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SETD1B Inhibits the Progression of Diffuse Large B Cell Lymphomas Via Regulating RAB 17

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KEYWORDS Apoptosis. DLBCL. Cancer. Histone Methylation. SET Domain Containing 1B

ABSTRACT The purpose of this study is to explore the role of SET domain containing 1B (SETD1B) in diffuse large B cell lymphomas (DLBCL). Gene expression is analysed by quantitative reverse transcription PCR and Western blot. Cell behaviours are analysed by cell counting kit-8, 5-Ethynyl-2'-deoxyuridine, terminal deoxynucleotidyl transferase dUTP risk end labelling, and flow cytometry assays. The interaction between SETD1B and RAB family member 17 (RAB17) is analysed by co-immunoprecipitation and chromatin immunoprecipitation assays. The researchers found that SETD1B expression is downregulated in DLBCL. Overexpression SETD1B promotes the apoptosis of DLBCL cells. Moreover, SETD1B promotes the H3K4me3 methylation and upregulation of RAB17. However, RAB17 knockdown promotes the survival of DLBCL cells. In summary, SETD1B exerts anti-tumour function in DLBCL. SETD1B drive the apoptosis of DLBCL via mediating histone methylation of RAB17.

INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is a popular hematological tumor (Kotlov et al. 2021; Nakhoda et al. 2023; Schmitz et al. 2018). DLBCL is characterised by the rapid proliferation of B cells. Cancerous B cells in DLBCL lose their ability to function properly and can spread to various organs (Chen et al. 2022; Pi et al. 2022). DLBCL is a highly heterogeneous disease, with significant variations in clinical presentation, genetic features, and treatment outcomes (Chapuy et al. 2018). The World Health Organisation (WHO) classification system recognises over a dozen subtypes of DLBCL, each with distinct genetic and molecular characteristics (Dabrowska-Iwanicka and Nowakowski 2024). Understanding the underlying molecular mechanisms driving DLBCL is crucial for developing more effective targeted therapies and improving patient outcomes.

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Objectives

The researchers aimed to explore the role of SETD1B in DLBCL and the underlying molecular mechanisms.

Recent Literature Review

SET domain containing 1B (SETD1B) is a histone lysine methyltransferase (Kranz and Anastassiadis 2020). SETD1B modifies histones by adding methyl groups, thereby influencing gene expression and cellular function (Roston et al. 2021). Recent studies have identified SETD1B mutations and deletions in a significant proportion of DLBCL cases. Specifically, SETD1B alterations occur in approximately 16 percent of DLBCL patients. Loss-function mutation of SETD1B is associated with resistance to apoptosis of cancer cells. SETD1B deficiency has been shown to confer resistance to Venetoclax, highlighting its importance in the pathogenesis of DLBCL (Portelinha et al. 2024). Its loss leads to the downregulation of these proteins, promoting cell survival and contributing to lymphomagenesis (Ozyerli-Goknar et al. 2023). Additionally, SETD1B cooperates with other genetic abnormalities, such as the loss of lysine methyltransferase 2D, to drive lymphoma de-

velopment (Shimada et al. 2021). Notwithstanding, the role of SETD1B in DLBCL remains unknown.

RAB family member 17 (RAB17) is a member of the RAB GTPase family, regulating intracellular vesicle trafficking and membrane dynamics (Sciarra et al. 2024). RAB17 has been implicated in various cellular processes that could contribute to cancer progression (Du et al. 2023). For instance, RAB17 has been shown to regulate the transport of signalling molecules and receptors, potentially influencing cell proliferation, survival, and migration (Wu et al. 2021; Zhou et al. 2021). Given its critical role in intracellular trafficking (Tajbakhsh et al. 2021), RAB17 may regulate the development of DLBCL.

The present study investigated the role SETD1B in DLBCL. The researchers hypothesise that SETD1B-mediated histone modifications may regulate RAB17 expression, thereby affecting intracellular trafficking and contributing to the aggressive phenotype of DLBCL. By elucidating the molecular mechanisms underlying this interaction, the researchers hope to identify potential therapeutic targets for DLBCL.

MATERIAL AND METHODS

Specimen

A total of 32 DLBCL patient samples were collected from Anhui Provincial Children's Hospital between 2020 and 2023. The inclusion criteria were newly diagnosed DLBCL patients with available fresh-frozen tissue samples and complete clinical data. Exclusion criteria included patients with prior treatment for lymphoma, secondary DLBCL, or insufficient tissue for analysis. The study was authorized by the Ethical Committee of Anhui Provincial Children's Hospital. Each patient handed in the informed consent.

Cell Culture

DLBCL cell lines, including SU-DHL-4, OCI-LY10, and DB, were provided by ATCC. Cells were cultured in RPMI-1640 medium containing 10 percent FBS at 37°C in 5 percent CO, .

Transfection

siRNA targeting RAB17 and SETD1B overexpression plasmids were transfected into OCI-Y10 cells by Lipofectamine 3000 (Thermo Fisher Scientific).

