BMC Cancer

RESEARCH

Open Access

Prognostic significance of CDK1 expression in diffuse large B-Cell lymphoma

Qiuni Chen[1,2], Lei Xu[1,2], Chuanyang Lu[1,2], Yujie Xue[3], Xue Gong[3], Yuye Shi[1,2], Chunling Wang[1,2*] and Liang Yu[1,2*]

Abstract

Background Diffuse large B-cell lymphoma (DLBCL) is the most common lymphoma in adult, characterized by uncontrolled cell proliferation and strong aggressiveness. Previous studies have found that cyclin-dependent kinase 1(CDK1) are related to tumor growth and metastasis. However, the role of CDK1 in DLBCL is exclusive. This study investigated the clinical implications and expression of CDK1 in DLBCL.

Methods Gene expression data for healthy subjects were sourced from the Genotype-Tissue Expression repository. Clinical details and survival statistics of patients with DLBCL were obtained from the Gene Expression Omnibus archive (GSE10846). Patients were categorized based on CDK1 expression levels, and differences in clinical outcomes between the groups were examined. Univariate and multivariate Cox regression analyses were used to ascertain whether CDK1 expression independently predicted DLBCL prognosis. The protein expression of CDK1 was gauged by immunohistochemistry. Additionally, we investigated the effect of CDK1 inhibition on DLBCL cell growth and death using the Cell Counting Kit-8 and flow cytometry.

Results In the control group, CDK1 expression was predominantly observed in the hematopoietic and reproductive systems. CDK1 levels in patients with DLBCL were notably elevated compared with those in controls. Significant differences were noted in the lactate dehydrogenase ratio and overall survival based on CDK1 expression. Statistical analyses confirmed that CDK1 was an independent predictor of DLBCL outcomes. Elevated CDK1 protein levels were observed in a significant number of DLBCL samples, in contrast to normal lymph node samples from individuals without lymphoma. The inhibitor Ro-3306 curtails DLBCL cell growth and enhances cell death in vitro.

Conclusions Elevated CDK1 levels are correlated with poor prognosis in patients with DLBCL.

Keywords Diffuse large B-cell lymphoma, CDK1, Bioinformatics, Genotype-tissue expression repository, Gene expression Omnibus archive

*Correspondence:
Chunling Wang
wcl6506@163.com
Liang Yu
yuliangha@163.com
[1]Department of Hematology, The Affiliated Huaian No.1 People's Hospital of Nanjing Medical University, Huaian 223300, Jiangsu Province, PR China
[2]Key Laboratory of Hematology, Nanjing Medical University, Nanjing 210029, Jiangsu Province, PR China
[3]Department of Pathology, The Affiliated Huaian No.1 People's Hospital of Nanjing Medical University, Huaian 223300, Jiangsu Province, PR China

Background

Diffuse large B-cell lymphoma (DLBCL) is the predominant subtype of non-Hodgkin's lymphoma (NHLs), accounting for approximately 30–58% of NHL cases [1]. The complexity of DLBCL is evident from its variable pathology, immunological presentation, clinical indicators, and patient results [2]. Through gene expression profiles, distinct molecular subtypes of DLBCL, including activated B cell-like(ABC) and germinal-center B cell-like (GCB) subtypes, have been characterized, providing insights into their varied responses to treatments and subsequent prognoses [3]. In recent years, advancements, such as those by Schmitz et al., have proposed genetics-based classifications by dividing DLBCL into unique categories [4, 5]. Other research groups, such as Chapuy et al. and Wright et al., introduced their own genetic subgroupings [6, 7].

Notably, despite these classifications, considerable variability in prognosis exists, even within the same subtype [8]. Therefore, molecular and genomic evaluations are imperative for the development of optimal therapeutic strategies.

A hallmark of malignancy is the unchecked progression of cell division. In-depth studies have identified cyclin-dependent kinases (CDKs) as instrumental in tumor development and progression [9, 10]. Specifically, CDK1, an integral member of the CDK family, oversees the G2/M phase transition during cell division [11]. Importantly, its association with the prognosis of diverse cancers, from lung to gastrointestinal stromal tumors, has been established [12–14]. In the hematological realm, elevated CDK1 levels have been identified in the bone marrow of patients with recurrent acute myeloid leukemia(AML) compared to their initial diagnoses [15] and indicating poor prognosis [16]. However, its precise role in DLBCL remains unknown.

The Genotype-Tissue Expression (GTEx) project serves as a foundational resource, enabling researchers to decipher the connection between genetic anomalies and tissue-specific gene expression [17, 18]. Similarly, the Gene Expression Omnibus (GEO) is an invaluable repository for a vast array of gene expression datasets contributed by the global scientific community [19].

Leveraging these platforms, our endeavor is to authenticate the significance of CDK1 in the context of DLBCL. This involves both bioinformatic assessments and tangible protein expression verification through immunohistochemistry (IHC). Furthermore, by probing the impact of CDK1 inhibition on DLBCL cellular dynamics, we aim to offer fresh perspectives on potential prognostic markers and therapeutic avenues for DLBCL.

