Oncogenic role and target properties of the lysine-specific demethylase KDM1A in chronic lymphocytic leukemia (CLL)

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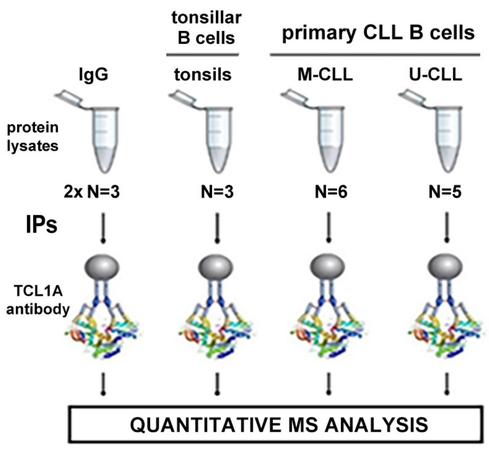
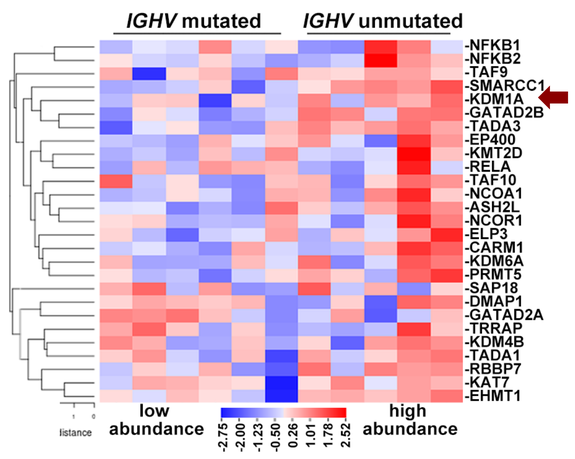
ABSTRACT

Aberrant expression of the T-cell leukemia 1A (TCL1A) oncogene is a hallmark of CLL, and high TCL1A levels are linked to aggressive disease. A better understanding of the functional networks surrounding TCL1A could lead to new treatment approaches for CLL. Our mass spectrometry-based proteome-screens revealed that KDM1A, a lysine-specific demethylase, interacts with TCL1A protein in CLL cells. Furthermore, KDM1A is overexpressed in B-cell lymphomas and is implicated in the development and sustenance of several other hematological malignancies. We show that TCL1A interacts with KDM1A in the nucleus of B-cells and increases KDM1A's demethylase activity. Higher KDM1A expression and its gene signature are associated with adverse clinical characteristics and a shorter PFS in CLL. *Kdm1a* knockdown inhibits leukemic cell growth and induces upregulation of p53 and proapoptotic pathways. KDM1A expression in the microenvironment also affects CLL progression. Pharmacologic inhibition of KDM1A with compound C12 induces apoptosis and affects H3K4/9 target methylation levels in primary CLL samples.

RESULTS

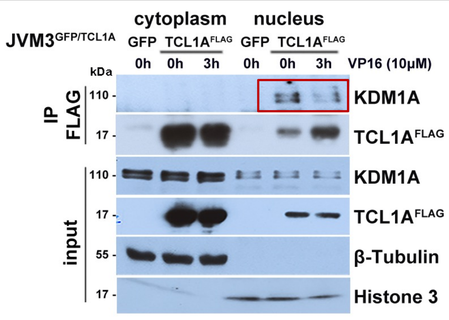
1 Mass-spectrometric analysis identifies epigenetic modifiers interacting with TCL1A

