Original Article

The m^{6}A methyltransferase WTAP plays a key role in the development of diffuse large B-cell lymphoma via regulating the m^{6}A modification of catenin beta 1

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Background: Diffuse large B-cell lymphoma (DLBCL) is the most frequently occurring subtype of lymphoma. Unfortunately, the fundamental processes underlying the pathogenesis of DLBCL remain little understood. N^6-methyladenosine (m^{6}A) methylation has been shown to be the most common internal alteration of mRNAs found in eukaryotes, and it is thought to play a key role in cancer pathogenesis. However, the precise relationship between m^{6}A mRNA methylation and DLBCL pathogenesis remains to be fully elucidated.

Methods: The mRNA and protein expression of Wilms tumor 1-associating protein (WTAP) were determined using quantitative real-time polymerase chain reaction (qRT-PCR) and Western blot analysis in lymphoma cells lines. The effects of WTAP expression on human lymphoma cells lines were assessed using cell proliferation assays, colony formation assays, and CCK8 assays. The Gene Expression Profiling Interactive Analysis (GEPIA) database was used to screen candidate gene targets of WTAP. Finally, the regulatory mechanisms of WTAP in DLBCL were investigated using methylated RNA immunoprecipitation (MeRIP) assays.

Results: This study investigated the precise function of WTAP in DLBCL formation. The results demonstrated that the levels of m^{6}A RNA methylation and WTAP expression were both elevated in DLBCL cell lines and tissues. Downregulation of WTAP expression in DLBCL cells caused a reduction in cell growth in a functional sense. WTAP knockdown reduced catenin beta 1 (*CTNNB1*) m^{6}A methylation and *CTNNB1* total mRNA levels. Furthermore, *CTNNB1* overexpression eliminated the WTAP-induced reduction of cell growth in DLBCL cells.

Conclusions: In conclusion, these findings demonstrated that WTAP promotes DLBCL development via modulation of m^{6}A methylation in *CTNNB1*.

Keywords: Wilms tumor 1-associating protein (WTAP); diffuse large B-cell lymphoma (DLBCL); *CTNNB1*; N^6-methyladenosine (m^{6}A); proliferation

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Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most prevalent lymphoma subtype, accounting for 30–40% of all adult non-Hodgkin lymphoma cases (1). Only about 50% of patients are cured with front line therapy with rituximab based therapy (2,3), due to the high number of refractory cases further develop of novel markers and therapeutics are needed to improve outcomes in DLBCL. A comprehensive understanding of the processes involved in DLBCL formation and progression is crucial for the development of novel therapeutic agents in the treatment of DLBCL.

The most common internal alteration of eukaryotic mRNAs is N^6-methyladenosine (m^{6}A) methylation (4-6). m^{6}A methylation occurs via a methyltransferase complex consisting of methyltransferase-like3 (METTL3), methyltransferase-like 14 (METTL14), and associated proteins, such as Wilms tumor 1-associating protein (WTAP) (7-12). Removal of this alteration can be brought about by m^{6}A demethylases, such as alkylation repair homolog protein 5 (ALKBH5) or fat mass and obesity-associated protein (FTO) (13,14). Coordinated control of the demethylases or m^{6}A methyltransferases in mammalian cells is required to maintain this reversible and dynamic RNA modification. Interestingly, WTAP has been shown to play a role in the pathogenesis of a variety of illnesses, including cancers (15-18). Many transcriptional regulators have been demonstrated to control the transcription of *CTNNB1*, which is a key regulator of the Wnt/β-catenin signaling pathway in DLBCL development (19). Nevertheless, the relevance of WTAP induced *CTNNB1* N^6-methyladenosine modfication in DLBCL development and the regulatory mechanisms involved remain not fully elucidated. The purpose of this study is to explore expression and mechanism of WTAP in DLBCL. We present the following article in accordance with the MDAR reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-3027/rc).