Methods

Data collection and patient characteristics

We extracted the Affymetrix microarray and clinical details of patients with DLBCL and healthy individuals from the GEO database (https://www.ncbi.nlm.nih.gov/geo). Healthy control data were obtained from the GTEx database (https://gtexportal.org/home/). Dataset GSE10846 comprised 420 DLBCL patient microarrays using the GPL570 platform. We collected patient characteristics and survival data and discarded incomplete datasets. The transcriptional values in fragments per kilobase of exon per million reads mapped of GSE10846 dataset were log 2 transformed into transcript per kilobase of exon model per million mapped reads via the "scale" method provided in the "limma" R 4.2.1. If a gene was repeated in the database, we reserved a row for that gene by calculating the mean value. Clinical data were obtained from GSE10846, and 114 patients with incomplete clinical information were excluded. We used the online GEPIA platform (http://gepia.cancer-pku.cn/index.html) to differentiate CDK1 mRNA expression between patients with DLBCL and healthy subjects. Raw datasets were normalized and log2 transformed via the "limma" R package (v4.2.1). The average value was retained for repeated genes in the dataset.

Prognostic value of CDK1 in DLBCL patients

Using the X-tile bioinformatics tool, we established a 7.6 CDK1 threshold for prognosis prediction (Supplementary Materials). Subjects were categorized into $CDK1^{low}$ (≤ 7.6; $N=45$) or $CDK1^{high}$ (>7.6; $N=261$). A comparative analysis of the clinical attributes of the cohort was conducted. We employed two-sided log-rank tests and Kaplan-Meier survival analysis to discern overall survival(OS) disparities between cohorts. Statistical significance was set at $P<0.05$. Furthermore, Cox regression models (both Univariate and multivariate) were used to determine the prognostic significance of CDK1 expression and other clinical factors.

IHC analysis

We obtained lymphoma tissue samples from patients with DLBCL and healthy lymph node tissues at the Affiliated Huaian No.1 People's Hospital of Nanjing Medical University. Tissue preparation included formalin fixation, paraffin embedding, and slicing into 3-μm sections. Following specific preparation procedures, tissues were treated with an anti-CDK1 antibody (1:500 dilution; Abcam, ab133327), and the results were interpreted by two independent pathologists. The imaging magnification was set at 20×. The staining section were reviewed and scored as follows by two pathologists: Cells with < 1% staining was scored as negative staining (-,0); cells with 1–33% staining was scored as (+,1); cells with 34–67%

staining was scored as (++,2); cells with 67–100% staining was scored as (+++,3).

Cell culture and reagents

The DLBCL cell lines U2932, SU-DHL-6, and Su-DHL-4 were sourced from Shanghai Zhong Qiao Xin Zhou Biotechnology Co., Ltd. and cultivated under specified conditions (cultured in RPMI-1640 medium [Gibco, CA, USA] containing 10% fetal bovine serum at 37 °C in a 5% CO_2 incubator). The CDK1 inhibitor, Ro-3306, was obtained from MedChemExpress Co., Ltd.

CCK-8 assay

The proliferation of DLBCL cell lines was assessed using the CCK-8 assay (PROTEINBIO, Nanjing, China). The U2932, Su-DHL-6, and Su-DHL-4 cell lines were cultured in 96-well plates at a seeding density of 1×10^4 cells per well. The cells were exposed to varying concentrations of Ro-3306 or 0.1% DMSO for 24 h. Next, a volume of 10 µl of CCK-8 solution was introduced into each well, followed by an incubation period of 4 h. Absorbed light was detected at a wavelength of 450 nm was ultimately accomplished using a microplate reader capable of measuring the entire wavelength range.

Cell apoptosis analysis

The YF-488 Annexin V-FITC and PI Apoptosis Detection Kits (P6002) were procured from PROTEINBIO Biotech Co., Ltd. (Nanjing, China). DLBCL cells were cultured in 6-well plates at a density of 1×10^6 cells/well. Cells were exposed to varying concentrations of 10 µM Ro-3306 or 0.1% DMSO for 24 h. Subsequently, the cells underwent three rounds of washing with cold PBS, followed by centrifugation at 1000 rpm for 5 min. In each tube, 5 µl of YF-488-Annexin V and 5 µl of PI staining solution were added. The tubes were incubated in the dark at room temperature for 15 min. Next, 400 µL of binding buffer was introduced, and the cells were subjected to flow cytometry analysis using the BD FACSCanto II instrument located in CA, USA.

Statistical analysis

Data analysis was performed using R software (version 4.2.1) and SPSS 26.0. Group-based categorical variable differences were assessed using the Mann−−Whitney U test or chi-squared test. Kaplan-Meier analysis was performed to determine the relationship between CDK1 expression and OS. Survival outcomes between the CDK1low and CDK1high groups were compared using Kaplan−−Meier survival curves and the log-rank test. To ascertain the optimal CDK1 cutoff, X-tile software (version 3.6.1; Yale University, New Haven, CT, USA) was used to determine. Both univariate and multivariate Cox proportional hazards models were used to identify the critical prognostic indicators. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. Significant factors from the univariate survival analyses, recognized by a p-value of less than 0.05, were then considered for multivariate analysis to confirm CDK1's prognostic significance. Statistical significance was defined as a two-tailed P-value <0.05.

Results

Expression of CDK1 at the mRNA level

According to the GTEx database findings, the hematopoietic system, particularly within the bone marrow, and reproductive organs, such as the vagina and testes, show pronounced expression of CDK1. When we juxtaposed CDK1 expression levels in DLBCL patients compared to those of healthy donors using GEPIA, it was evident that CDK1 was expressed at a diminished rate in healthy samples compared to DLBCL samples (detailed in Supplementary Figure S1).

