



ENPP2 mediates lipid metabolism and tumorigenesis in chronic lymphocytic leukemia through AMPK signaling pathway

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Introduction

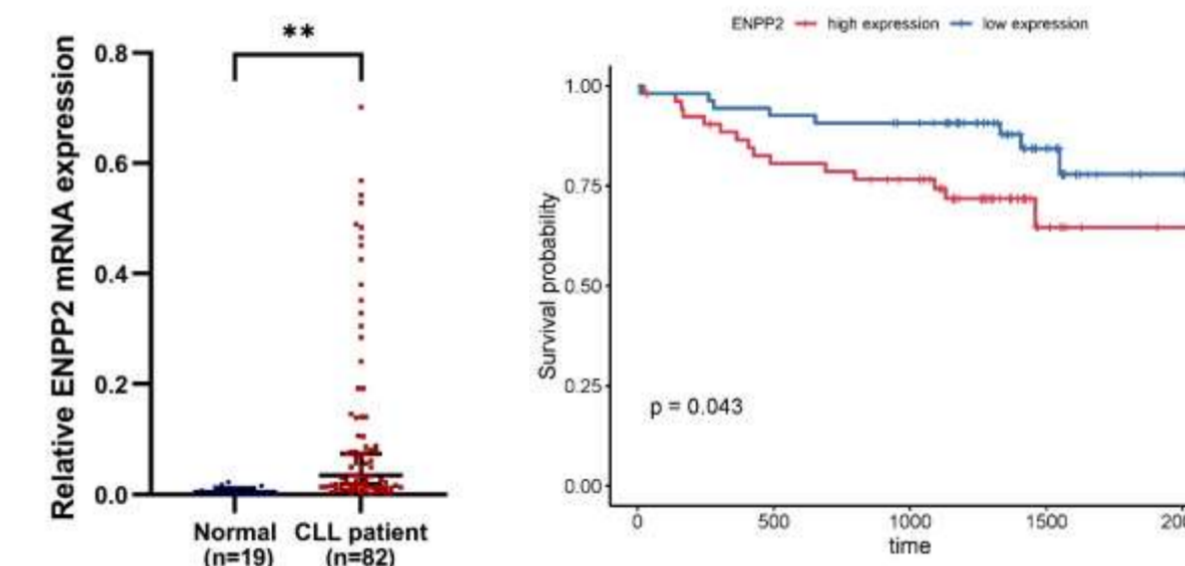
- Disorders of lipid metabolism are critical factors in the progression of chronic lymphocytic leukemia (CLL).
- Ectonucleotide pyrophosphatase/phosphodiesterase 2 (ENPP2), an adipocyte-derived lysophospholipase D, is closely correlated with obesity and disorders of glucolipid metabolism in obese individuals.
- This study was to investigate the functional mechanism and clinical significance of ENPP2 regulation in CLL.