Methods

Tissue specimens

A total of 38 clinical specimens, including 19 inflammatory lymph glands and 19 resected DLBCL lymph glands, were obtained from The First Affiliated Hospital, and College of Clinical Medicine of Henan University of Science and Technology between 2016 and 2020. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by committee board of The First Affiliated Hospital, and College of Clinical Medicine of Henan University of Science and Technology (No. 2022-03-B060). Informed consent was taken from all the patients.

Quantitative real-time polymerase chain reaction (qRT-PCR)

Total RNA was extracted from cell lines or sample tissues using TRIzol reagent, and cDNA was synthesized using the One-Step RT-PCR Kit (Thermo Fisher Scientific). ACTIN was used as an internal reference control. Primers were as follows:

CTNNB1 forward, 5'-TCAGGCGTCTGTAGAGGCTT-3', and reverse, 5'-ATGCACATCCTTCGATAAGACTG-3'; WTAP forward, 5'-GACGCCATCAACACCGAGTT-3', and reverse, 5'-CTTTGTCGTTGGTTAGCTGGT-3';

ACTIN forward, 5'-TGTGGGCATCAATGGATTTGG-3', and reverse, 5'-ACACCATGTATTCCGGGTCAAT-3'.

Western blot

Western blot analysis was conducted as described previously (20). Primary antibodies were listed as below: WTAP (ABCAM:80233, USA, 1:1,000, anti-rabbit), ACTIN (ABCAM:82433, USA, 1:10,000, anti-rabbit), *CTNNB1* (ABCAM:80931, USA, 1:1,000, anti-rabbit). ACTIN was used as a protein loading control.

Cell culture

The human DLBCL cell lines Farage, OCILy10, SU-DHL4, HBL1, and U293, as well as the human B lymphocyte cell line GM12878 were obtained from the American Type Culture Collection (ATCC). Under normal conditions, cells were cultured with Dulbecco's Modified Eagle Medium (DMEM) supplemented with 1% penicillin/streptomycin and 10% fetal bovine serum (FBS).

Cell proliferation assay

Cell proliferation was assessed using the Cell Counting Kit-8 (CCK-8; Beyotime, Shanghai, China) as described previously (21).

Lentivirus production and transfection

The short hairpin (sh) RNA lentiviral expression plasmid

targeting WTAP and the human *CTNNB1* cDNA lentivirus (LV-CTNNB1) were obtained from Shanghai Genelily BioTech Co., Ltd. Cells were transfected with Lipofectamine 3000 (Invitrogen) for 48 hours according to the manufacturer's instructions. The transfection efficiency was evaluated using RT-qPCR. The 5'-3' sequences of shRNA were as follows: shRNA-NC: 5'-CGGGUAGAGAGGGCAGUGGGAGG-3': shRNA-WTAP: 5'-AGUGGUGGAAGAGGUGGGUCG-3'.

Quantification of m^{6}A

The degree of m^{6}A methylation in the total RNA extracted from cells or tissue was determined using the Abcam m^{6}A RNA Methylation Assay Kit (15). A microplate reader was used to assess the absorbance at 450 nm.

Methylated m^{6}A RNA immunoprecipitation (Me-RIP) assay

The Me-RIP analysis was performed as previously described (15).

RNA stability assay

The stability of the *CTNNB1* transcripts was determine as previously described (22) using qRT-PCR.

Statistics

All data are presented as mean ± standard deviations (SD). The unpaired two-tailed Student's *t*-test was used to compare groups. Analysis of variance (ANOVA) or repeated ANOVA was used for multiple comparisons using the GraphPad Prism R version 6.0 software. A Bonferroni post hoc test was subsequently conducted. A P value <0.05 was considered statistically significant.