CDK1 expression and characteristics of DLBCL patients

We examined data from 306 patients with DLBCL; the breakdown of their attributes is shown in Table 1. Of these, 56.21% were men, and 45.42% were below the age of 60 years. Moreover, 134 of these patients originated from the GCB, and 116 exhibited signs of extranodal invasion. A significant number of patients were classified as either stage II or IV (30.71% and 30.39%, respectively) according to the Ann Arbor staging system. Regarding treatment modalities, there was an almost even split between patients who received CHOP-like treatment and those who received R-CHOP-like treatment (46.41% and 53.59%, respectively). Segmentation based on CDK1 expression revealed 45 patients in the $CDK1^{low}$ cohort and 261 in the $CDK1^{high}$ cohort, respectively. An interesting observation was the reduced LDH levels in the $CDK1^{low}$ cohort (with a significance value of $P=0.022$). Other patient characteristics such as sex, age, cell origin, extranodal invasion sites, Ann Arbor stage, ECOG status, and treatment modalities did not differ significantly between the two CDK1 cohorts.

Prognostic value of CDK1 in DLBCL patients

Subjects were categorized into $CDK1^{low}$ (≤7.6; $N=45$) or $CDK1^{high}$ (>7.6; $N=261$). The $CDK1^{high}$ group had poorer OS than did its $CDK1^{low}$ counterpart (Fig. 1), indicating its potential as a DLBCL prognosis determinant.

CDK1 expression is an independent prognostic factor of DLBCL

Univariate and multivariate analyses were conducted to explore prognostic factors influencing OS in patients with DLBCL. Our findings pinpointed that the presence of CDK1 was a crucial predictor of OS in DLBCL

Table 1 Characteristics of 306 subjects with diffuse large B-cell lymphoma (DLBCL)

Characteristics	Total ($n=306$)	CDK1-high ($n=45$)	CDK1-low ($n=261$)	*P*
Gender(%)				0.674
male	172(56.21)	24(53.33)	148(56.70)	
female	134(43.79)	21(46.67)	113(43.30)	
Age(%)				0.429
<60	139(45.42)	18(40)	121(46.36)	
≥ 60	167(54.58)	27(60)	140(53.64)	
Cell of origin(%)				0.104
GCB	134(43.79)	26(57.78)	108(41.38)	
ABC	125(40.85)	15(33.33)	110(42.15)	
UC	47(15.36)	4(8.89)	43(16.48)	
Count of extranodal invasion(%)				0.100
0	190(62.09)	23(51.11)	167(63.98)	
≥ 1	116(30.39)	22(48.89)	94(36.02)	
LDH ratio(%)				**0.022**
≤ 1	157(51.31)	16(35.56)	141(54.02)	
>1	149(48.69)	29(64.44)	120(45.98)	
Ann-Arbor stage(%)				0.307
I	50(16.34)	7(15.57)	43(16.48)	
II	94(30.71)	14(31.11)	80(30.65)	
III	69(22.55)	6(13.33)	63(24.14)	
IV	93(30.39)	18(40)	75(28.74)	
ECOG(%)				0.386
0	69(22.55)	7(15.56)	62(23.75)	
1	162(52.94)	24(53.33)	138(52.87)	
2	48(15.69)	7(15.56)	41(15.71)	
3	22(7.19)	5(11.11)	17(6.51)	
4	5(1.63)	2(4.44)	3(1.15)	
Treatment(%)				0.183
CHOP-like	142(46.41)	25(55.56)	117(44.83)	
R-CHOP-like	164(53.59)	20(44.44)	144(55.17)	

patients ($P=0.0008$; HR, 0.4843; 95% CI 0.3173–0.7391), as depicted in Fig. 2a. Furthermore, when applying multivariable Cox regression analyses, CDK1 expression emerged as an independent predictor of OS in DLBCL patients ($P=0.0149$, HR 0.5798, 95% CI 0.3738–0.8992) (Fig. 2b).

CDK1 protein expression

The role and significance of CDK1 in DLBCL were corroborated by immunohistochemistry. Our findings revealed an elevated level of CDK1 protein in lymphoma samples compared to that in regular lymph node samples (Fig. 3a and b). This underscores the fact that lymphoma tissues exhibit more pronounced expression of the CDK1 protein compared to their normal counterparts. Moreover, we detected the expression of CDK1 in 30 patients with DLBCL by immunohistochemical analysis and divided the patients into 1+, 2+, and 3+groups according to their CDK1 immunohistochemical scores of DLBCL patients. The results of the analysis of the clinical characteristics among the three groups are reported in Supplementary Table 1. The expression level of CDK1 was closely related to the Ki-67 positive rate of patients, and DLBCL patients with higher CDK1 expression had a higher Ki-67 positive rate ($P=0.024$).

Ro-3306 inhibited proliferation and promoted apoptosis of DLBCL cells in vitro

The effect of Ro-3306 on DLBCL cell proliferation was assessed using the CCK-8 assay. The proliferation of DLBCL cells was inhibited in a concentration-dependent manner by Ro-3306, as shown in Fig. 4a, b, **and c**. Subsequently, DLBCL cells were subjected to a 24-hour treatment with Ro-3306. Flow cytometry analysis revealed that the administration of Ro-3306 induced apoptosis in DLBCL cells (Fig. 5a-f). This emphasizes that CDK1 inhibition can potentially curtail DLBCL cell proliferation and enhance apoptosis, thus shedding light on potential therapeutic strategies.

