Abstract. Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma worldwide. Several studies have indicated that Homo sapiens (hsa)-microRNA (miR)-429 exerts a tumor-suppressive effect on a variety of malignant tumors. To the best of our knowledge, the molecular function and mechanism of action of hsa-miR-429 in DLBCL have not been evaluated to date. The present study demonstrated that the expression of hsa-miR-429 in DLBCL cells was significantly reduced. hsa-miR-429 inhibited the proliferation of the DLBCL cell lines, SUDHL-4 and DB, and promoted apoptosis. A dual luciferase reporter assay was used to demonstrate that chromobox 8 (CBX8) was the target gene of hsa-miR-429. Overexpression of CBX8 promoted the proliferation of SUDHL-4 and DB cells and inhibited apoptosis, thereby playing a cancer-promoting role. Transfection of hsa-miR-429 mimic into DB cells overexpressing CBX8 antagonized the effect of CBX8 on the proliferation of DB cells. Moreover, the apoptotic rate was increased in DB cells overexpressing CBX8 and transfected with hsa-miR-429 mimic, while the proportion of cells in the G2/M phase was significantly reduced. These results demonstrated the antagonistic effect of hsa-miR-429 on the oncogenic function of CBX8. Therefore, in DLBCL, the tumor suppressor effect of hsa-miR-429 may be achieved by targeted downregulation of CBX8, suggesting that hsa-miR-429 may be used as a diagnostic marker and a potential nucleic acid drug for DLBCL. CBX8 may also represent an effective therapeutic target for DLBCL.

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma globally, accounting for 30-40% of all cases in different geographic regions. DLBCL is an aggressive disease with heterogeneous genes, phenotypes and clinical characteristics (1). The patients most often present with a rapidly growing tumor mass in a single or multiple lymph nodes, and even outside the lymph nodes. Combining rituximab and cyclophosphamide, Adriamycin, vincristine and prednisone (CHOP regimen) can significantly improve the prognosis of patients with DLBCL, and the 3-year recurrence-free survival period can reach 65-80%. However, 30-40% of patients with DLBCL will relapse or develop refractory disease, which is still the main cause of patient-related deaths. Therefore, molecular discovery may be the best way forward for designing new therapies in precision medicine. In addition to traditional diagnostic functions, it is also necessary to explore prognostic markers and potential therapeutic targets (2).

MicroRNA (miRNA/miR) is a type of endogenous non-coding RNA, 18-25 nucleotides in length, which is ubiquitously expressed both intra- and extracellularly. Its biological function can lead to mRNA degradation or translation inhibition, thereby playing an important regulatory role in animal and plant cells (3). This post-transcriptional regulation can directly affect the function of target genes and participate in the physiological and pathological processes of multiple systems of the body, including the digestive system. At present, a large number of clinical and basic studies have revealed that miRNA can act as an oncogene or tumor suppressor and has key functions in tumorigenesis and malignant progression (4,5).

Several studies have suggested that Homo sapiens (hsa)-miR-429 acts as a tumor suppressor in a variety of malignant tumors. hsa-miR-429 can inhibit the Raf/MEK/ERK pathway by targeting CRK like proto-oncogene adaptor protein to reduce the migration of liver cancer cells and reverse epithelial-mesenchymal transition (6,7). Moreover, it can inhibit hepatocyte proliferation and liver regeneration by targeting the JUN/MYC/BCL2/cyclin D1 axis (8). hsa-miR-429 exerts a tumor-suppressive effect by targeting fascin actin-bundling protein 1 in gastric cancer cells (9).
In addition, the expression of hsa-miR-429 in patients with bladder cancer surviving for 5 years was revealed to be significantly higher compared with that in deceased patients, and it was a potential prognostic indicator of bladder cancer (10). hsa-miR-429 can also promote the proliferation of bladder cancer cells by inhibiting cyclin-dependent kinase inhibitor 2B (11). hsa-miR-429 can inhibit the progression and metastasis of osteosarcoma by targeting zinc finger E-box binding homeobox 1 (12). hsa-miR-429 also regulates the proliferation and apoptosis of Wilms' tumor cells by targeting c-Myc, reduces the perineural invasion of pancreatic cancer by inhibiting neurotrophic factor-3, and inhibits the migration and invasion of esophageal squamous cell carcinoma cells by targeting Slug (13-15).