Results

The levels of m^{6}A RNA methylation and WTAP expression are elevated in DLBCL

To determine the role of m^{6}A modification in the pathogenesis of DLBCL, 19 inflammatory lymph glands and 19 DLBCL tissues were collected and the bulk m^{6}A RNA methylation was examined. The m^{6}A levels were significantly higher in DLBCL tissues compared to control inflammatory lymph glands (*Figure 1A*). Similarly, DLBCL cell lines including SU-DHL4, OCILy10, Farage, U2932, and HBL1 also showed elevated levels of m^{6}A compared to the human B lymphocyte cell line GM12878 (*Figure 1B*). qRT-PCR experiments demonstrated that WTAP mRNA levels were increased in DLBCL tissues compared to inflammatory lymph gland tissues (*Figure 1C*). These results were further supported by data collected from the Gene Expression Profiling Interactive Analysis (GEPIA) database (*Figure 1D*). Furthermore, enhanced WTAP protein expression in DLBCL tissues was confirmed by Western blot analysis (*Figure 1E*). In addition, upregulation of WTAP mRNA levels was observed in DLBCL cell lines (*Figure 1F*). These findings suggested that WTAP, through modulating m^{6}A methylation, may function as a pro-tumor gene implicated in DLBCL pathogenesis.

Silencing WTAP expression inhibited the proliferation of DLBCL cells

A lentivirus-mediated shRNA was used to knock down WTAP expression in the DLBCL cell lines SU-DHL4 and HBL1. qRT-PCR and Western blot analysis demonstrated that the expression of WTAP was suppressed in sh-WTAP transfected cells, suggesting good transfection efficiency (*Figure 2A,2B*). CCK-8 assays showed that the proliferation capacity of DLBCL cells was inhibited when WTAP expression was suppressed (*Figure 2C*). Furthermore, the colony-forming ability of WTAP-silenced cells was lower than that of control cells (*Figure 2D*). These results suggested that WTAP knockdown inhibited DLBCL cell growth *in vitro*.

WTAP knockdown impeded CTNNB1 expression and m^{6}A methylation of CTNNB1 mRNA

The role of *CTNNB1*, an upstream Wnt pathway component, in WTAP-mediated DLBCL cell proliferation was examined. Data from the GEPIA database showed that *CTNNB1* was positively linked with WTAP in a variety of malignancies, including DLBCL tissues (*Figure 3A*). While *CTNNB1* mRNA expression was significantly elevated in DLBCL tissues, there was a positive association between WTAP levels and upregulated *CTNNB1* expression in DLBCL tissues (*Figure 3B*). To determine whether WTAP is involved in the regulation of *CTNNB1* expression in DLBCL cells, HBL1 and SU-DHL4