Discussion

DLBCL is undeniably complex. While R-CHOP remains the therapeutic cornerstone for DLBCL, the sad reality is that 30–40% of those treated will find little solace in it, often succumbing to treatment resistance and consequent grim clinical outcomes [20]. Thus, refining the risk classifications for DLBCL is imperative to tailor treatments according to individual needs. In this domain, tumor biomarkers are potential indicators. In this study, we highlighted the prognostic value of CDK1 in DLBCL by leveraging both bioinformatics assessments and IHC analysis validations to provide comprehensive insights.

We initially juxtaposed CDK1 expression between normal and DLBCL samples. Our findings unequivocally indicated subdued CDK1 expression in healthy donors compared with that in DLBCL patients. When analyzing survival patterns across the $CDK1^{low}$ and $CDK1^{high}$ groups, a conspicuous trend emerged; heightened CDK1 expression was strongly correlated with adverse outcomes in patients with DLBCL. Risk plots further corroborated this finding, with patient risk scores revealing distinct survival status bifurcations based on CDK1 expression. High CDK1 levels are associated with diminished survival odds and increased mortality rates. Both univariate and multivariate analyses reinforced CDK1's role as a prognostic factor for DLBCL. Furthermore, we performed immunohistochemistry to investigate the CDK1 expression patterns in DLBCL. These results demonstrated a correlation between LDH and CDK1 expression. LDH, a key enzyme in glycolysis, was included in the risk assessment of the International Prognostic Index in 1993 and is one of the most significant indicators for

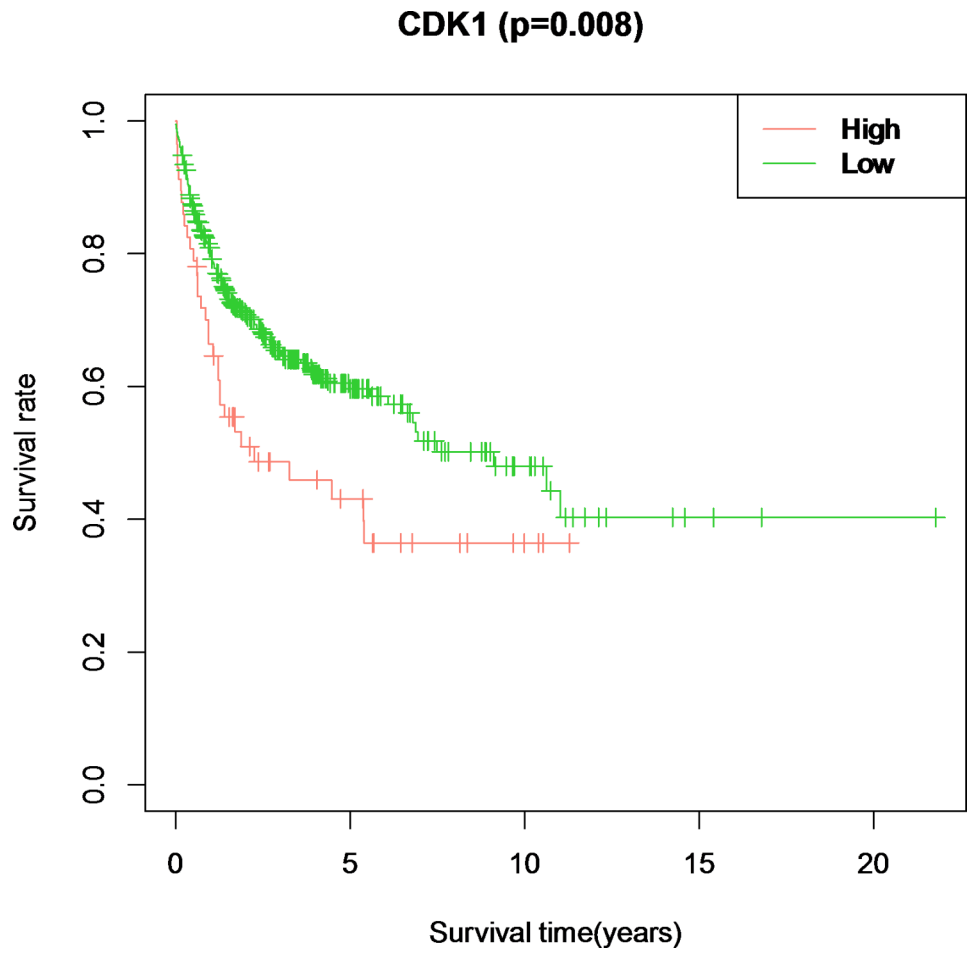

Fig. 1 Survival analysis graph showing OS across different risk categories for DLBCL patients