Previous studies have suggested that long non-coding RNA (lncRNA) small nuclear RNA host gene 6 (SNHG6) is a regulatory factor of hsa-miR-429. When the expression levels of SNHG6 increase, the concentration of free hsa-miR-429 in the cell is significantly reduced, which promotes the progression of Wilms' tumor (16).

The role of hsa-miR-429 in breast cancer is controversial. A previous study has revealed that hsa-miR-429 inhibits the proliferation and invasion of breast cancer cells by inhibiting the Wnt/β-catenin signaling pathway (17). Moreover, in erb-b2 receptor tyrosine kinase 2 positive (HER2) breast cancer, hsa-miR-429 could regulate the hypoxia-inducible factor 1 subunit α (HIF1α) pathway by directly targeting von Hippel-Lindau tumor suppressor mRNA, an important molecule that degrades HIF1α. Overexpression of hsa-miR-429 in HER2+ breast cancer was revealed to lead to an increase in breast cancer cell proliferation and migration, whereas silencing of hsa-miR-429 could delay tumor growth. This suggests that hsa-miR-429 may play a dual role in different tumors (18). However, to the best of our knowledge, the molecular function and mechanism of action of hsa-miR-429 in DLBCL have never been evaluated.

**Materials and methods**

**Cell culture.** The DLBCL cell lines, SUDHL-4 and DB, were provided by The Chinese Academy of Sciences Stem Cell Bank. Both are suspension cells, cultured with 90% RPMI-1640 + 10% FBS (both from HyClone; Cytiva) at 37°C and 5% CO2.

**Clinical sample collection.** A total of 10 newly diagnosed patients with DLBCL admitted to the Department of Hematology, Jingzhou Central Hospital from January 2019 to June 2019 were included in the present study. There were 7 males and 3 females with a median age of 65 years (50-76 years). Inclusion criteria were as follows: lymph node enlargement was the first manifestation of all patients. The lymph nodes with suspected lesions were completely resected and further analyzed by immunohistochemistry after paraffin embedding. The immunohistochemical analysis included CD20, CD3, CD5, CD10, CD45, CD30, Bcl-2, Bcl-6, Ki-67, Mum-1, and MYC. The pathological diagnosis was in line with the World Health Organization (WHO) diagnostic criteria for hematopoietic and lymphoid tissue tumors in 2008. Exclusion criteria were as follows: previous hematopoietic and lymphoid tumor. Normal tissue was obtained from patients hospitalized at the Department of Hematology at the same period, with lymphadenopathy as the main manifestation, and lymphadenitis confirmed by immunohistochemical analysis after complete excision of disaffected lymph nodes. The samples used in this study were collected from the discarded samples after lymph node biopsy of patients without affecting the disease diagnosis and treatment of patients, with the consent of patients and their family members. Ethical approval was obtained from The Ethics Committee of Jingzhou Central Hospital (Jingzhou, China). Written informed consent was obtained from the patients for their anonymized information to be published in this article. All patients consented to participate in the study by having their samples used in clinical research.

**Quantitative PCR (qPCR).** Total RNA was extracted using TRIzol® reagent (Thermo Fisher Scientific, Inc.) from DLBCL tissue. Bulge-Loop hsa-miR-429 Primer Set (cat. no. MQPS0001297-1-100) was used to quantify hsa-miR-429 by qPCR with SYBR-Green (FP411-02; TIANGEN). The thermocycling conditions were as follows: Initial denaturation, 95°C, 15 min; followed by a 45-cycle, 94°C, 20 sec, 60°C, 34 sec. The primer sequences of U6 (internal reference) were as follows: forward, 5'-CTCGCTTCGGCAGCACA-3' and reverse, 5'-AACGCTTCAGAATTTGCG-3'. The aforementioned kit was purchased from Guangzhou RiboBio Co., Ltd. It was used according to the manufacturer's instructions. The relative expression levels were calculated using the 2^-ΔΔCt method (19).