Quantitative Real-Time PCR (qRT-PCR)

Total RNA was extracted from OCI-Y10 cells. RNA was purified and quantified. cDNA was synthesised by a cDNA Synthesis Kit (Bio-Rad, USA). PCR was conducted by a PCR kit (Bio-Rad, USA). Results were calculated by the $2^{-\ddot{A}\ddot{A}Ct}$ method. GAPDH served as the internal control.

Western Blot

Protein was harvested from OCI-Y10 cells. Protein concentration was calculated. Protein was separated by sodium dodecyl sulfate-polyacrylamide gel electrophoresis and moved onto polyvinylidene fluoride membranes. After sealing with 5 percent non-fat milk, the membrane was incubated with primary antibodies against SETD1B (ab177288; Abcam, UK), BCL-2 associated X (BAX) (ab32503; Abcam, UK), cl-caspase 3 (cl-CASP3) (ab2302; Abcam, UK), RAB17 (ab155135; Abcam, UK) and â-actin (ab8226; Abcam, UK). Membranes were then incubated with secondary antibodies including goat-anti-rabbit (ab6721; Abcam, UK) and goat-anti-mouse (ab205719. Bands were detected using Western Electrochemiluminescence Blotting Substrate (Bio-Rad).

Chromatin Immunoprecipitation (ChIP) Assay

ChIP was performed to analyse SETD1B-mediated histone modifications, specifically H3K4me3, in DLBCL cell lines. Cells were cross-linked with 1 percent formaldehyde. Chromatin was sonicated to an average fragment size of 200-500 bp. Chromatins were immunoprecipitated using antibodies against H3K4me3 (Abcam, ab8580) and SETD1B (Abcam, ab177288). DNA was extracted from immunoprecipitated chromatin and subjected to qRT-PCR.

Cell Counting Kit-8 (CCK-8) Assay

OCI-Y10 cells were seeded in a 96-well plate. After 48 hours, cells were added with 10 μL of CCK-8 solution. Optic values were detected by a microplate reader (BioTek).

Flow Cytometry

After transfection, OCI-Y10 cells were stained with Annexin V-FITC and propidium iodide. Apoptotic cells were calculated using a flow cytometry.

Statistical Analysis

Data was analysed using GraphPad8.0 and presented as mean ± SD. Comparisons were analysed using Student's t-test or one-way ANOVA. $P < 0.05$ were considered statistically significant. All experiments were conducted in triplicate.

RESULTS

SETD1B is Downregulated in DLBCL Patients

SETD1B exerts anti-tumour function in various cancers (Cheon et al. 2022; Friedman et al. 2024). SETD1B was markedly downregulated in DLBCL patients. The area under the ROC curve is 0.891, with 95 percent confidence interval (CI): 0.813~0.969 (Fig. 1A). Therefore, SETD1B mRNA expression in DLBCL patients can be a sensitive biomarker (Fig. 1B). Additionally, downregulated DLBCL predicted advanced stages (Fig. 1C) and distance metastasis (Fig. 1D).

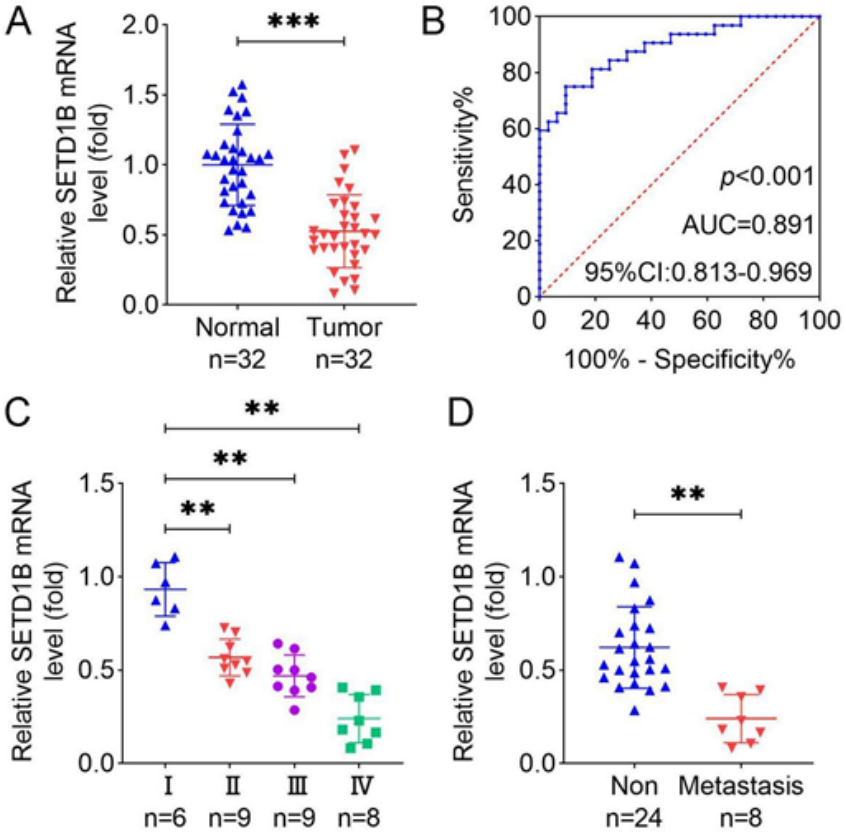


Fig. 1. SETD1B is overexpressed in DLBCL patients
(A) SETD1B mRNA levels in DLBCL patients were analysed by RT-qPCR
(B) ROC curve analysis of A
(C-D) SETD1B mRNA levels in DLBCL patients were analysed by RT-qPCR
$^{**}P < 0.01$, $^{***}P < 0.001$