Methods

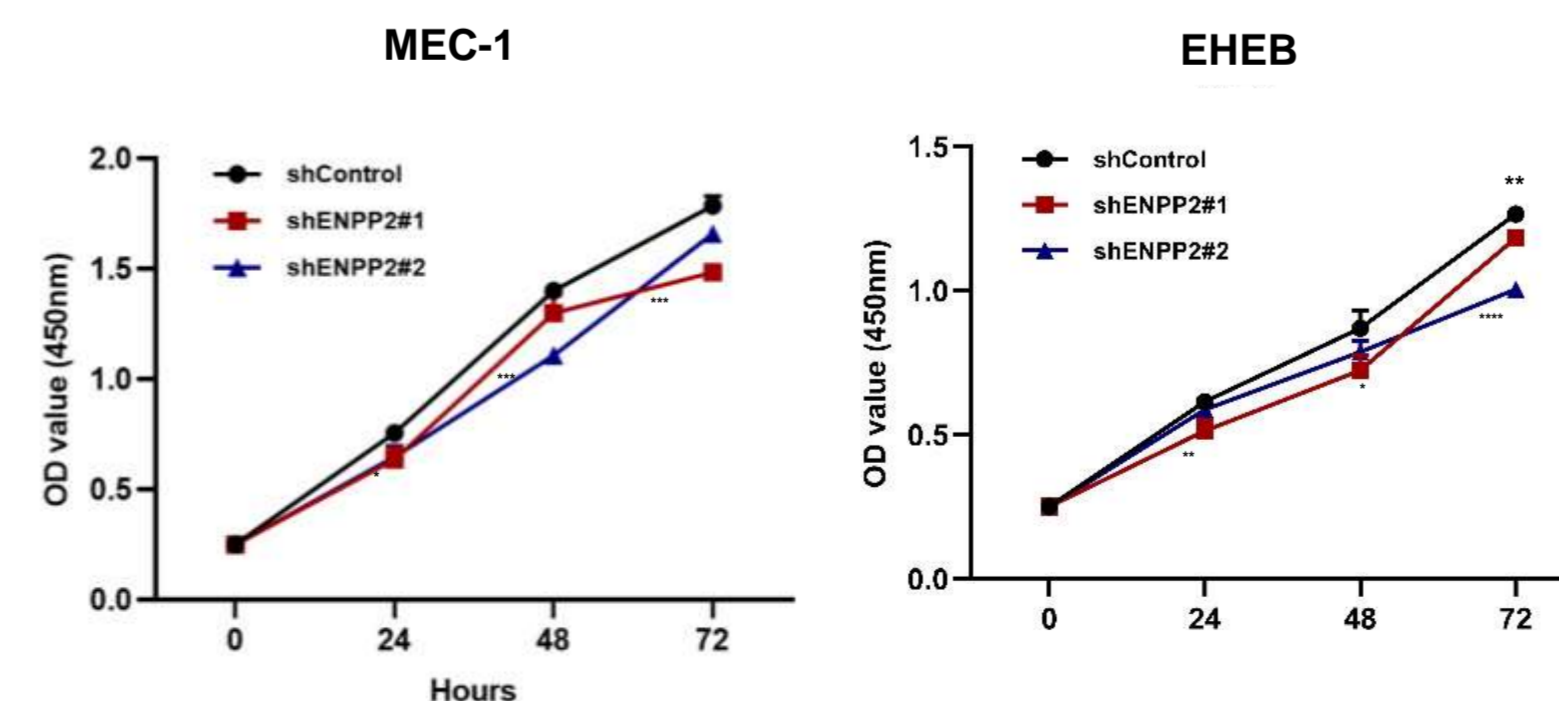
- Peripheral blood samples of 82 de novo patients diagnosed with CLL were collected at the Department of Hematology in Shandong Provincial Hospital.
- The mRNA expressions levels of ENPP2 in CLL patients were determined by quantitative RT-PCR.
- Plasmids were utilized to knockdown and overexpression ENPP2 expression in MEC1 and EHEB CLL cells.
- RNA-sequencing and functional enrichment analysis were performed.
- Cell viability and apoptosis were assessed by cell counting kit-8 and annexin V-PE/7AAD staining. Bodipy staining was used to explore lipid deposition in CLL cells.

Results

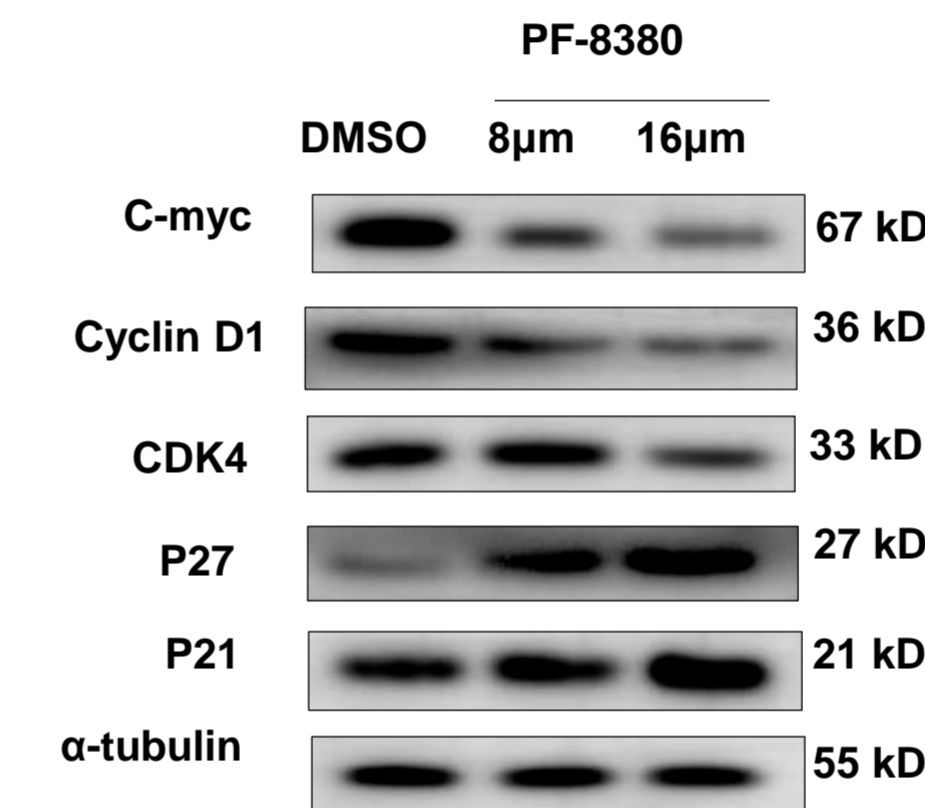
- RT-PCR confirmed the significant upregulation of ENPP2 in CLL patients compared to normal B cells ($p < 0.01$). Kaplan-Meier curves showed higher ENPP2 expression patients were associated with adverse overall survival (HR=2.33, $p < 0.043$).