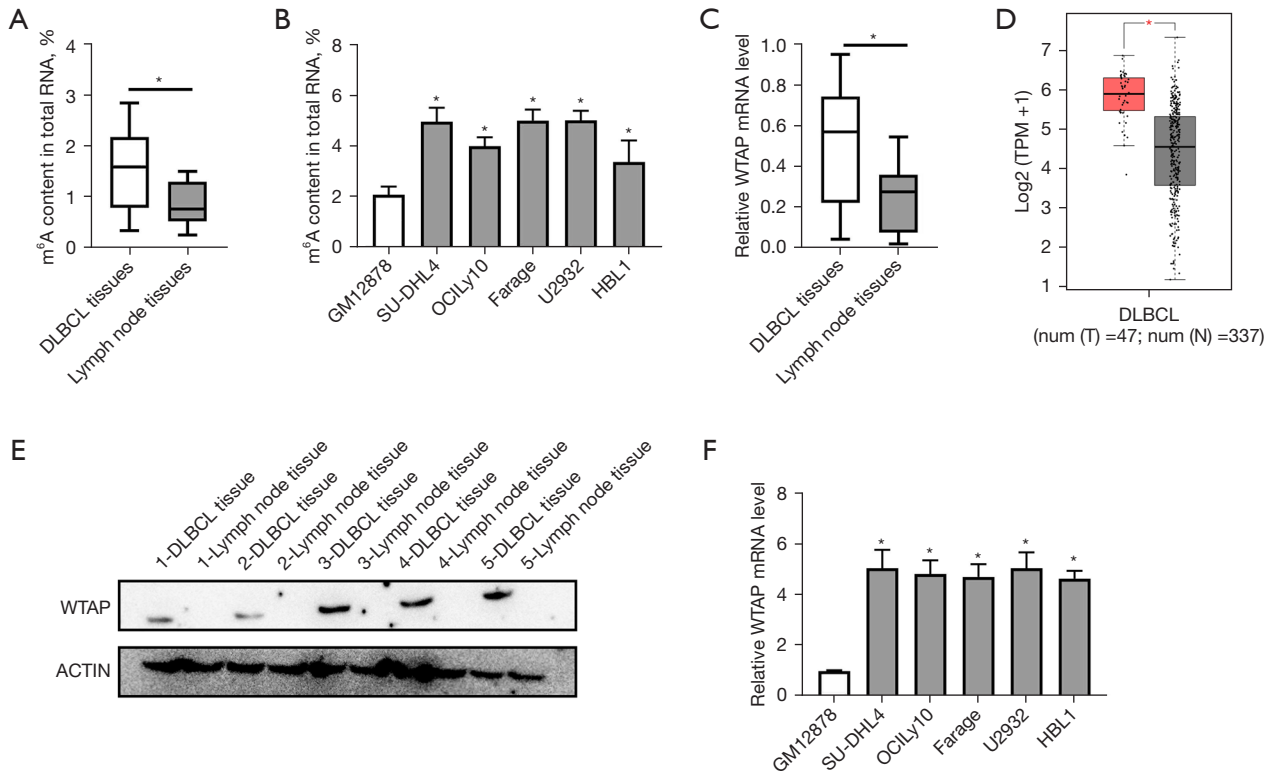

Figure 1 m^{6}A RNA methylation and WTAP expression were elevated in DLBCL. (A) The bulk m^{6}A RNA methylation in 19 inflammatory lymph glands and 19 DLBCL tissues. *P<0.05. (B) The bulk m^{6}A RNA methylation in DLBCL cell lines and GM12878. *P<0.05. (C) qRT-PCR was used to examine WTAP mRNA expression in 18 inflammatory lymph nodes and 18 DLBCL tissues. *P<0.05. (D) WTAP expression in DLBCL tissues and normal counterparts in the GEPIA database *P<0.05. (E) Western blot was used to examine WTAP protein expression in 5 DLBCL tissues and 5 inflammatory lymph nodes. (F) The mRNA expression of WTAP in DLBCL cell lines and GM12878 was investigated using qRT-PCR. *P<0.05. WTAP, Wilms tumor 1-associating protein; DLBCL, diffuse large B-cell lymphoma; qRT-PCR, quantitative real-time polymerase chain reaction; TPM, transcript per million; T, tumor; N, normal.

cells were transfected with sh-WTAP. Silencing WTAP resulted in lower *CTNNB1* mRNA and protein expression (*Figure 3C,3D*). Furthermore, silencing WTAP decreased m^{6}A methylation in *CTNNB1* mRNAs (*Figure 3E*). RNA stability tests were performed to determine if reduced m^{6}A methylation impacted *CTNNB1* mRNA stability in cells. *CTNNB1* gene transcripts had a shorter half-life in HBL1 and SU-DHL4 cells transfected with sh-WTAP (*Figure 3F*). Together, these results suggested that the reduced *CTNNB1* expression induced by silencing WTAP may be mediated, in part, by decreased mRNA stability associated with altered m^{6}A methylation levels. Therefore, we hypothesized that WTAP silencing in DLBCL cells reduces *CTNNB1* expression via modulation of mRNA methylation (m^{6}A).

WTAP knockdown inhibited DLBCL cell proliferation, while CTNNB1 overexpression ameliorated this effect

To investigation whether *CTNNB1* is involved in the inhibition of DLBCL cell growth caused by WTAP knockdown, SU-DHL4 and HBL1 cells were transfected with a negative control (NC) plasmid, the sh-WTAP plasmid, LV-*CTNNB1* plasmid, or the sh-WTAP + LV-*CTNNB1* plasmids. The expression of CTNNB1 in the transfected cells was assessed by Western blot and qRT-PCR (*Figure 4A,4B*). *CTNNB1* overexpression significantly reduced the effect of WTAP silencing on proliferation and colony formation in DLBCL cells (*Figure 4C,4D*). This suggested that *CTNNB1* overexpression eliminated the inhibitory impact of WTAP knockdown on DLBCL cell