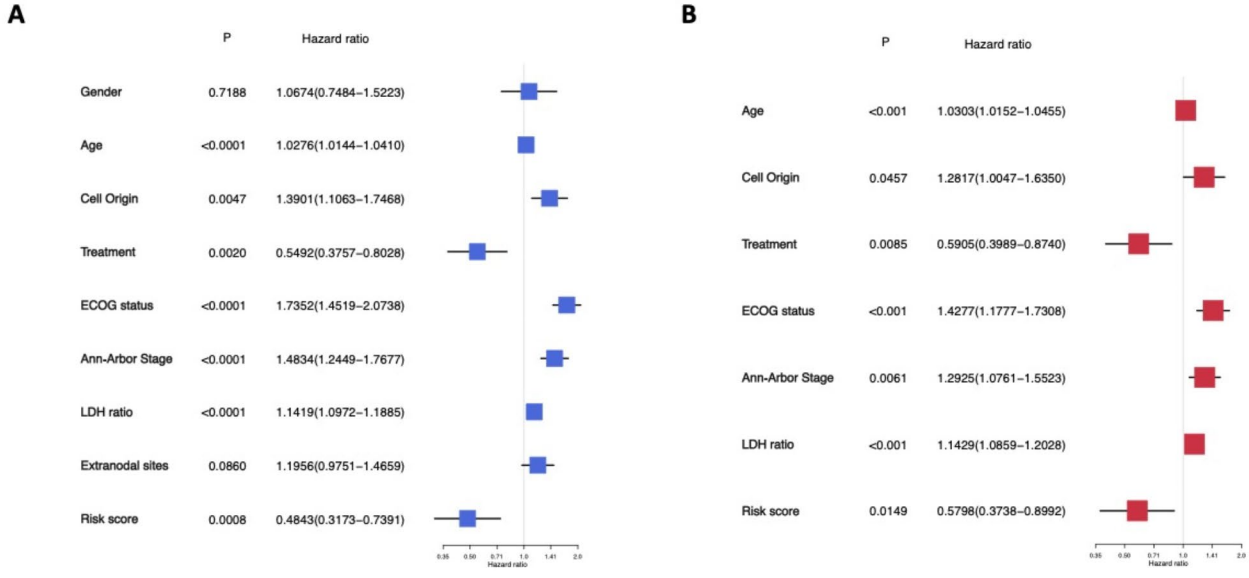

Fig. 2 Illustration of Cox regression outcomes. (**A**, **B**) Singular and collective Cox regression examinations of participants from the GSE10846 dataset

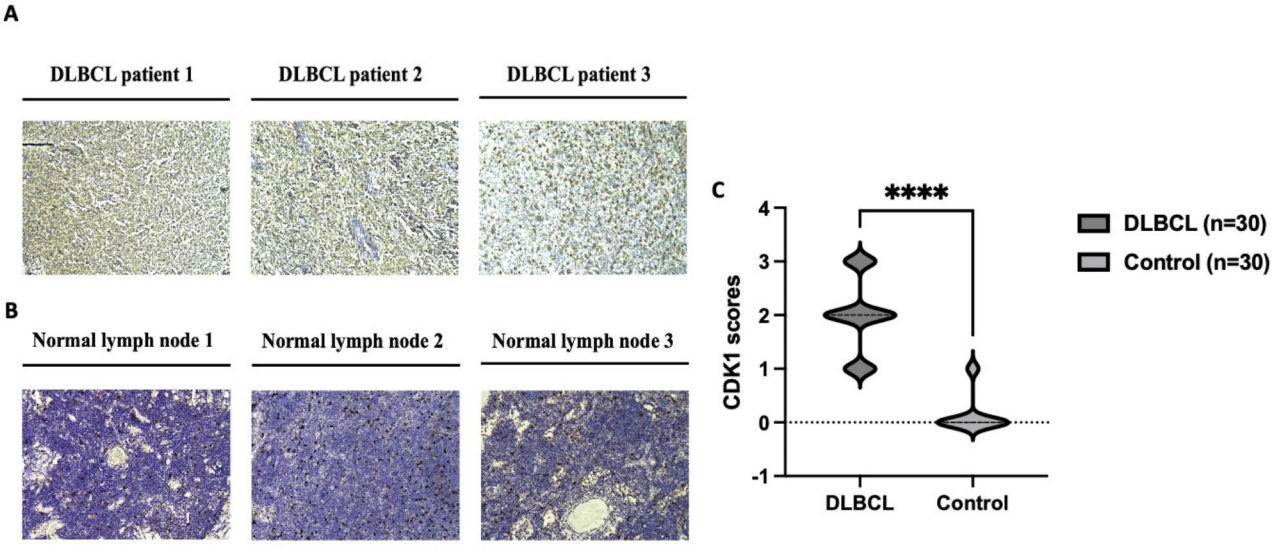

Fig. 3 Visual representation of CDK1 protein levels in lymphoma samples (**A**) and in regular lymph node samples (**B**) as determined by immunohistochemistry

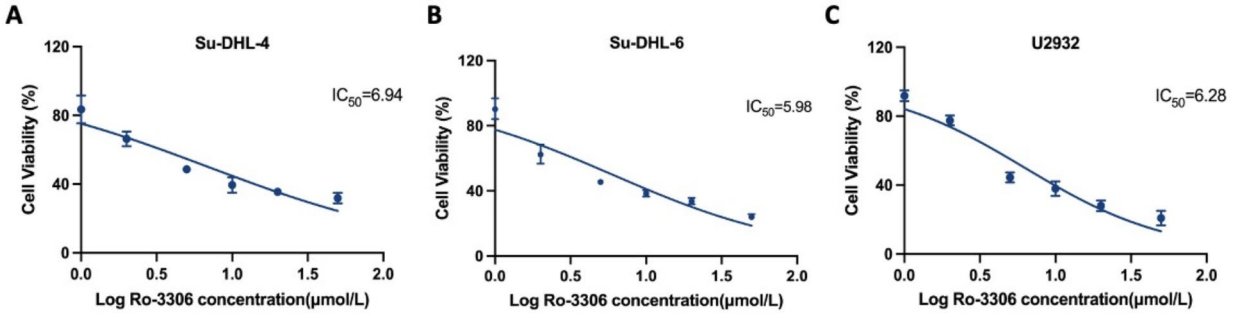

Fig. 4 Illustration of Ro-3306's influence on DLBCL cell growth. (**A**) U2932 cells, (**B**) Su-DHL-6 cells, and (**C**) Su-DHL-4 cells were arranged in 96-well formats and subjected to various concentrations of Ro-3306 or a 0.1% DMSO solution for 24 h. Cell viability was gauged using CCK8 solution, with measurements taken at 450 nm using a full-spectrum plate reader