**Transfection.** hsa-miR-429 mimic (cat. no. miR10001536-1-5; sequence: 5'-UAAUACUGUCUGUAUUACCCU-3'), mimic negative control (cat. no. miR10000001-1-5; sequence: 5'-UUUGAUCAUCACAAAGUACUG-3'), hsa-miR-429 inhibitor (cat. no. miR200001536-1-5; sequence: 5'-ACGGUUUAAACGACAGAUAUUA-3') and inhibitor negative control (cat. no. miR20000001-1-5; sequence: 5'-CAGUACUUUGUGUAGUACAAA-3') were purchased from Guangzhou RiboBio Co., Ltd. miRNA mimic and inhibitor were transfected into cell culture plates with Ribofect™ CM Reagent (cat. no. C10511-05; Guangzhou RiboBio Co., Ltd.), and cultured at 37°C for 48 h. The transfection concentrations were 50 nM (miRNA mimic) and 100 nM (miRNA inhibitor). A total of 20 μM miRNA mimic or inhibitor was diluted with 1X Ribofect™ CM Buffer as recommended and gently mixed. The Ribofect™ CM Reagent was added, mixed gently, and incubated at room temperature for 10-15 min. The Ribofect™ CM mixture was added to the complete medium and mixed gently. Subsequently, the culture plate was placed in a CO2 incubator at 37°C for 48 h, and the related cellular and molecular experiments were carried out.

**Cell proliferation experiment.** Cell proliferation was evaluated using a Cell Counting Kit-8 (CCK-8; cat. no. C0037; Beyotime Institute of Biotechnology) assay. A total of 1x10³ cells in 100 μl medium were plated into a 96-well plate. After 48 h incubation at 37°C, 10 μl of CCK8 was added to each well and incubated at 37°C in dark for 1 h. The absorbance was measured at 450 nm.

**Cell colony formation assay.** The cells were seeded into a 6-well plate at a concentration of 1x10³ cells in 2 ml complete
medium and incubated at 37°C, 5% CO₂ for 14 days. The medium was changed every 3 days. After the formation of visible colonies, the cells were fixed with 4% formaldehyde for 20 min at room temperature and stained with 0.1% crystal violet for 10-15 min at room temperature. After washing away the background color, photomicrographs were obtained and the number of colonies was counted by eye.

Apoptosis analysis. The cells were stained with Annexin V-FITC Apoptosis Detection kit (cat. no. C1062L; Beyotime Institute of Biotechnology) at room temperature in dark for 10 min. The kit was used according to the manufacturer's instructions. The apoptotic rate was detected by flow cytometry (BD LSRFortessa and FlowJo7.6.5; BD Biosciences).

Cell cycle analysis. The cells at 70% confluence were collected by centrifugation at 1,000 x g for 5 min at 22°C and fixed with ice-cold 70% ethanol at 4°C for 30 min or longer. The cells were stained with Cell Cycle and Apoptosis Analysis kit (cat. no. C1052; Beyotime Institute of Biotechnology) at 37°C in dark for 30 min. The kit was used according to the manufacturer's instructions. The cell cycle distribution was detected by flow cytometry (BD LSRFortessa and FlowJo7.6.5; BD Biosciences).

Target gene prediction. TargetScan Human 7.2 (version 7.2; targetscan.org/vert_72/) was used to predict the target gene of hsa-miR-429.