SETD1B Drives DLBCL Cell Apoptosis

SETD1B was markedly downregulated in DLBCL cells, particularly in OCI-Y10 cells (Fig. 2A). Therefore, OCI-Y10 cells were used in further study. SETD1B was remarkably upregulated by its overexpression plasmids (Fig. 2B). Overexpressed SETD1B significantly inhibited OCI-Y10 cell viability (Fig. 2C). Overexpressed SETD1B markedly promoted the apoptosis of OCI-Y10 cells (Fig. 2D) and increased the percentages of TUNEL positive cells (Fig. 2E). Additionally, overexpressed SETD1B remarkably upregulated BAX and cl-CASP3 (Fig. 2F). These results suggested that SETD1B promotes the apoptosis of DLBCL.

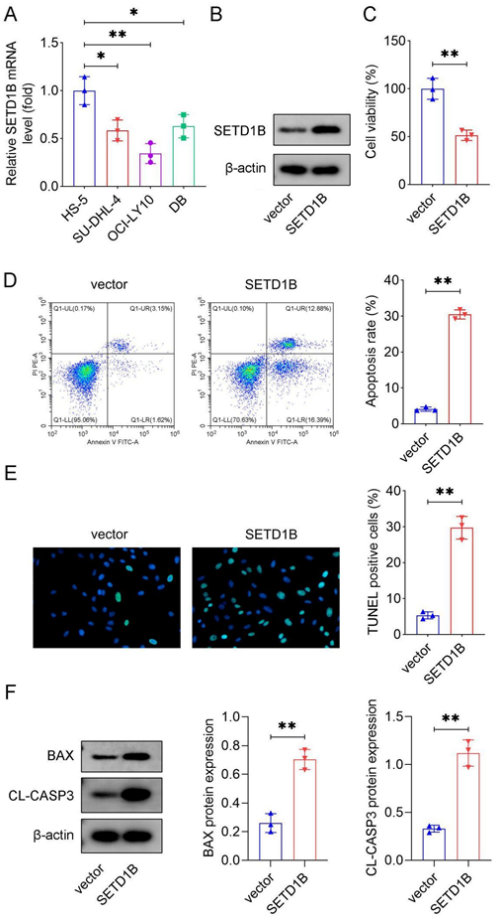


Fig. 2. SETD1B promotes the apoptosis of DLBCL cells
(A-B) SETD1B levels were detected by RT-qPCR
(C) Cell proliferation was analysed by CCK-8
(D) Cell apoptosis was analysed by flow cytometry
(E) Cell death was analysed by TUNEL staining
(F) Protein expression was analysed by Western blot
$^{**}P$ **<0.01**

SETD1B Upregulates RAB17 Via Promoting Histone Methylation

GSE273152 was used to analysed the differentially expressed genes (DEGs) after SETD1B knockout. RAB17 expression was markedly downregulated (Fig. 3A). Overexpressed SETD1B markedly remarkably upregulated RAB17 (Fig. 3B). SETD1B regulates gene expression via mediating histone methylation in its promoter (Hanna et al. 2022; Lin et al. 2025). SETD1B overexpression markedly upregulated the protein expression of H3K4me3 and RAB17 (Fig. 3C). Moreover, the occupancy of H3K4me3 was markedly increased on the promoter of RAB17 (Fig. 3D). However, SETD1B markedly reduced the occupancy of H3K4me3 on the promoter of RAB17 (Fig. 3E). These results suggested that SETD1B regulates RAB17 expression via mediating histone methylation on its promoter in DLBCL.

RAB17 Knockdown Inhibits the Apoptosis of OCI-Y10 Cells

RAB17 expression was markedly reduced by its siRNA (Fig. 4A). RAB17 knockdown significantly promoted OCI-Y10 cell viability (Fig. 4B). Moreover, RAB17 knockdown significantly inhibited OCI-Y10 cell apoptosis (Fig. 4C-E). Moreover, RAB17 knockdown markedly downregulated BAX and cl-CASP3 (Fig. 4F).

DISCUSSION

In the present study, SETD1B was downregulated in DLBCL, which predicted poor clinical outcomes. Interestingly, SETD1B overexpression inhibited the malignant behaviours as well as promoted DLBCL cell apoptosis. Moreover, SETD1B promoted the histone methylation and upregulation of RAB17. However, RAB17 was downregulated in DLBCL. RAB17 knockdown contributed to malignant behaviours of DLBCL cells.

