ELSEVIER

Blood 142 (2023) 1652–1653

The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

622.LYMPHOMAS: TRANSLATIONAL-NON-GENETIC

Lactate-Mediated Histone H3K9 Lactylation Facilitates Tumorigenesis of T-Cell Lymphoma Via Activation of SFXN1 Expression

Zhuoya Yu[1], *Xiangxiang Zhou*[2,2], *Yiqing Cai*[1], *Tiange Lu*[1], *Mengfei Ding*[1], *Xin Wang*[1,3]

[1]Department of Hematology, Shandong Provincial Hospital, Shandong University, Jinan, China
[2]Department of Hematology, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, China
[3]Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, China

Introduction

Lactate-derived histone lactylation is a novel epigenetic modification that facilitates gene transcription. As the Warburg effect is one of the hallmarks of cancer, cancer cells tend to convert glucose into lactate to produce energy even under aerobic conditions. T-cell lymphomas (TCLs) are rare heterogeneous lymphoid malignancies usually associated with epigenetic modifications and dysregulated metabolic activity. Thus, the metabolism-chromatin axis may contain potential therapeutic targets, and the potential function of histone lactylation in TCL oncogenesis deserves further exploration.

Methods

Lymph node biopsy tissues from 70 de novo TCL patients and 22 reactive hyperplasia cases were collected with informed consent. The glycolysis inhibitor 2-DG and the LDH inhibitor oxamate were added to the cells to observe changes in lactate and biological processes. Detection of the crucial histone lactylation site was accomplished by western blotting. RNA-sequencing and Chip-seq were performed to detect genes regulated by histone lactylation modifications. Through the construction of SFXN1 stable knockdown and overexpression models, the biological function of SFXN1 was evaluated. This study was approved by the Medical Ethical Committee of Shandong Provincial Hospital.

Results

A significant enrichment in the glycolytic metabolic pathway was found in the transcriptomic data between normal and TCL patients. A subsequent immunohistochemistry study revealed that de novo TCL patients had a significantly higher level of lactylation modification than normal controls. According to the survival analysis, a high level of lactylation was associated with aggressive disease processes (**Figure 1A**). Particularly, lactylation modification levels were positively correlated with LDH levels in patients with TCL.

To further investigate the oncogenesis of lactylation modifications in TCL patients, glycolysis inhibitors 2-DG and oxamate were applied to TCL cells. Using glycolysis inhibitors 2-DG and oxamate, we observed a significant reduction in lactate levels in TCL cells. Histone H3 lysine 9 lactylation (H3K9la) was found to be the main downregulated locus after lactate levels decreased. Accordingly, we hypothesized that lactate regulates the progression of TCL cells primarily through the modification of H3K9la levels. Meanwhile, the decreased histone lactylation level efficiently inhibited TCL cell proliferation and induced cell cycle arrest in G0/G1 phase.

To further investigate how histone lactylation promotes TCL progression, RNA-seq and ChIP-seq were performed. The results indicated that histone lactylation facilitates transcriptional activation of the gene mainly by modulating the transcription start site of the gene. KEGG analysis showed that the modulated genes were mainly enriched in metabolic pathways such as carbon metabolism and glycolysis. Among these, sideroflexin 1 (SFXN1) is a mitochondrial serine transporter required for one-carbon metabolism. Meanwhile, the genomic position of the SFXN1 promoter has been identified as having a marked enrichment of H3K9la peaks (**Figure 1B**). Furthermore, we confirmed that aberrant SFXN1 activation significantly promoted TCL cell progression. Suppression of SFXN1, on the other hand, suppressed cell proliferation and arrested the cell cycle. Our conclusions were also validated in vivo. Taken together, the results of these studies suggested that the histone lactylation process activates the transcription of the SFXN1 gene.

Conclusions

The present study suggested that abnormal lactylation modifications were widespread in TCL patients and were strongly associated with poor prognoses. Additionally, it highlights the role of H3K9 lactylation in SFXN1 transcriptional activation. Collectively, inhibition of SFXN1 in TCL was anticipated to be a promising therapeutic option.

Disclosures No relevant conflicts of interest to declare.

Figure 1

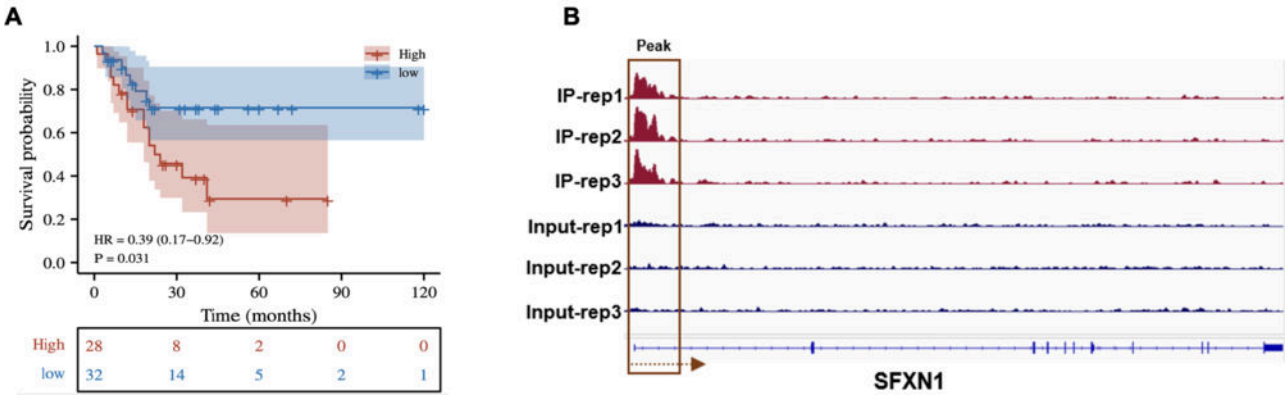

Figure 1

https://doi.org/10.1182/blood-2023-184663