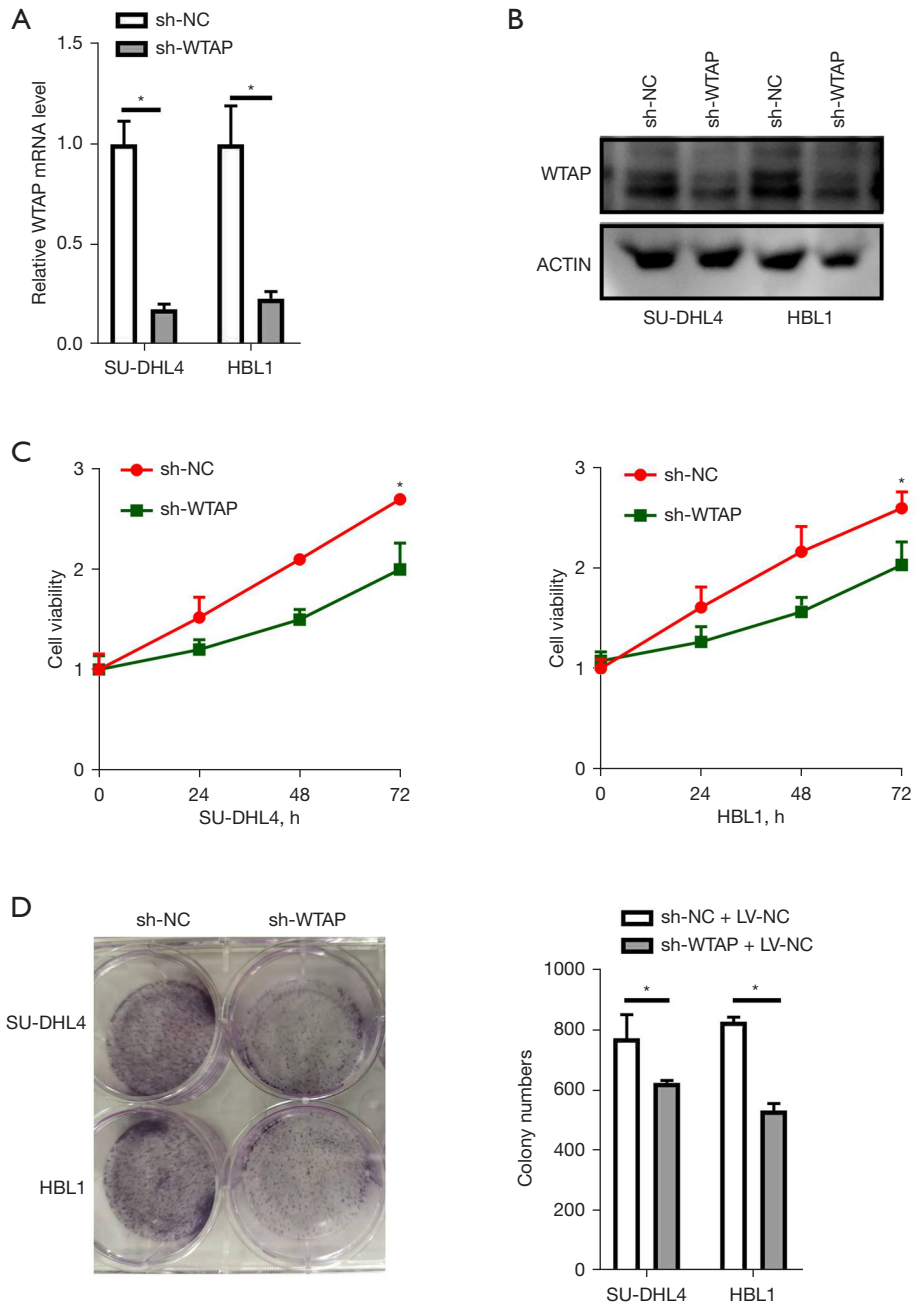

Figure 2 WTAP knockdown prevented DLBCL cell proliferation. The efficiency of WTAP silencing in SU-DHL4 and HBL1 cells were assess by (A) qRT-PCR and (B) Western blot *P<0.05. (C) The CCK-8 assay was used to assess the viability of DLBCL cells. *P<0.05. (D) Colony formation assays (0.1% crystal violet, magnification ×1). *P<0.05. WTAP, Wilms tumor 1-associating protein; DLBCL, diffuse large B-cell lymphoma; qRT-PCR, quantitative real-time polymerase chain reaction; CCK-8, Cell Counting Kit 8; sh, short hairpin; NC, negative control; LV, lentivirus.