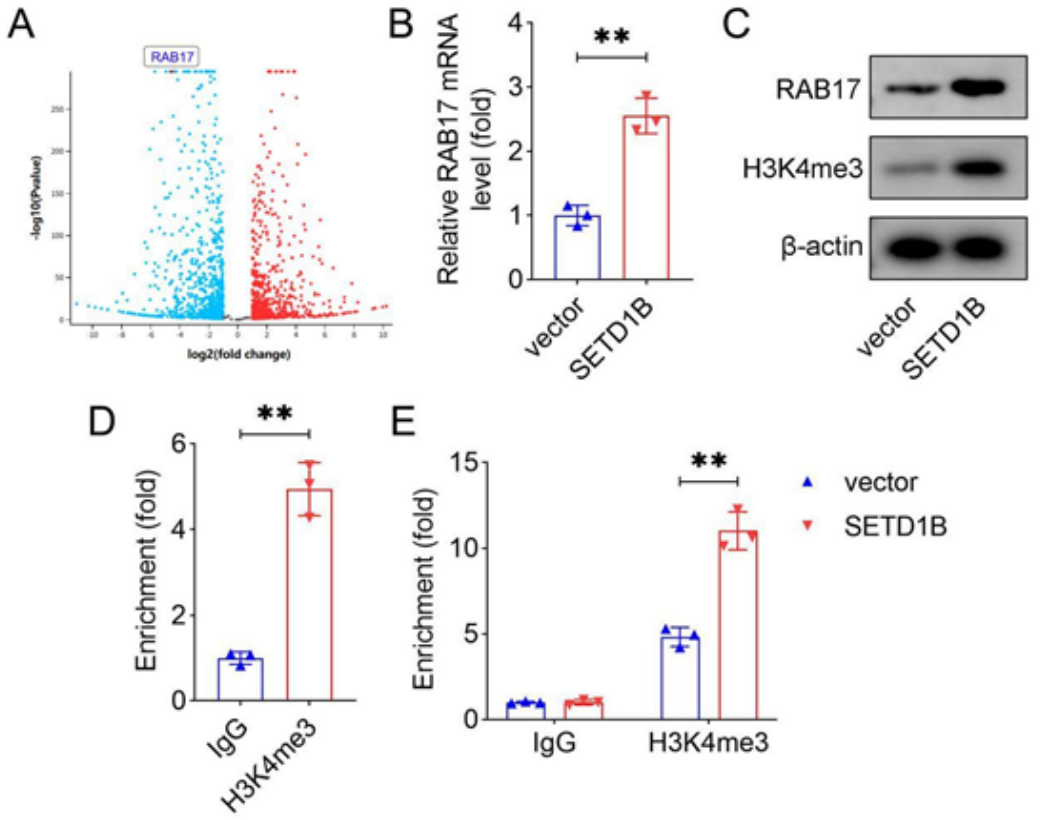


Fig. 3. SETD1B upregulates RAB17 via promoting histone methylation
(A) GSE273152 was used to analyse the DEGs after the SETD1B knockout
(B) mRNA expression was detected using T-qPCR
(C) Protein expression was detected using Western blot
(D-E) H3K4me3 methylation of RAB17 was detected using ChIP assay
$^{**}P < 0.01$

SETD1B is dysregulated in tumorigenesis. For example, SETD1B mutation contributes to apoptosis-resistance in B cell lymphoma (Sciarra et al. 2024). However, overexpressed SETD1B predicts unsatisfactory outcomes of patients with hepatocellular carcinoma or colorectal cancer (Chen et al. 2019; Lindner et al. 2020). These findings dictated that SETD1B functions as a tumour-suppressor as well as tumour-promoter, which varies with the types of tumours. In this study, downregulated SETD1B in DLBCL patients predicted poor prognosis. However, overexpressed SETD1B promoted DLBCL cell apoptosis.

The alteration of histone methylation is a key hallmark of tumorigenesis (Chen et al. 2020; Sutopo et al. 2023). Recent studies have demonstrated that dysregulated histone methylation contributes to the progression of DLBCL (Huang et al. 2021). For instance, SETD1B deficiency-mediated inhibition of methylation of H3K4 promotes the tumour growth of DLBCL (Portelinha et al. 2024). NCAPD3-mediated H3K9 monomethylation on Sirt1 promotes the proliferation of DLBCL (Lu et al. 2025). In this study, downregulated SETD1B inhibited the methylation of H3K4 and induced the progression of DLBCL. Intriguingly, overexpressed SETD1B drove H3K4 methylation and upregulation of RAB17. RAB17