predicting the prognosis of non-Hodgkin's patients [21]. The increase in glycolysis leads to a continuous increase in LDH synthesis and stimulation of surrounding tissues, and a large amount of reactive LDH is released and eventually detected in the peripheral blood [22]. Moreover, DLBCL patients exhibiting high expression of CDK1 also presented elevated levels of LDH, indicating increased disease severity in these individuals. This observation was further supported by our investigation of the effects of anti-CDK1 treatments on the behavior of DLBCL cells, specifically regarding their proliferative and apoptotic dynamics.

Previous studies have highlighted the deleterious consequences of CDK1 dysfunction, linking it to aggressive tumor expansion, chromosomal anomalies, and cancer cell proliferation spurts [23]. Specifically, its overexpression has also been implicated in various cancers, resulting in poor prognosis in colorectal, cervical, and thyroid cancers [24–26]. A study by Radomska et al. underscores CDK1's potential as a therapeutic target, especially in FLT3ITD mutant leukemia contexts resistant to conventional FLT3 inhibitors [27]. Similarly, targeting CDK1 in OCI-AML3 cells with DNMT3A mutations resulted in noticeable proliferation restraint and increased apoptosis rates [28]. Despite these insightful findings, the role of CDK1 in DLBCL remains unexplored. In fact, as early as more than 20 years ago, the prognostic significance of CDK1 in lymphoma patients was discovered, and studies pointed out that CDK1 showed a significant prognostic value in complete remission and overall survival of non-Hodgkin patients [29]. Subsequent studies identified phosphorylation of p70S6K and overexpression of Cdc2/CDK1 in most patients with DLBCL. Combining small molecules that target p70S6K phosphorylation and Cdc2/CDK1 synergistically induces apoptosis and arrests the cell cycle at G1 and G2 phases, indicating their potential