A

Tumor	R	P vaule
ACC	0.3	0.0072
BLCA	0.41	0
BRCA	0.29	0
CESC	0.3	8.20E−08
CHOL	0.49	0.0025
COAD	0.38	9.70E−11
DLBC	0.75	1.30E−09
ESCA	0.26	0.00046
GBM	0.16	0.38
HNSC	0.34	2.70E−15
KICH	0.58	3.50E−07
KIRC	0.55	0
KIRP	0.52	0
LAML	0.56	1.30E−15
LGG	0.38	0
LIHC	0.39	8.00E−15
LUAD	0.2	9.10E−06
LUSC	0.15	0.0013
MESO	0.31	0.0034
OV	0.45	0
PAAD	0.39	6.40E−08
PCPG	0.6	0
PRAD	0.57	0
PEAD	0.57	3.20E−09
SARC	0.079	0.2
SKCM	0.14	0.002
STAD	0.36	1.30E−13
TGCT	0.46	1.40E−08
THCA	0.71	0
THYM	0.5	6.40E−09
UCEC	0.62	0
UCS	0.39	0.0025
UVM	0.37	0.00082

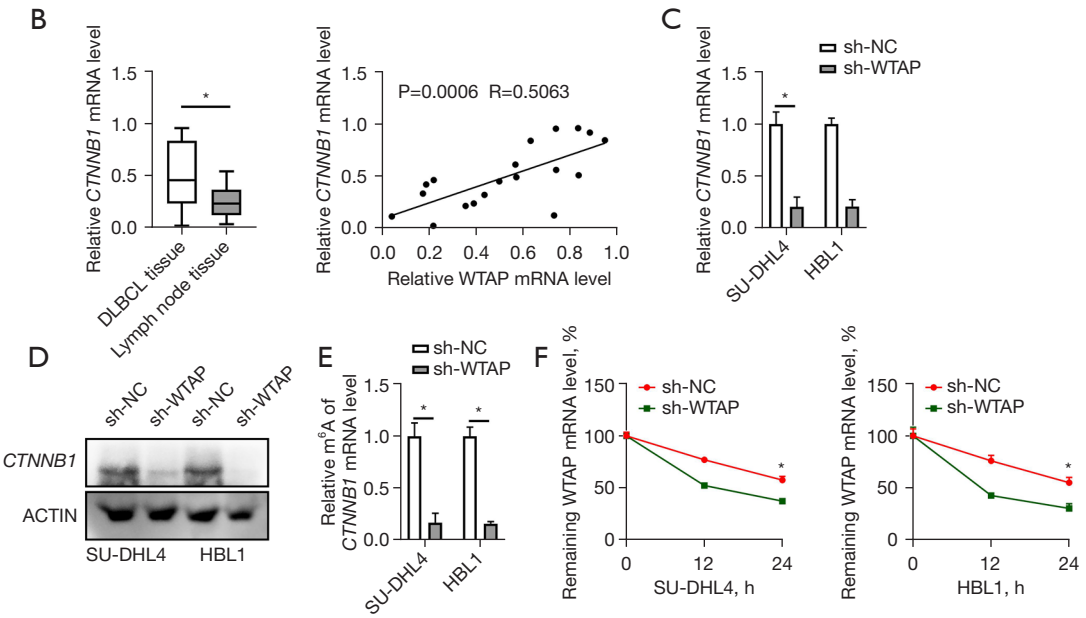

Figure 3 WTAP silencing reduced *CTNNB1* expression and m^{6}A methylation in *CTNNB1* mRNAs. (A) The GEPIA database was used to determine *CTNNB1* expression in DLBCL tissues and to determine the association between WTAP expression and *CTNNB1* expression in DLBCL tissues. (B) qRT-PCR was used to assess the mRNA expression of *CTNNB1* in 19 DLBCL tissues and 19 inflammatory lymph gland specimens. *P<0.05. Linear regression analysis revealed a favorable connection between WTAP and *CTNNB1* mRNA expression. (C) qRT-PCR and (D) Western blot analysis were performed to analyze the mRNA and protein expression of *CTNNB1* in SU-DHL4 and HBL1 cells transfected with sh-WTAP. *P<0.05. (E) The Me-RIP assay was used to detect m^{6}A methylation in *CTNNB1* transcripts in SU-DHL4 and HBL1 cells transfected with sh-WTAP. *P<0.05. (F) The half-life ($T_{1/2}$) of *CTNNB1* mRNA transcripts in HBL1 and SU-DHL4 cells transfected with sh-WTAP. *P<0.05. GEPIA, Gene Expression Profiling Interactive Analysis; WTAP, Wilms tumor 1-associating protein; DLBCL, diffuse large B-cell lymphoma; *CTNNB1*, catenin beta 1; qRT-PCR, quantitative real-time polymerase chain reaction; sh, short hairpin; NC, negative control; Me-RIP, methylated m^{6}A RNA immunoprecipitation.