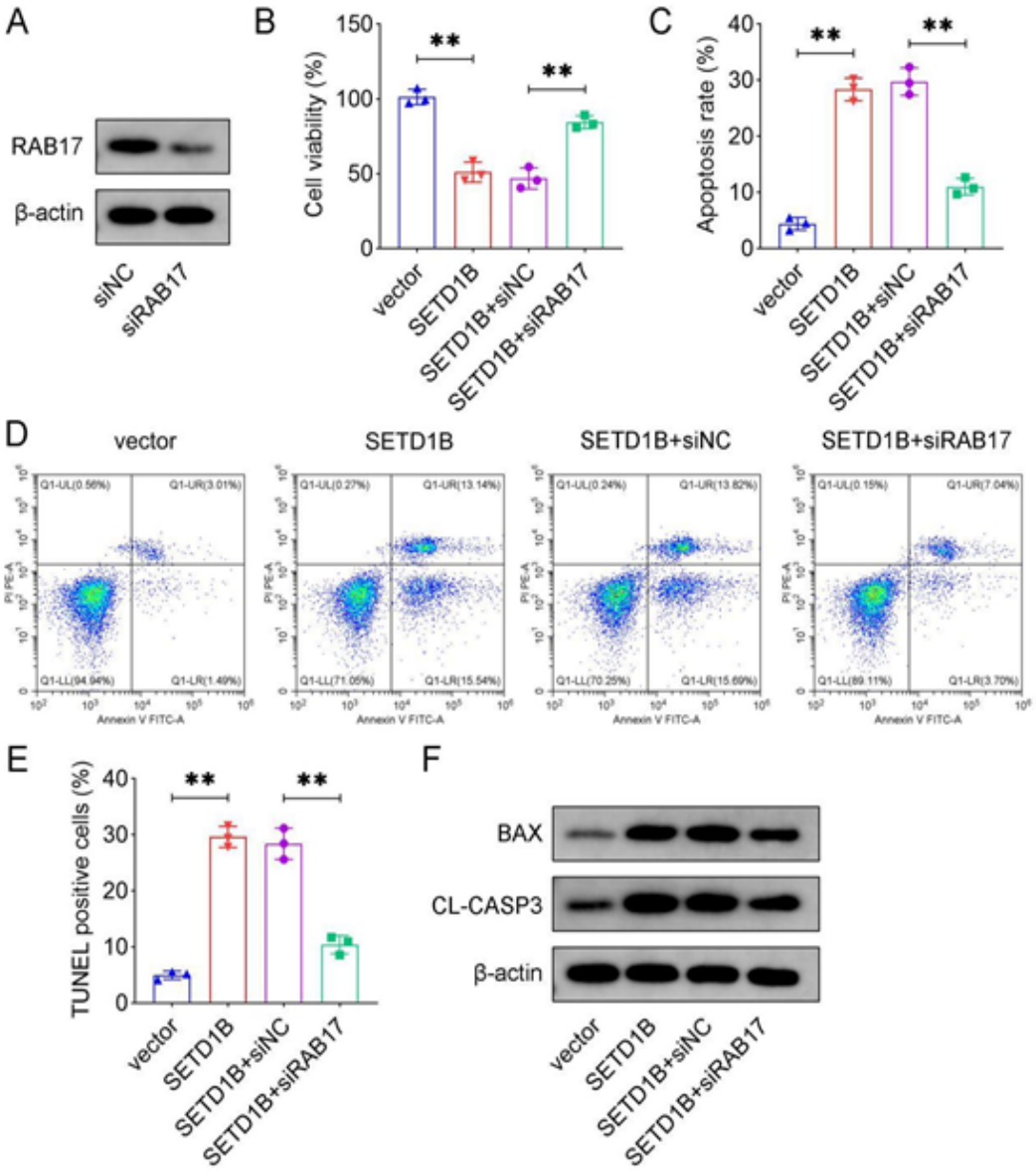
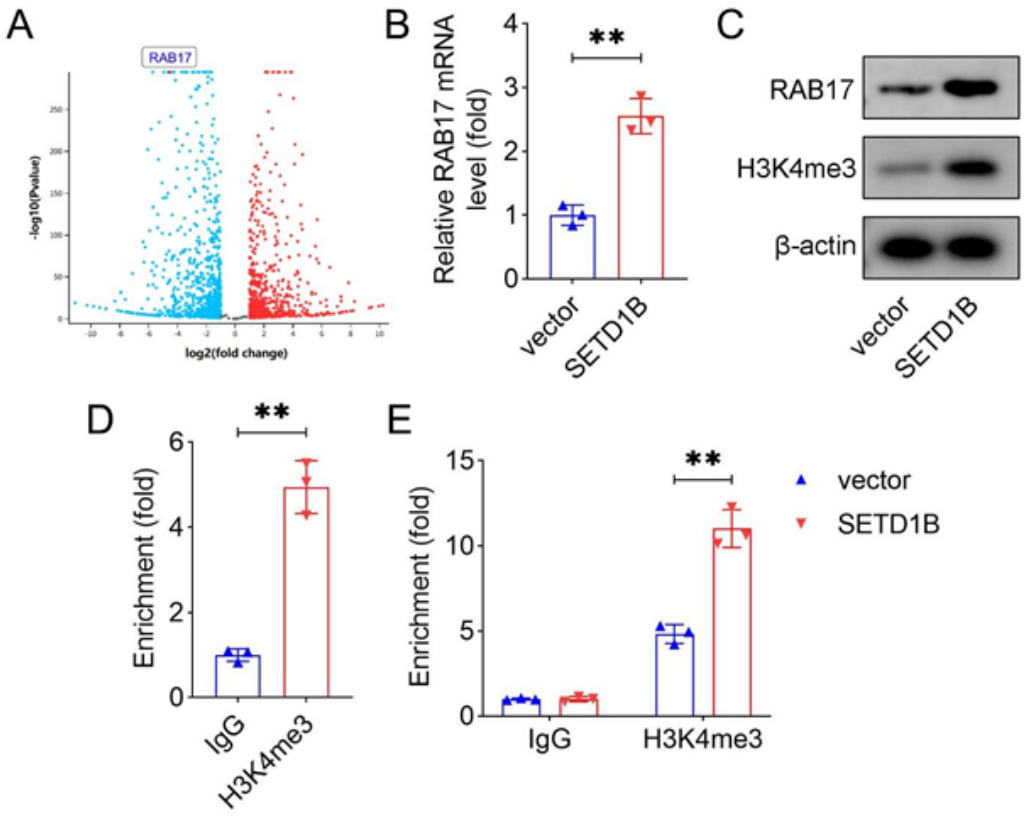
