Deubiquitinase PSMD14 Promotes Progression of Chronic Lymphocytic Leukemia by Stabilizing CSDE1

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Introduction

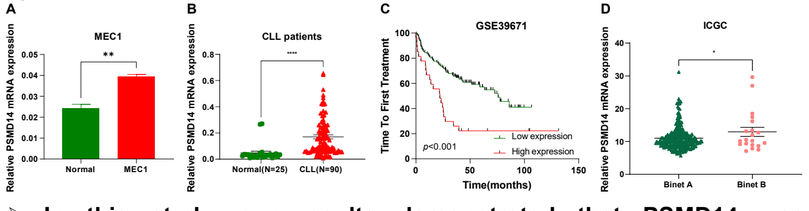
- Chronic lymphocytic leukemia (CLL) is a heterogeneous B-cell malig- nancy that lacks specific biomarkers and drug targets.
- The deubiquitinating enzyme 26S proteasome non-ATPase regulatory subunit 14 (PSMD14) has been reported to act as an oncogene in sever- al human cancers. However, the roles and mechanisms of PSMD14 in CLL is not yet elucidated.

Methods

- Quantitative real-time polymerase chain reaction was used to identify the expression of PSMD14 in CLL cell lines and CLL patients.
- CCK-8 assays were used to detect cell proliferation viability. The effect of PSMD14 on CLL cell apoptosis and cell cycle was analyzed by cell apoptosis and cell cycle assays.
- Ubiquitinated 4D-Label free quantitative proteome analysis was employed to probe the molecular mechanism of PSMD14.
- Deubiquitination assay was performed for explore the regulatory mechanism between PSMD14 and CSDE1.

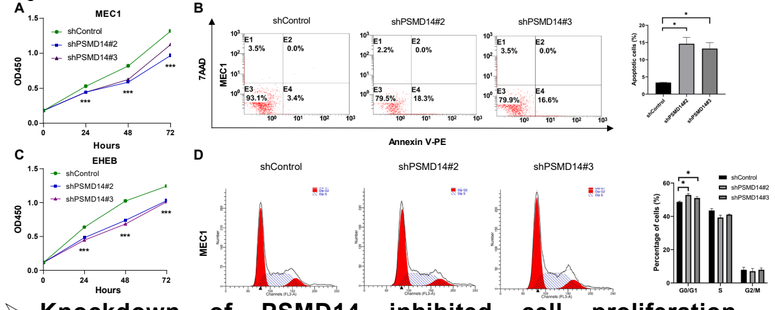
Results

Figure 1



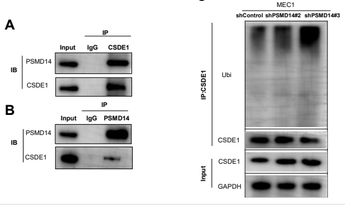
- In this study, our results demonstrated that PSMD14 was significant- ly up-regulated in CLL cell lines and primary CLL specimens (Figure 1A, B).
- The up-regulation of PSMD14 expression predicted shorter overall survival and time to first treatment in patients with CLL, which was correlated with Binet stage of CLL patients (Figure 1C, D).

Figure 2



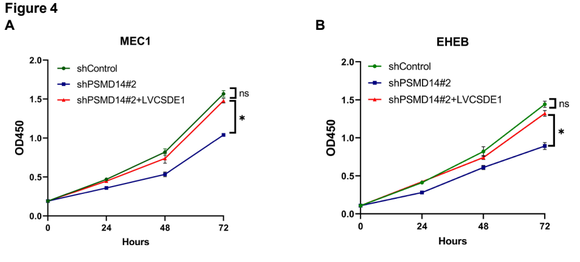
- Knockdown of PSMD14 inhibited cell proliferation, promoted apoptosis and blocked the cell cycle in the G1/S phase (Figure 2A-D).
- Furthermore, pharmacological inhibition of PSMD14 with thiolutin (THL) suppressed the malignant behavior of CLL cells. Interesting- ly, the combination of THL and ibrutinib improves the sensitivity of CLL cells to ibrutinib.

Figure 3



- Mechanistically, we identified PSMD14 as a novel post-translational regulator of CSDE1. PSMD14 interacted with CSDE1 and inhibited deg- radation of CSDE1 via deubiquitinating this oncoprotein in CLL cells (Figure 3A-C).

Figure 4



- Furthermore, rescue of CSDE1 expression was able to reverse the biological effects of PSMD14 knockdown (Figure 4A, B), suggesting that PSMD14 exerts oncogenic effects through CSDE1.
- In addition, PSMD14 knockdown also attenuated the DNA repair po- tential in CLL. The PSMD14 knockdown groups were noted to have in- creased levels of phosphorylated ATM, CHK2 and H2AX.

Conclusions

- In conclusion, our findings suggest that PSMD14 could serve as a promising therapeutic candidate for CLL.
- THL exhibits potent anti-tumor activities in CLL cells, highlighting a novel molecule-based strategy for CLL.