activity.

Discussion

To the best of our knowledge, this study is the first to demonstrate the functional involvement of WTAP and m^{6}A RNA alteration on the development of DLBCL. The bulk m^{6}A RNA methylation and WTAP expression was significantly higher in DLBCL cell lines and tissues compared to B lymphocytes and control inflammatory lymph glands, respectively. m^{6}A methylation is a chemical change in mRNAs that has been shown to play a key role in cancer formation and WTAP gene mutations have also been linked to a variety of malignancies. Functional tests revealed that silencing WTAP inhibited the growth of DLBCL cells. These data suggested that WTAP acts as an oncogene in the development of DLBCL, possibly through regulation of mRNA methylation.

Abnormal levels of Wnt signaling have been implicated in the development of DLBCL (23-26). Many transcriptional regulators have been demonstrated to control the transcription of *CTNNB1*, which is a key regulator of the Wnt/β-catenin signaling pathway (27-30). Previous study indicated that m^{6}A mRNA methylation regulates *CTNNB1* to promote the proliferation of hepatoblastoma (31). The results of this investigation lead us to believe that elevated m^{6}A levels in *CTNNB1* mRNAs might have potential involvement in WTAP-controlled DLBCL cell proliferation regulation, more research into the regulatory significance of the WTAP/*CTNNB1* axis in DLBCL formation is needed. This study confirmed that WTAP-mediated RNA m^{6}A methylation is required in DLBCL. Therefore, future studies will explore specific WTAP inhibitors for the clinical treatment of DLBCL.