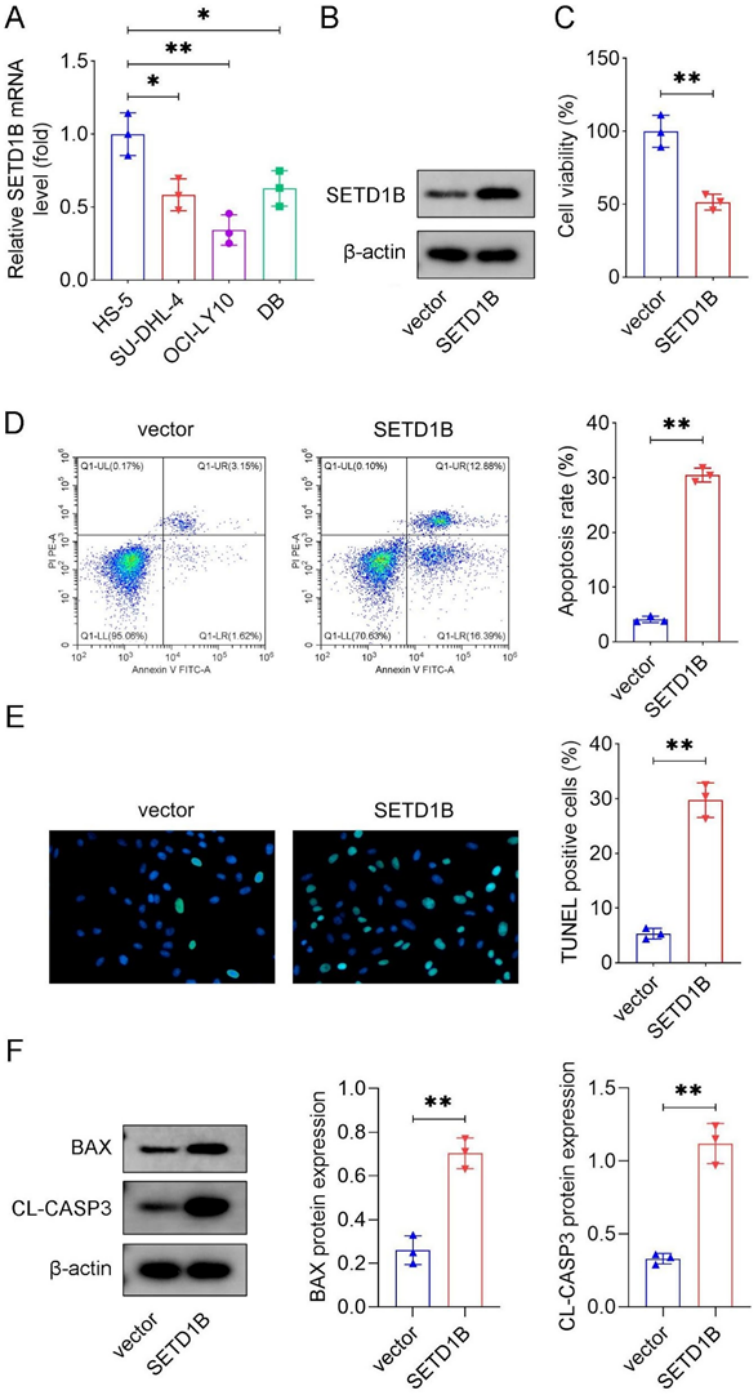