Dual luciferase reporter gene assay. hsa-miR-429 mimic (cat. no. miR10001536-1-5; Sequence: 5'-UUAUACUGUCUGGU AAAACCAGU-3'), mimic negative control (cat. no. miRNA0000001-5;sequence:5'-UUUGUAACUACAAAAGUAUGUG-3'), hsa-miR-429 inhibitor (cat. no. miR20001536-1-5;sequence: 5'-ACGGUUUACCAGACAGUAUUA-3') and inhibitor negative control (cat. no. miR2N0000001-1-5;sequence: 5'-ACUGUUUACCAGACAGUAUUA-3') were purchased from Guangzhou RiboBio Co., Ltd. A dual luciferase reporter assay was used to verify the binding of hsa-miR-429 to the 3' untranslated region (UTR) of CBX8. The 3'-UTR wild-type (WT) sequence and 3'-UTR mutant (MUT) sequence of CBX8 were cloned into the pGL6-miR plasmid (cat. no. D2106; Beyotime Institute of Biotechnology). The recombinant plasmid (2 μg) and hsa-miR-429 mimic (50 nM) or mimic negative control (50 nM) were co-transfected into 293T cells at 40% confluence (supplied by the Chinese Academy of Sciences Stem Cell Bank) seeded in a 6-well plate. The transfection reagent was Lipofectamine 3000 (cat. no. L3000008; Thermo Fisher Scientific). After 48 h at 37 °C, the relative luciferase activity was detected with Dual-Luciferase Reporter Assay Systems (Promega Corporation). The results were normalized with Renilla luciferase activity.

Overexpression and knockdown of CBX8. The coding sequence of the human CBX8 (gene ID, 57332) was cloned into the pcDNA3.1 (Invitrogen; Thermo Fisher Scientific, Inc.) vector to generate an overexpression vector. Small interfering RNA (siRNA) was used to knock down the expression of the CBX8 gene. CBX8 siRNA was purchased from Guangzhou RiboBio Co., Ltd. In order to avoid off-target effects, two different pairs of CBX8 siRNA were selected for the experiment (cat. no. siG000057332A-1-5 and siG000057332B-1-5; siG000057332A-1-5 target sequence: 5'-GAGGAAAACATCCTGGATGC-3'; and siG000057332B-1-5 target sequence: 5'-TGCTCGCACCTTTGGAGGAA-3'). siN0000002-1-5 (Guangzhou RiboBio Co., Ltd.; target sequence: 5'-TTTCTCCGAAACGTTCGAACGT-3') was used as a negative control. Cells were transfected with the CBX8 expression vector (6 μg DNA per 10-cm dish) and siRNA (100 nM) to overexpress or knock down the expression of CBX8 by PolyFect Transfection Reagent (cat. no. 301108; QIAGEN) at room temperature, respectively. The transfection lasted 6 h. The medium containing the transfection reagent was removed and replaced with fresh medium. After culturing in a CO₂ incubator at 37°C for 48 h, the subsequent experiments were carried out.

Western blot analysis. The anti-CBX8 (cat. no. 61237), anti-GAPDH (HRP-conjugated; cat. no. HRP-60004) and goat anti-rabbit IgG (HRP-conjugated; cat. no. SA00001-2) antibodies were purchased from ProteinTech Group, Inc. The total protein was extracted by RIPA lysis buffer (P0013B, Beyotime Biotechnology). The protein was quantified by BCA method. A total of 10 μg of protein was loaded per lane of 10% SDS-PAGE gel. PVDF membrane was used. The PVDF membrane was blocked with 5% skimmed milk at room temperature for 30 min. The primary antibodies were diluted at a ratio of 1:1,000 and the secondary antibodies were diluted at a ratio of 1:5,000. PVDF membrane was incubated with primary and secondary antibodies at room temperature for 1 h each. It was washed with TBST with 0.05% Tween-20. Western blotting was performed according to conventional methods. Finally, ECL chemiluminescence solution (SuperSignal™ West Pico PLUS, 34577; Thermo Fisher Scientific, Inc.) was used to develop the image.

Statistical analysis. All experiments were repeated three times. The data were analyzed using SPSS 17.0 software (SPSS, Inc.) package and are presented as the mean ± SD. One-way ANOVA was used to analyze the data and S-N-K method was used as the post hoc test. P<0.05 was considered to indicate a statistically significant difference. Graphs were...
Expression of hsa-miR-429 is significantly downregulated in DLBCL tissue. Tumor and normal tissue samples from 10 patients with DLBCL were collected. The expression of hsa-miR-429 was detected by qPCR. The results revealed that hsa-miR-429 expression was significantly reduced in DLBCL tissue (P<0.01; Fig. 1).