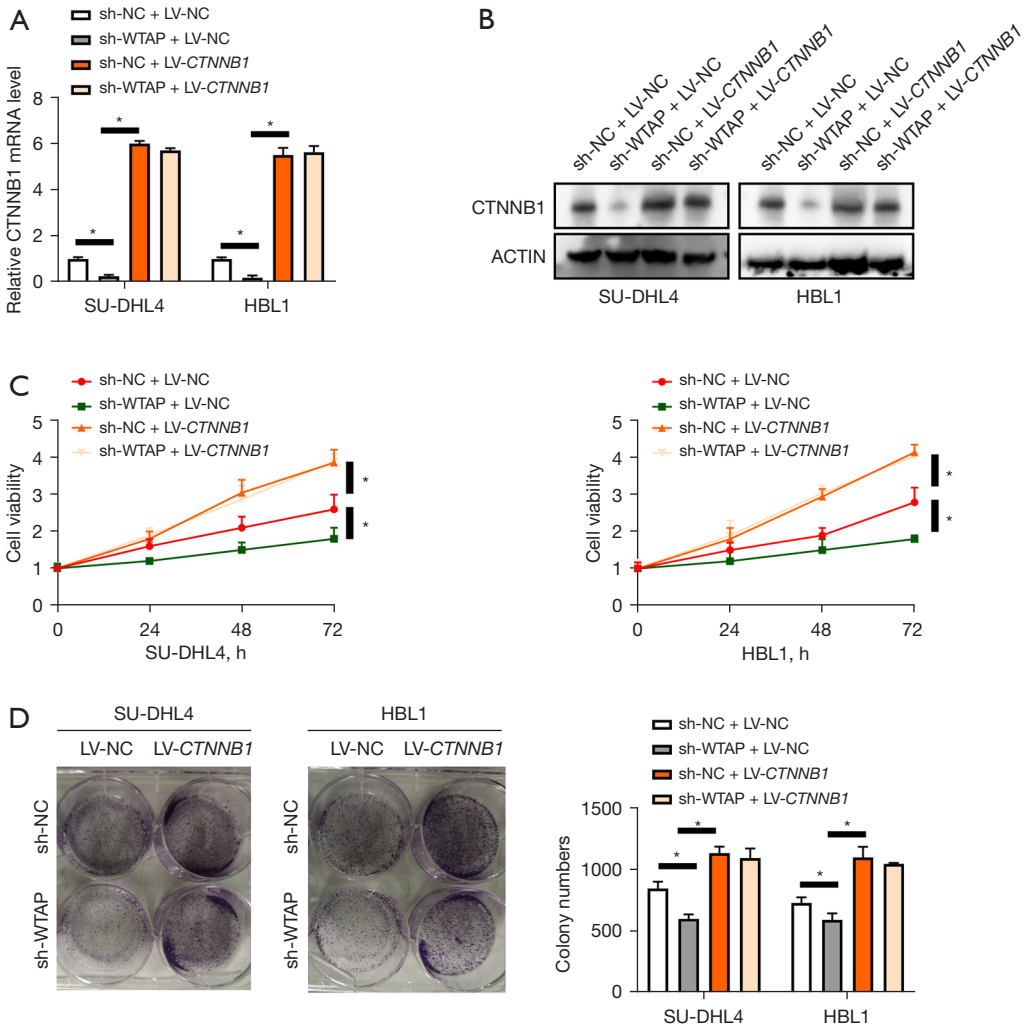

Figure 4 WTAP knockdown inhibited DLBCL cell growth, and this effect was reversed by overexpression of *CTNNB1*. (A) qRT-PCR and (B) Western blot analyses were used to assess *CTNNB1* expression at the mRNA and protein levels, respectively. (C) CCK8 and (D) colony formation assays were used to determine the viability and apoptosis rate in SU-DHL4 and HBL1 cells (0.1% crystal violet, magnification ×1). Cells were transfected with Lv-NC, Lv-shWTAP, Lv-*CTNNB1*, or Lv-shWTAP + Lv-*CTNNB1*. *P<0.05 *vs.* the control groups. WTAP, Wilms tumor 1-associating protein; DLBCL, diffuse large B-cell lymphoma; *CTNNB1*, catenin beta 1; qRT-PCR, quantitative real-time polymerase chain reaction; CCK-8, Cell Counting Kit 8; sh, short hairpin; NC, negative control; LV, lentivirus.

In conclusion, our findings indicated that the m^{6}A methyltransferase WTAP is involved in the regulation of m^{6}A modifications in *CTNNB1* mRNAs, thereby, regulating DLBCL cell growth. Indeed, the WTAP/*CTNNB1* axis may be a potential therapeutic target for the treatment of DLBCL.

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Footnote

Reporting Checklist: The authors have completed the MDAR reporting checklist. Available at https://atm.amegroups.

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Data Sharing Statement: Available at https://atm.amegroups.com/article/view/10.21037/atm-22-3027/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-3027/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by committee board of The First Affiliated Hospital, and College of Clinical Medicine of Henan University of Science and Technology (No. 2022-03-B060). Informed consent was taken from all the patients.

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