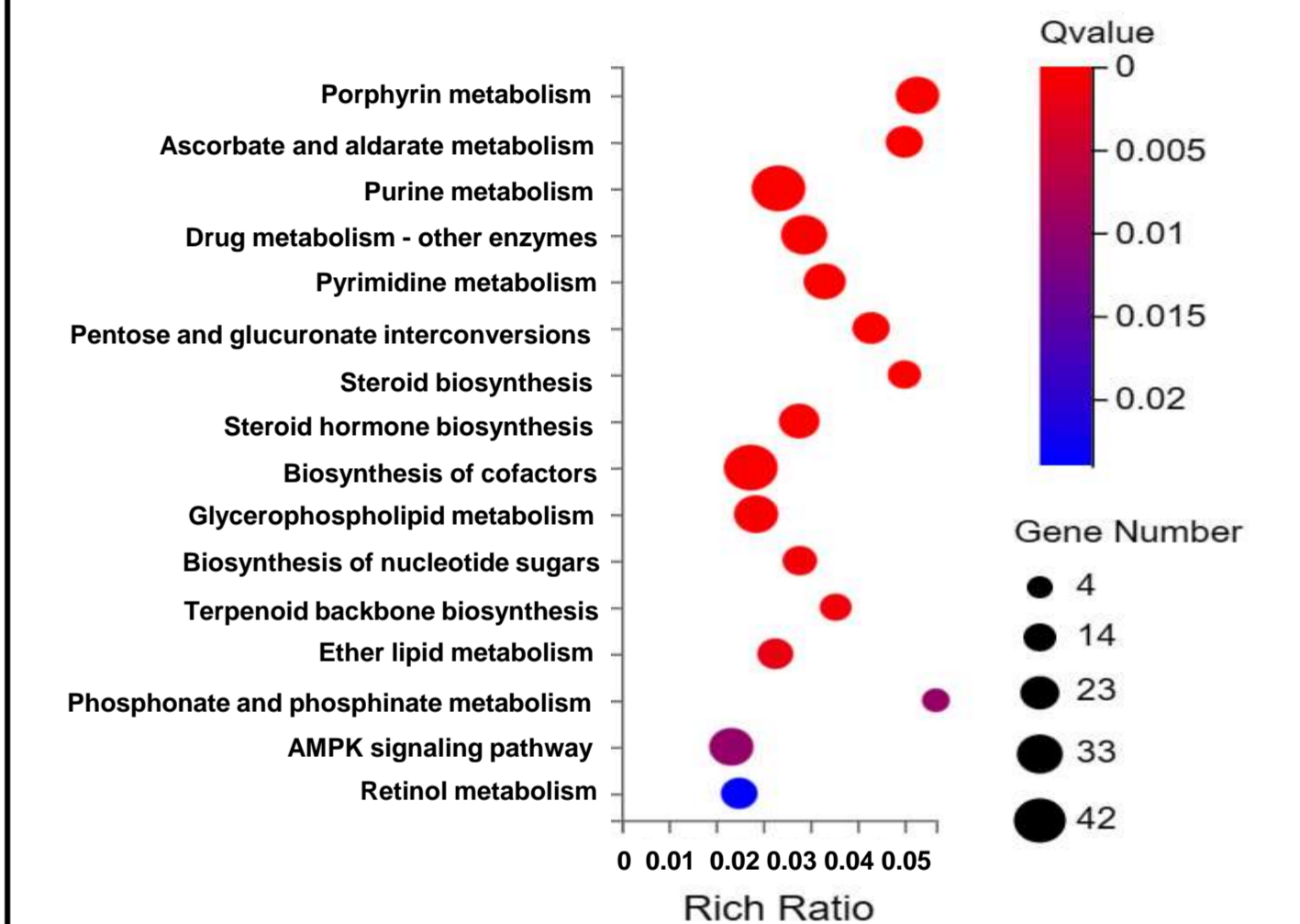
- Functional assays were performed. CLL cells with ENPP2 knockdown resulted in slow proliferation, G0/G1 phase cell cycle arrest, increased apoptosis and lipid accumulation in CLL cells.



- The expression of cyclin-related proteins, including C-myc, Cyclin D1, CDK4, P21, and P27 was reduced by treated with PF-8380.



- ENPP2 was involved in the regulation of lipid metabolism in slow lymphoid cells through participation in the AMPK/SREBP1/FAS signaling pathway.



Conclusion

Taken together, the present study was the first investigation on the role of ENPP2 in the tumorigenesis of CLL. ENPP2 expression was aberrantly increased in CLL cells, and affected cell lipid metabolism through the AMPK pathway. ENPP2 targeted inhibitor PF-8380 inhibited CLL cell proliferation and induced apoptosis, highlighting potent therapeutic potential.

References

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