**Results**

Expression of hsa-miR-429 inhibits the proliferation and promotes the apoptosis of SUDHL-4 and DB cells. SUDHL-4 and DB cells were generated using GraphPad Prism 5 software (GraphPad Software, Inc.).

Figure 2. hsa-miR-429 inhibits the proliferation of SUDHL-4 and DB cells and promotes apoptosis. (A) The transfection effect was detected by reverse transcription-quantitative PCR. (B) Cell Counting Kit-8 assays were used to detect the effect of hsa-miR-429 on the proliferation of diffuse large B-cell lymphoma cells. (C) Results of cell colony formation assays. (D) The effect of hsa-miR-429 on the cell apoptotic rate was detected by flow cytometry. (E) The effect of hsa-miR-429 on the cell cycle distribution was detected by flow cytometry. **P<0.01 and ***P<0.001. hsa, Homo sapiens; miR, microRNA; Ctrl, control.
transfected with hsa-miR-429 mimic and inhibitor (Fig. 2A). CCK-8 and colony formation assay results revealed that transfection with hsa-miR-429 mimic significantly inhibited cell proliferation, while transfection with hsa-miR-429 inhibitor significantly promoted cell proliferation (Fig. 2B and C). Moreover, the detection of the cell apoptotic rate and cell cycle distribution by flow cytometry indicated that transfection with hsa-miR-429 mimic resulted in a significant increase in the cell apoptotic rate and decrease in the proportion of cells in the G2/M-phase of the cell cycle. The experimental groups transfected with hsa-miR-429 inhibitor revealed the opposite results (Fig. 2D and E). The aforementioned results indicated that hsa-miR-429 could inhibit the proliferation and promote the apoptosis of DLBCL cells.

CBX8 is the target gene of hsa-miR-429. TargetScanHuman 7.2 (http://www.targetscan.org/vert_72/) predicted that CBX8 may be the target gene of hsa-miR-429 (Fig. 3A). CBX8 exerts cancer-promoting effects on a variety of malignant tumors, such as liver, colon and esophageal cancer (20-25). CBX8 promotes tumorigenesis and radiation tolerance of esophageal squamous cell carcinoma cells by targeting APAF1 (23). It has also been demonstrated to interact with Y-box binding protein 1 (YBX1) to promote the proliferation of liver cancer cells (22). CBX8 promotes tumorigenesis and radiation tolerance of esophageal squamous cell carcinoma cells by targeting APAF1 (23). It has also been reported that, in hepatocellular carcinoma, CBX8 exhibits oncogenic activity through AKT/β-catenin activation (20,21).

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CBX8 promotes the proliferation and inhibits the apoptosis of SUDHL-4 and DB cells. Overexpression of CBX8 in SUDHL-4 and DB cells led to a significant increase in cell proliferation (Fig. 4A-D), a distinct decrease in the cell apoptotic rate (Fig. 4E) and a marked increase in the proportion of cells in the G2/M phase (Fig. 4F). CBX8 knockdown had the opposite effects. The aforementioned results indicated that CBX8 may promote oncogenesis in DLBCL cells.

hsa-miR-429 antagonizes the effect of CBX8 on DB cell proliferation and inhibition of apoptosis. hsa-miR-429 mimic was transfected into DB cells overexpressing CBX8. Western blot analysis demonstrated that hsa-miR-429 mimic significantly downregulated the protein and mRNA expression levels of CBX8 in DB cells (Fig. 5A and B). The results of the cell proliferation experiments and cell colony formation assays revealed that hsa-miR-429 mimic antagonized the positive effect of CBX8 on the proliferation of DB cells (Fig. 5C and D). In addition, the apoptotic rate of DB cells overexpressing CBX8 transfected with hsa-miR-429 mimic was increased (Fig. 5E), and the proportion of cells in the G2/M phase was significantly reduced (Fig. 5F). The aforementioned results demonstrated the antagonistic effect of hsa-miR-429 on the oncogenic role of CBX8.