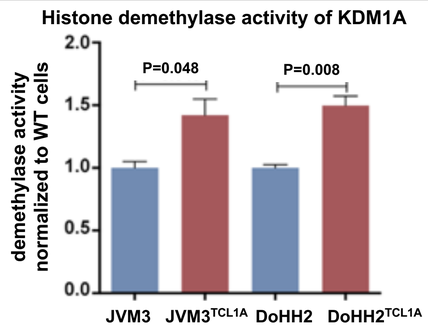




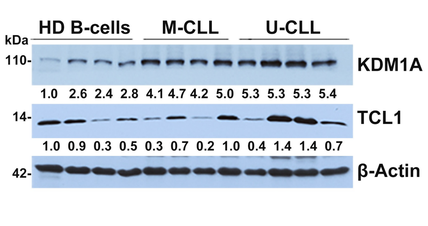
A mass spectrometry analysis of TCL1A-interacting molecules was performed in primary CLL samples categorized according to their immunoglobulin heavy chain variable region (IGHV) mutation status (mutated: M, unmutated: U). Heatmap showing chromatin-modifying enzymes interacting with TCL1A. KDM1A tended to interact with TCL1A at a higher abundance in U-CLL vs. M-CLL.

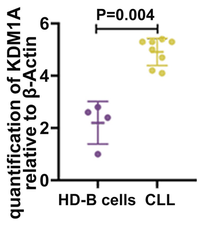
2 TCL1A interacts with KDM1A in nucleus and increases KDM1A's activity





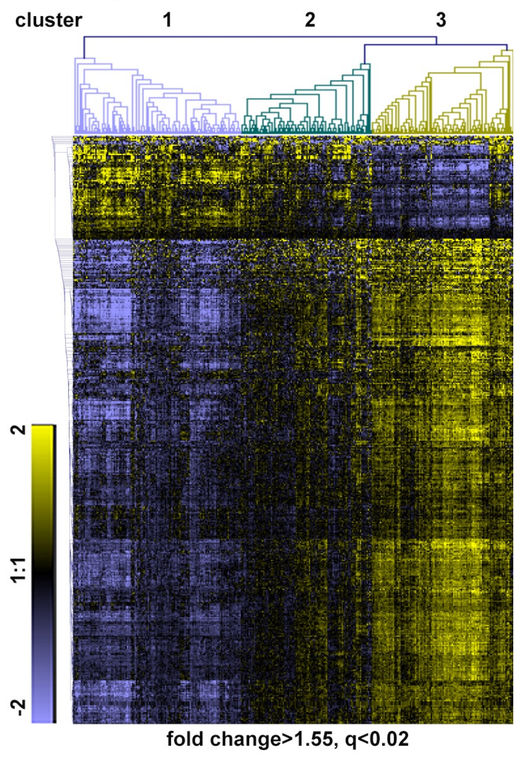
3 KDM1A is overexpressed in CLL B-cells



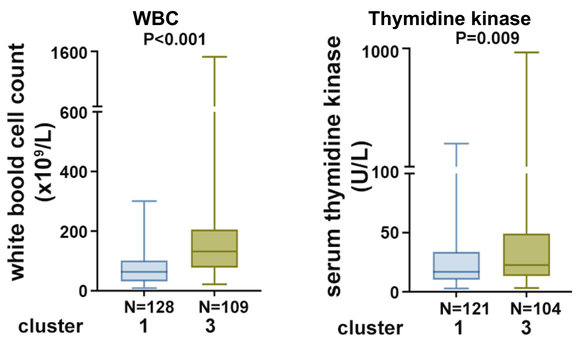


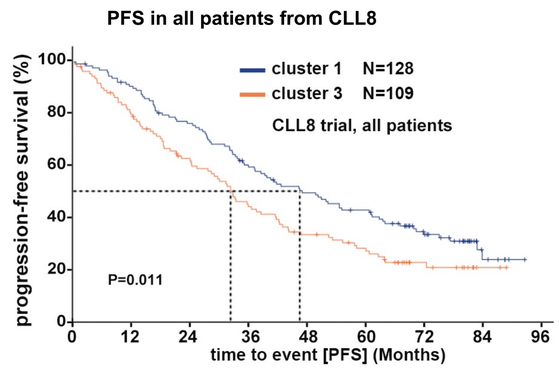
4 Higher KDM1A levels correlate with adverse prognostic features in CLL

Top 449 differentially expressed genes for low vs. high *KDM1A* quartile in 337 CLL patients