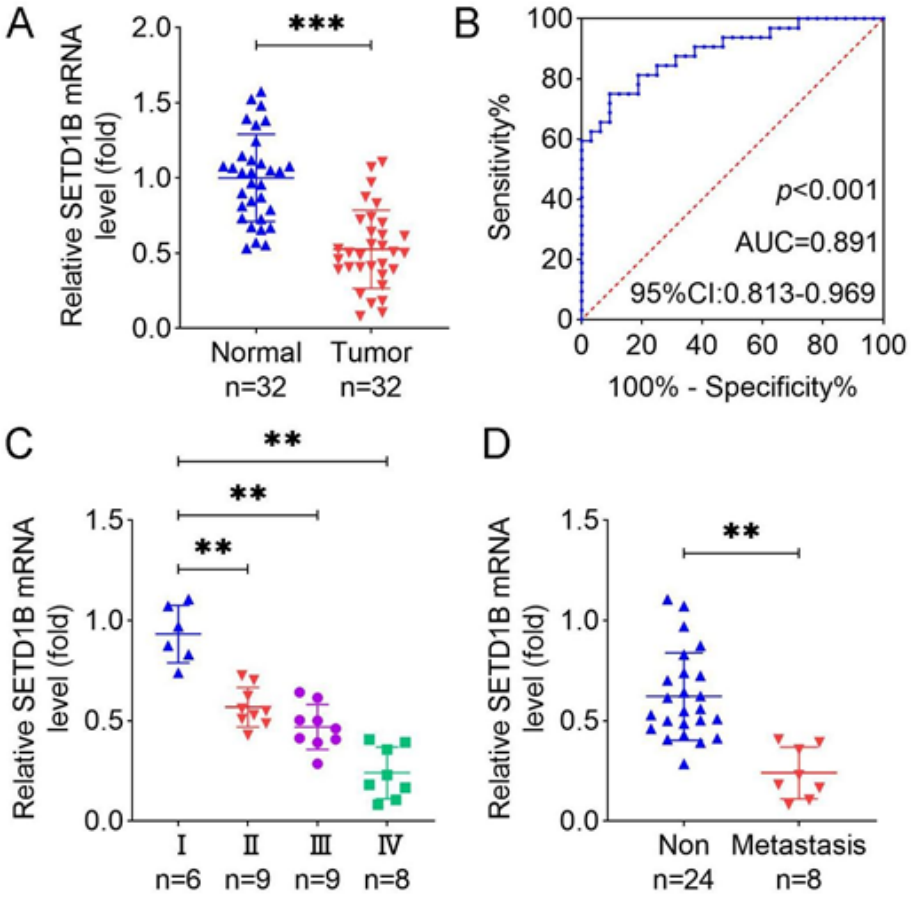
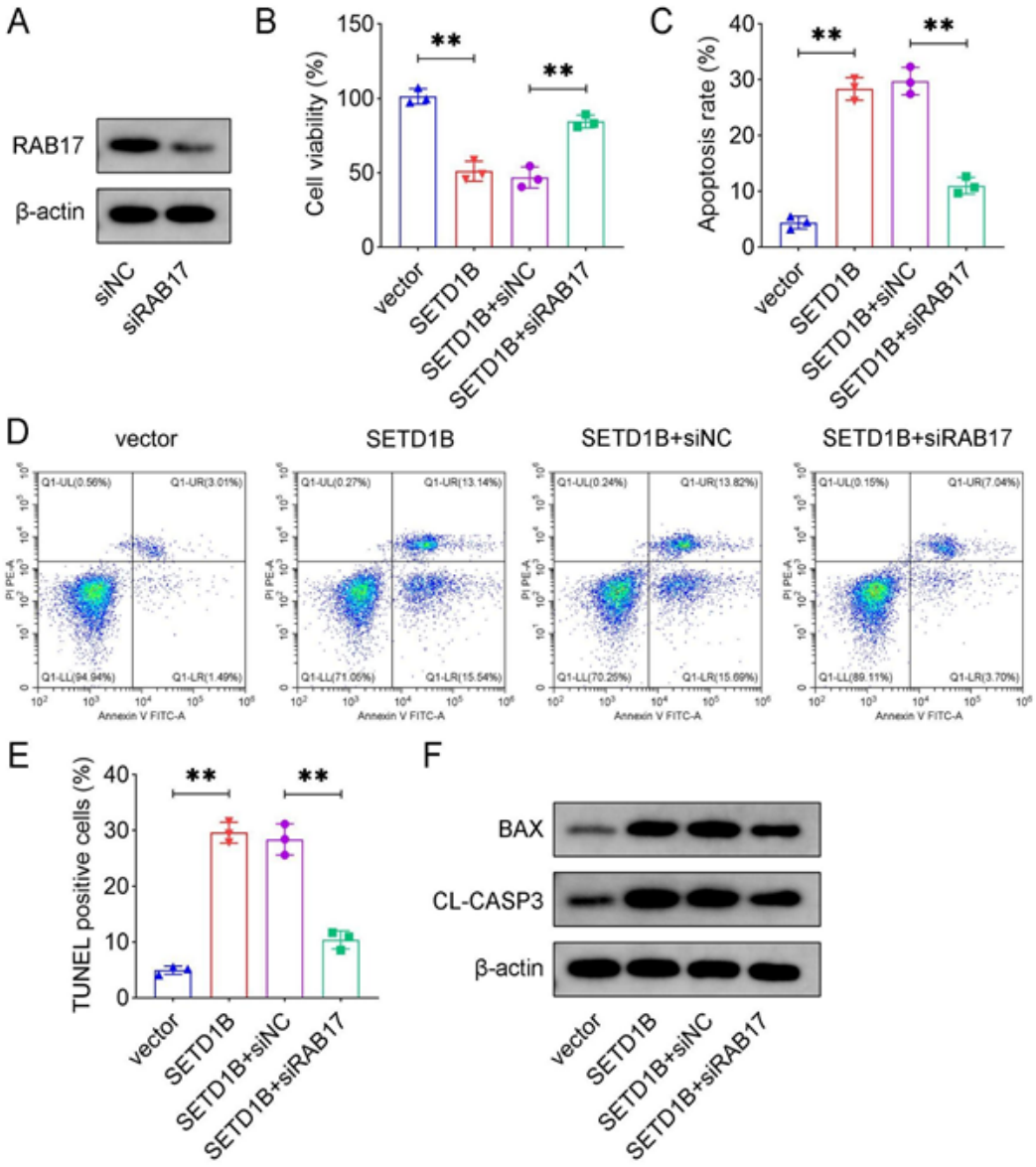