Discussion

miRNA is widely expressed in animal and plant cells. miRNA can be combined with lipids or lipoproteins and other components in cells to form microvesicles, which can be disseminated outside of the cell and enter the peripheral blood circulation. It can also enter recipient cells through endocytosis, thereby exerting specific biological effects and regulating target genes (4,5). Previous studies have revealed that different types of malignant tumors may aberrantly express specific tumor-associated miRNA molecules (4,5). The aberrant expression of miRNA can play a key role in multiple biological processes, such as tumor cell survival, invasion and metastasis.

In the present study, hsa-miR-429 played a tumor-suppressive role in DLBCL. High levels of hsa-miR-429 inhibited cell proliferation, promoted apoptosis and changed the distribution of cells in the cell cycle. Bioinformatics prediction revealed that CBX8 was the target of hsa-miR-429. The dual luciferase experiment demonstrated that hsa-miR-429 regulated its transcription levels by targeting the 617-623 positions in the 3'-UTR of CBX8. It has been reported that, in hepatocellular carcinoma, CBX8 exhibits oncogenic activity through AKT/β-catenin activation (20,21). It has also been demonstrated to interact with Y-Box binding protein 1 (YBX1) to promote the proliferation of liver cancer cells (22). CBX8 promotes tumorigenesis and radiation tolerance of esophageal squamous cell carcinoma cells by targeting APAF1 (23). It has also been reported that CBX8 participates in the DNA repair process and promotes the occurrence of esophageal cancer (24). In addition, CBX8 has been revealed to promote the progression and drug resistance of colon cancer, breast cancer, leukemia, bladder cancer and prostate cancer (25-29). To the best of our knowledge, the role of CBX8 in DLBCL has not yet been studied. The present study demonstrated that CBX8 also played a role in promoting DLBCL. Overexpression of CBX8 in SUDHL-4 and DB cells led to a significant increase in cell proliferation, a notable decrease in the cell apoptotic rate and a marked increase in
the proportion of cells in the G2/M phase of the cell cycle. Transfection of hsa-miR-429 mimic into cells reversed these results. Therefore, in DLBCL, the tumor-suppressive effect of hsa-miR-429 was achieved by targeted downregulation of CBX8. This result indicated that hsa-miR-429 may be used as a diagnostic marker and a potential nucleic acid drug for DLBCL. CBX8 may also become an effective therapeutic target for DLBCL.
Figure 5. hsa-miR-429 antagonizes the positive effect of CBX8 on DLBCL cell proliferation and on the inhibition of apoptosis. (A) Western blot analysis revealed that hsa-miR-429 mimic significantly downregulated the protein expression levels of CBX8 in cells. (B) The transfection effect was detected by reverse transcription-quantitative PCR. (C) Cell Counting Kit-8 assays indicated that hsa-miR-429 mimic significantly inhibited the increase in proliferation of DLBCL cells following overexpression of CBX8. (D) Results of cell colony formation assay. (E) Recovery of the cell apoptotic rate by hsa-miR-429 mimic was detected by flow cytometry. (F) Recovery of the cell cycle distribution by hsa-miR-429 mimic was detected by flow cytometry. "P<0.01 and """"P<0.001.

DLBCL, diffuse large B-cell lymphoma; hsa, Homo sapiens; miR, microRNA; CBX8, chromobox 8; UTR, untranslated region; OE, overexpression; Ctrl, control.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

YL and ZJY performed the experiments. ML, HML, JZZ, TX and YYT confirmed the authenticity of all the raw data. YL and ZJY performed the statistical analysis. ML, HML, JZZ, TX and YYT performed the bioinformatics analysis. ZPH designed the study and YL drafted the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of Jingzhou Central Hospital (Jingzhou, China). All participants signed informed consent forms.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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