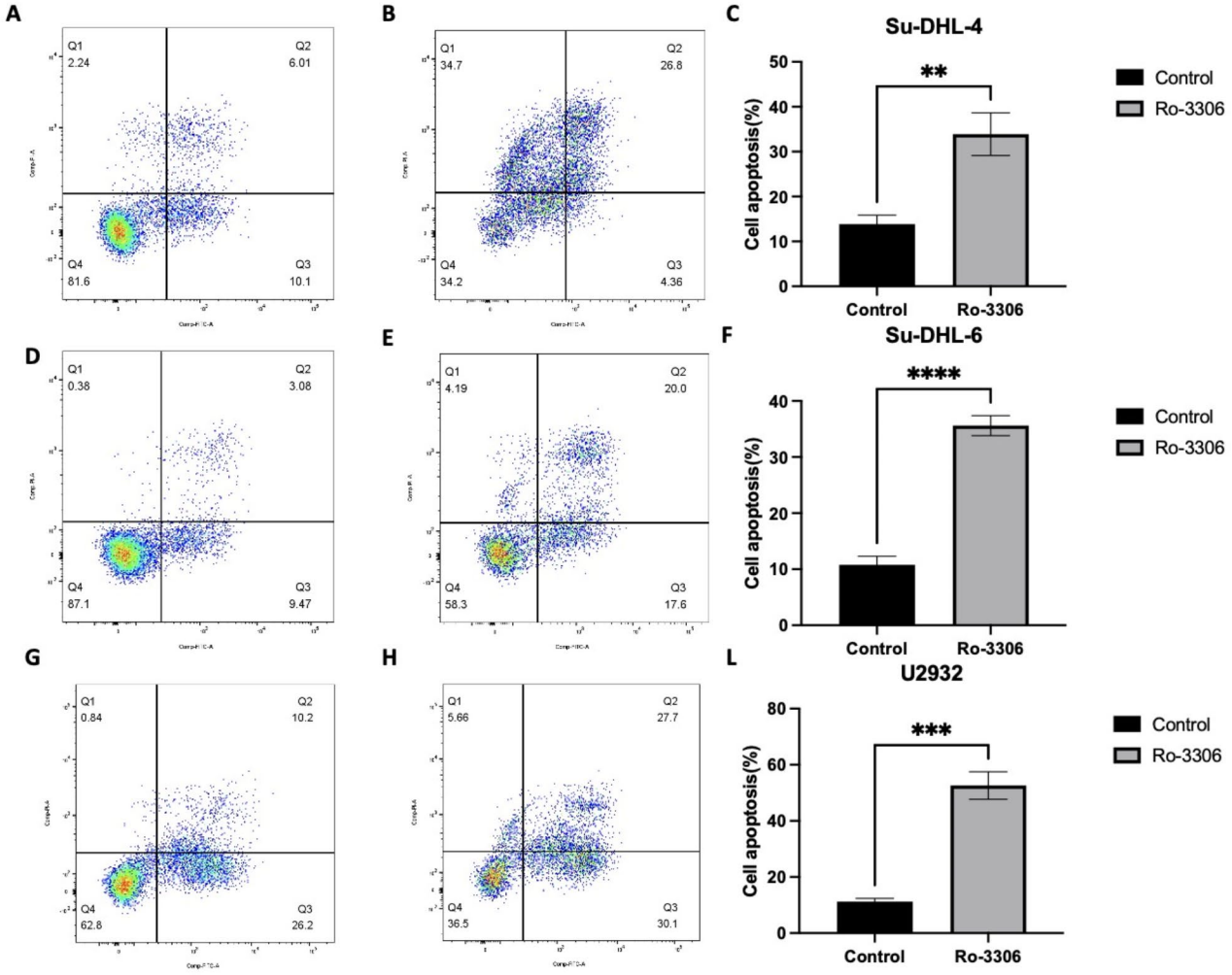

Fig. 5 Depiction of Ro-3306's role in enhancing DLBCL cell apoptosis in vitro. For U2932 cells: (**A**-**C**) treatment with 0.1% DMSO and treatment with 10 μM Ro-3306. For Su-DHL-6 cells: (**D**-**F**) treatment with 0.1% DMSO and 10 μM Ro-3306. For Su-DHL-4 cells: (**G**-**L**) with 0.1% DMSO and with 10 μM Ro-3306. After treatment, the cells were stained using Annexin V-FITC and PI, followed by flow cytometric evaluation. The apoptosis assay was repeated in triplicate

as molecular targets for DLBCL therapy [30]. Burkitt's lymphoma, a common lymphatic system cancer in adults with poor prognosis, shows suppressed cell proliferation following CDK1 knockdown in Burkitt lymphoma cells [31]. In Raji cells, CDK1 knockdown restores the drug sensitivity of Raji/dinaciclib-resistant cell lines to dinaciclib, highlighting the therapeutic potential of targeting CDK1 in lymphoma treatment [32]. In addition, the simultaneous targeting of CDK1 and survivin showed favorable therapeutic effects in a mouse model of nasal NK/T-cell lymphoma [33]. Our study attempted to bridge this knowledge gap by suggesting the potential of CDK1-focused therapeutic strategies for DLBCL treatment.

It is important to acknowledge the limitations of the present study. Therefore, there is an urgent need for an in-depth exploration of the underlying mechanisms. Furthermore, given that our insights are anchored in public databases, real-world validation through clinical trials in patients with DLBCL is indispensable.

Conclusions

CDK1 was highly expressed in DLBCL and was associated with poor prognosis. CDK1 inhibitors showed to inhibit proliferation and promote apoptosis of DLBCL cells. CDK1 was a potential target for DLBCL therapy.

Abbreviations

AML	Acute Myeloid Leukemia
CDK	Cyclin-Dependent Kinase
CDK1	Cyclin-Dependent Kinase 1
CHOP	Cyclophosphamide, Hydroxydaunorubicin, Oncovin (Vincristine), and Prednisone
CIs	Confidence Intervals
DLBCL	Diffuse Large B-Cell Lymphoma
DMSO	Dimethyl Sulfoxide
ECOG	Eastern Cooperative Oncology Group
FLT3ITD	Fms-Like Tyrosine Kinase 3 Internal Tandem Duplication
GEO	Gene Expression Omnibus

GEPIA	Gene Expression Profiling Interactive Analysis
GCB	Germinal-Center B Cell-Like
GTEx	Genotype-Tissue Expression
HRs	Hazard Ratios
IHC	Immunohistochemistry
LDH	Lactate Dehydrogenase
NHL	Non-Hodgkin's Lymphoma
NK	Natural Killer
OS	Overall Survival
PI	Propidium Iodide
R-CHOP	Rituximab, Cyclophosphamide, Hydroxydaunorubicin, Oncovin (Vincristine), and Prednisone
RPMI-1640	Roswell Park Memorial Institute-1640

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-024-13388-y.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Acknowledgements
The authors thank the Affiliated Huaian No.1 People's Hospital of Nanjing Medical University for financially supporting this work.

Author contributions
Qiuni Chen and Chuanyang Lu wrote the main manuscript text. Yuye Shi and Lei Xu performed the data analyses. Xue Gong and Yujie Xue are responsible for the immunohistochemistry. Chunling Wang and Liang Yu helped funding acquisition.

Funding
This research was supported by grants from the Affiliated Huaian No.1 People's Hospital of Nanjing Medical University [grant number QC2022018] and the Huaian city Science and Technology Bureau project [grant number HAB2024002].

Data availability
The affymetrix microarray and clinical details of DLBCL patients and healthy individuals were extracted from the GEO database under accession number GSE10846 (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi? acc=GSE10846).

Declarations

Ethics approval and consent to participate
All experiments on humans and/or the use of human tissue samples were performed in accordance with relevant guidelines and regulations. Informed consent from all of the participants in the study was obtained. The research conducted on human participants underwent a thorough evaluation and received approval from the Institutional Review Board (IRB) of the Affiliated Huaian No.1 People's Hospital of Nanjing Medical University(KY-2023-181-01).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 12 June 2024 / Accepted: 23 December 2024
Published online: 07 January 2025