Fig. 4. RAB17 deficiency suppresses DLBCL cell apoptosis
(A) Protein expression was analysed by Western blot
(B) Cell proliferation was analysed by CCK-8
(C-D) Cell apoptosis was analysed by flow cytometry
(E) Cell death was analysed by TUNEL staining
(F) Protein expression was analysed by Western blot
$^{**}P$ **<0.01**


A
RAB17
-log10(Pvalue)
log2(fold change)
B
Relative RAB17 mRNA level (fold)
**
vector
SETD1B
C
RAB17
H3K4me3
β-actin
vector
SETD1B
D
**
Enrichment (fold)
IgG
H3K4me3
E
**
Enrichment (fold)
IgG
H3K4me3
vector
SETD1B


A
Relative SETD1B mRNA level (fold)
HS-5
SU-DHL-4
OCI-LY10
DB
B
SETD1B
β-actin
vector
SETD1B
C
Cell viability (%)
vector
SETD1B
D
vector
SETD1B
Q1-UL(0.17%)
Q1-UR(3.15%)
Q1-LL(95.06%)
Q1-LR(1.62%)
Q1-UL(0.10%)
Q1-UR(12.88%)
Q1-LL(70.63%)
Q1-LR(16.39%)
PI PE-A
Annexin V FITC-A
Apoptosis rate (%)
E
vector
SETD1B
TUNEL positive cells (%)
F
BAX
CL-CASP3
β-actin
BAX protein expression
CL-CASP3 protein expression


A
Relative SETD1B mRNA level (fold)
2.0
1.5
1.0
0.5
0.0
***
Normal n=32
Tumor n=32
B
Sensitivity%
100
80
60
40
20
0
p<0.001
AUC=0.891
95%CI:0.813-0.969
0 20 40 60 80 100
100% - Specificity%
C
Relative SETD1B mRNA level (fold)
1.5
1.0
0.5
0.0
**
**
**
I n=6
II n=9
III n=9
IV n=8
D
Relative SETD1B mRNA level (fold)
1.5
1.0
0.5
0.0
**
Non n=24
Metastasis n=8


A
RAB17
β-actin
siNC
siRAB17
B
Cell viability (%)
150
100
50
0
**
**
vector
SETD1B
SETD1B+siNC
SETD1B+siRAB17
C
Apoptosis rate (%)
40
30
20
10
0
**
**
vector
SETD1B
SETD1B+siNC
SETD1B+siRAB17
D
vector
SETD1B
SETD1B+siNC
SETD1B+siRAB17
Q1-UL(0.56%)
Q1-UR(3.01%)
Q1-LL(94.94%)
Q1-LR(1.49%)
Q1-UL(0.27%)
Q1-UR(13.14%)
Q1-LL(71.05%)
Q1-LR(15.54%)
Q1-UL(0.24%)
Q1-UR(13.82%)
Q1-LL(70.25%)
Q1-LR(15.69%)
Q1-UL(0.15%)
Q1-UR(7.04%)
Q1-LL(89.11%)
Q1-LR(3.70%)
PI PE-A
Annexin V FITC-A
E
TUNEL positive cells (%)
40
30
20
10
0
**
**
vector
SETD1B
SETD1B+siNC
SETD1B+siRAB17
F
BAX
CL-CASP3
β-actin
vector
SETD1B
SETD1B+siNC
SETD1B+siRAB17

exerts anti-tumour function in various cancers. For instance, low levels of RAB17 predict unfavourable outcomes of kidney renal clear cell carcinoma (Zeng et al. 2023). RAB17 deficiency promotes invasion of NSCLC (Wang et al. 2020). However, overexpressed RAB17 suppresses the aggressiveness of ovarian cancer (Guo et al. 2020). In this study, RAB17 expression was reduced in DLBCL. RAB17 knockdown mediated DLBCL cell survival. Therefore, SETD1B may inhibit the progression of DLBCL via regulating RAB17.

However, several limitations of the study should be acknowledged. While the genetic and epigenetic analyses provided valuable sight on the potential of SETD1B in DLBCL, the functional assays were primarily performed in cell lines. Further validation in *in vivo* models is necessary. Additionally, the downstream signalling pathways regulated by SETD1B in DLBCL cells warrant further investigation to fully elucidate the molecular mechanisms underlying its role in apoptosis.

CONCLUSION

In conclusion, SETD1B exerts an anti-tumour function in DLBCL. Overexpressed SETD1B effectively drives DLBCL cell apoptosis. Moreover, SETD1B upregulates RAB17 expression through driving histone methylation on its promoter. However, RAB17 deficiency contributes to the progression of DLBCL.

RECOMMENDATIONS

SETD1B may be a sensitive biomarker of DLBCL. Targeting SETD1B may be a promising strategy for DLBCL.

DECLARATIONS

COMPETING INTERESTS

The authors declare that they have no conflict of interest.

AVAILABILITY OF DATA AND MATERIAL

The data sets used and analysed in the current study are available on reasonable request from the corresponding authors.

FUNDING

Not applicable.

ACKNOWLEDGEMENTS

Not applicable.

CONFLICT OF INTEREST

Not applicable.

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