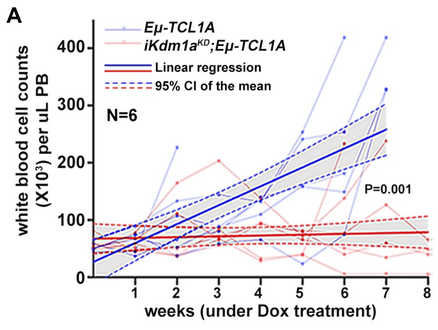


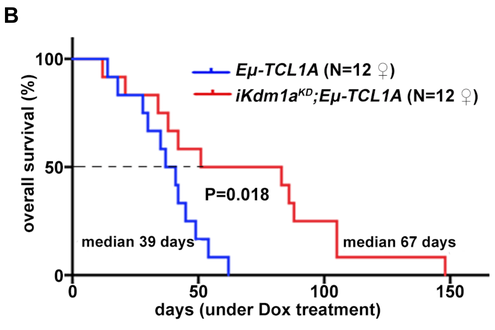
Higher KDM1A levels and the associated gene signatures correlate with inferior clinical outcomes



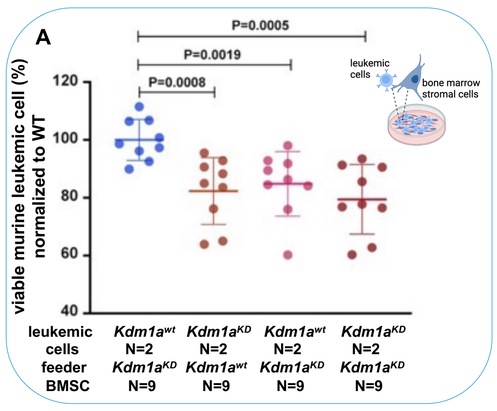


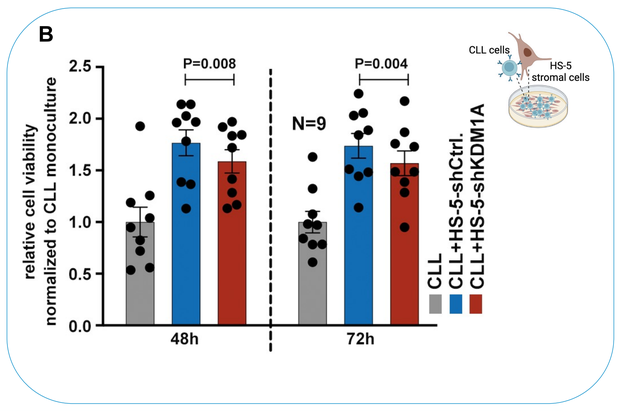
5 *Kdm1a-KD* decreases leukemic burden and prolongs overall survival in murine CLL

