3B-8800 and BTK inhibitors significantly enhanced apoptosis in primary CLL cells. These results suggest that dual targeting of SF3B1 and BTK disrupts leukemia cell metabolism and BCR signaling, offering potent anti-leukemia efficacy.

Figure 3

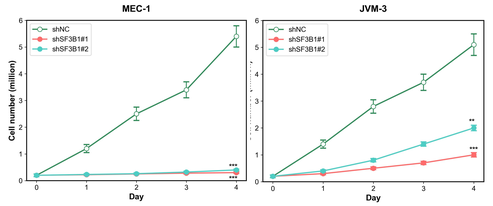


Figure 4

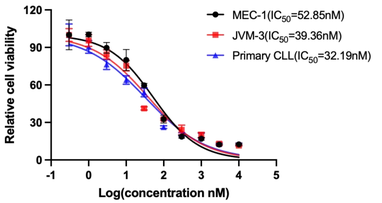


Figure 5

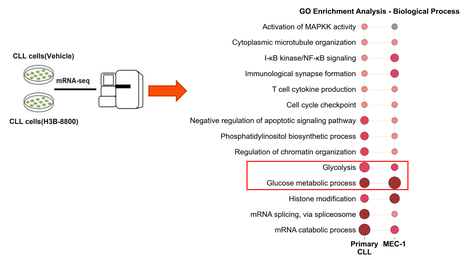


Figure 6

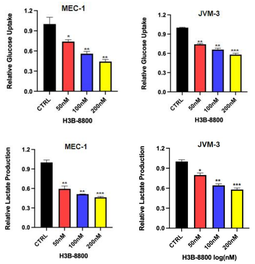


Figure 7

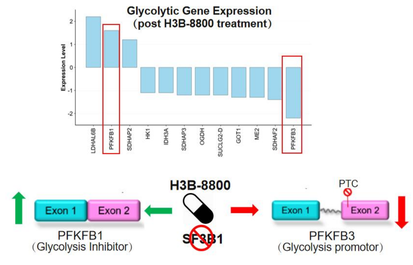
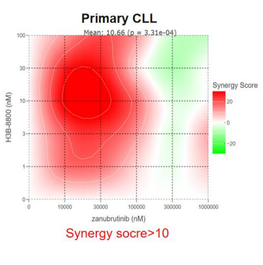


Figure 8



Synergy socre>10

CONCLUSIONS

- Our study identifies wild-type SF3B1 as a key metabolic regulator in CLL through PFKFB-mediated glycolysis control. The splicing modulator H3B-8800 disrupts the PFKFB1/PFKFB3 balance, inducing metabolic disruption and potent anti-leukemic effects. We highlight SF3B1 as a therapeutic target in CLL, regardless of mutational status, and support a dual-target strategy combining SF3B1 modulation with BTK inhibition for effective CLL treatment.

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.