References

1. Li Z, et al. Gene set-based identification of two immune subtypes of diffuse large B cell lymphoma for guiding immune checkpoint blocking therapy. Front Genet. 2022;13:1000460.
2. Takahara T et al. The Immunology of DLBCL. Cancers (Basel), 2023. 15(3).
3. Lossos IS. Diffuse large B cell lymphoma: from gene expression profiling to prediction of outcome. Biol Blood Marrow Transpl. 2008;14(1 Suppl 1):108–11.
4. Alduaij W et al. Molecular determinants of clinical outcomes in a real-world diffuse large B-cell Lymphoma Population. Blood, 2022.
5. Schmitz R, et al. Genetics and Pathogenesis of diffuse large B-Cell lymphoma. N Engl J Med. 2018;378(15):1396–407.
6. Chapuy B, et al. Molecular subtypes of diffuse large B cell lymphoma are associated with distinct pathogenic mechanisms and outcomes. Nat Med. 2018;24(5):679–90.
7. Wright GW, et al. A probabilistic classification Tool for genetic subtypes of diffuse large B cell lymphoma with therapeutic implications. Cancer Cell. 2020;37(4):551–e56814.
8. Modi D, Potugari B, Uberti J. *Immunotherapy for Diffuse Large B-Cell Lymphoma: Current Landscape and Future Directions*. Cancers (Basel), 2021. 13(22).
9. Asghar U, et al. The history and future of targeting cyclin-dependent kinases in cancer therapy. Nat Rev Drug Discov. 2015;14(2):130–46.
10. Chou J, et al. Transcription-Associated cyclin-dependent kinases as targets and biomarkers for Cancer Therapy. Cancer Discov. 2020;10(3):351–70.
11. Sunada S, et al. CDK1 inhibitor controls G2/M phase transition and reverses DNA damage sensitivity. Biochem Biophys Res Commun. 2021;550:56–61.
12. Huang Z, Shen G, Gao J. CDK1 promotes the stemness of lung cancer cells through interacting with Sox2. Clin Transl Oncol. 2021;23(9):1743–51.
13. Zou Y, et al. CDK1, CCNB1, and CCNB2 are prognostic biomarkers and correlated with Immune Infiltration in Hepatocellular Carcinoma. Med Sci Monit. 2020;26:e925289.
14. Lu X, et al. Integrated screens identify CDK1 as a therapeutic target in Advanced gastrointestinal stromal tumors. Cancer Res. 2021;81(9):2481–94.
15. Hedblom A, et al. CDK1 interacts with RARγ and plays an important role in treatment response of acute myeloid leukemia. Cell Cycle. 2013;12(8):1251–66.
16. Qian Z, et al. Expression profiling of CD34 + hematopoietic stem/ progenitor cells reveals distinct subtypes of therapy-related acute myeloid leukemia. Proc Natl Acad Sci U S A. 2002;99(23):14925–30.
17. The Genotype-Tissue Expression (GTEx) project. Nat Genet. 2013;45(6):580–5.
18. Tukiainen T, et al. Landscape of X chromosome inactivation across human tissues. Nature. 2017;550(7675):244–8.
19. Barrett T, et al. NCBI GEO: archive for functional genomics data sets–update. Nucleic Acids Res. 2013;41(Database issue):D991–5.
20. He MY, Kridel R. Treatment resistance in diffuse large B-cell lymphoma. Leukemia. 2021;35(8):2151–65.
21. Zhou Z, et al. An enhanced International Prognostic Index (NCCN-IPI) for patients with diffuse large B-cell lymphoma treated in the Rituximab era. Blood. 2014;123(6):837–42.
22. Qi J, et al. Elevated lactate dehydrogenase levels display a poor prognostic factor for Non-hodgkin's lymphoma in Intensive Care Unit: an analysis of the MIMIC-III Database Combined with External Validation. Front Oncol. 2021;11:753712.
23. Yasukawa M, et al. CDK1 dependent phosphorylation of hTERT contributes to cancer progression. Nat Commun. 2020;11(1):1557.
24. Li J, et al. CDK1 and CDC20 overexpression in patients with colorectal cancer are associated with poor prognosis: evidence from integrated bioinformatics analysis. World J Surg Oncol. 2020;18(1):50.
25. Tang J, et al. MiR-495-3p and mir-143-3p co-target CDK1 to inhibit the development of cervical cancer. Clin Transl Oncol. 2021;23(11):2323–34.
26. Zheng HP, et al. Integrated assessment of CDK1 upregulation in thyroid cancer. Am J Transl Res. 2019;11(12):7233–54.
27. Radomska HS, et al. Targeting CDK1 promotes FLT3-activated acute myeloid leukemia differentiation through C/EBPα. J Clin Invest. 2012;122(8):2955–66.
28. Yang Y et al. DNMT3A Mutation-Induced CDK1 overexpression promotes leukemogenesis by modulating the Interaction between EZH2 and DNMT3A. Biomolecules, 2021. 11(6).
29. Wolowiec D, et al. CDK1 and cyclin A expression is linked to cell proliferation and associated with prognosis in non-hodgkin's lymphomas. Leuk Lymphoma. 1999;35(1–2):147–57.
30. Zhao XF, Gartenhaus RB. Phospho-p70S6K and cdc2/cdk1 as therapeutic targets for diffuse large B-cell lymphoma. Expert Opin Ther Targets. 2009;13(9):1085–93.

31. Zou H, et al. miR-129 targets CDK1 and iASPP to modulate Burkitt lymphoma cell proliferation in a TAp63-dependent manner. J Cell Biochem. 2018;119(11):9217–28.
32. Zhao H, et al. Study of the mechanism by which dinaciclib induces apoptosis and cell cycle arrest of lymphoma Raji cells through a CDK1-involved pathway. Cancer Med. 2019;8(9):4348–58.
33. Nagato T, et al. Cyclin-dependent kinase 1 and survivin as potential therapeutic targets against nasal natural killer/T-cell lymphoma. Lab Invest. 2019;99(5):612–24.

Publisher's note