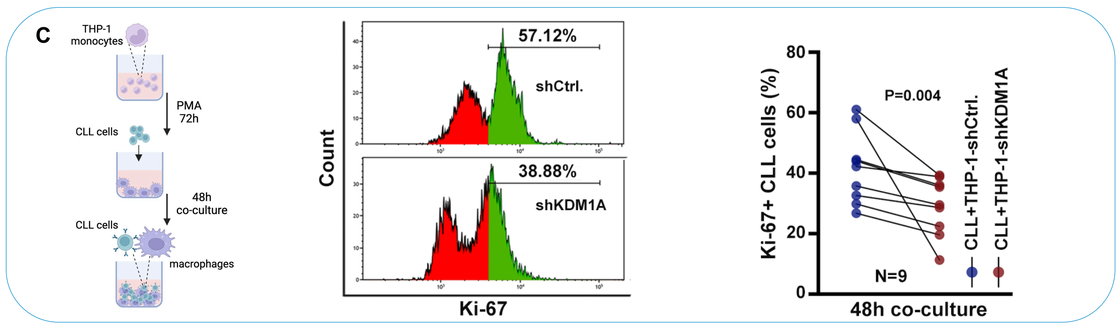




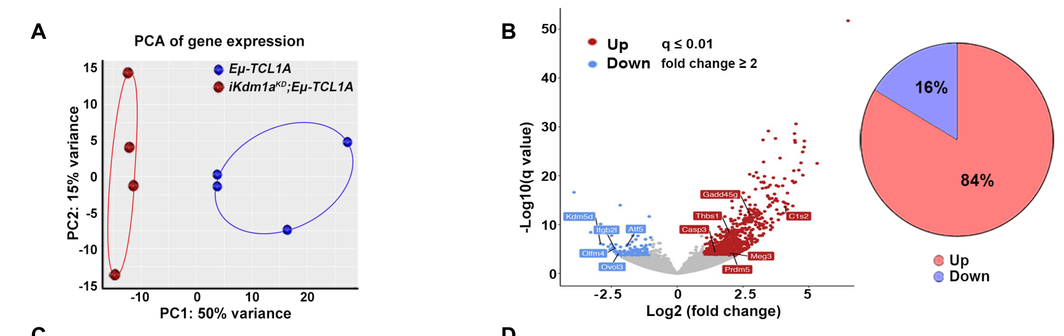
6 *KDM1A-KD* results in an impaired supporting effect of macrophages and stromal cells for CLL cells





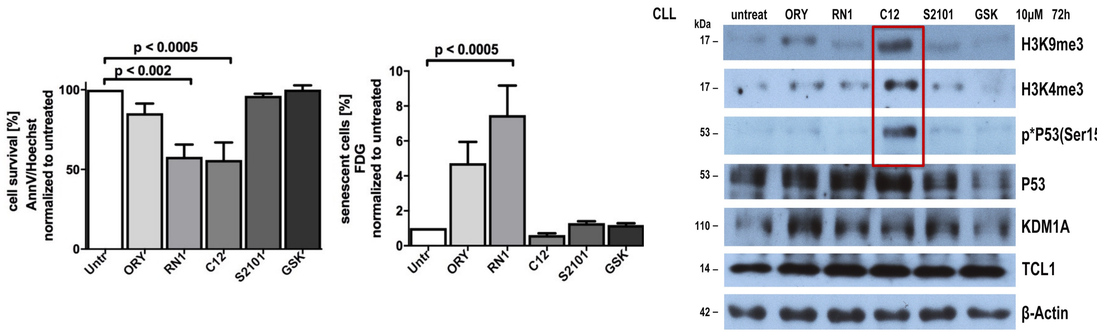


7 Kdm1a seems to act as a transcriptional repressor in murine CLL



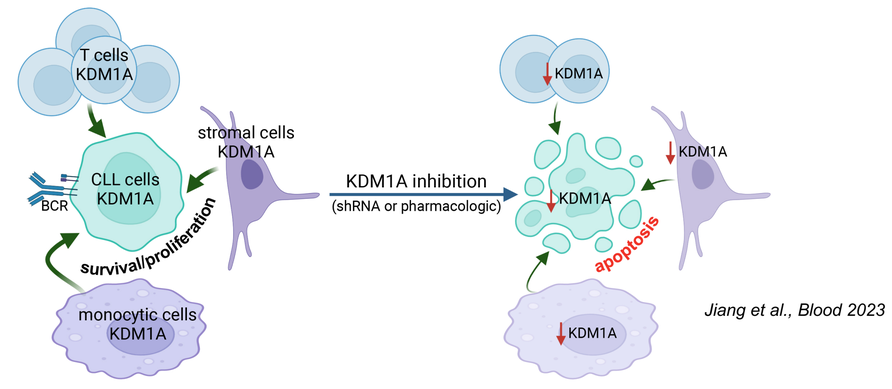
A. Principal component analysis shows distinct groups by genotype, B. Volcano plot for differential gene expression upon *Kdm1a* knock down. Pie chart displaying the percentage of up or down regulated genes. 804 out of 54019 genes are differentially expressed upon *Kdm1a* knock down. C. Gene set over-representation analysis identified that P53 and apoptosis pathways are upregulated upon *Kdm1a-KD*. D. Gene set enrichment analysis of P53 (left) and apoptosis (right) pathways.

8 KDM1A inhibitor C12 increases tri-methylation of H3K4/9 and elicits cytotoxicity in CLL



SUMMARY and OUTLOOK

KDM1A as a pro-oncogenic marker in CLL cells and their microenvironment



→ investigate the functional role of KDM1A in CLL microenvironment

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