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LncRNA PCAT1 enhances cell proliferation, migration and invasion by miR-508-3p/NFIB axis in diffuse large B-cell lymphoma

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Abstract. – OBJECTIVE: In previous studies, PCAT1 has been proved to be a key carcinogenic driver in hepatocellular carcinoma. However, the regulatory mechanism of PCAT1 remains poorly understood in diffuse large B-cell lymphoma (DLBCL).

PATIENTS AND METHODS: The expression of PCAT1, miR-508-3p and NFIB in DLBCL was detected by RT-qPCR assay. CCK-8 assay and transwell assay were used to measure cell proliferation, migration and invasion of DLBCL cells. Western blot assay was used to explore the protein expression of NFIB. Dual-Luciferase reporter assay was applied to measure the correlation between PCAT1, miR-508-3p and NFIB.

RESULTS: PCAT1 was demonstrated to be up regulated in DLBCL tissues and cell lines. Besides, PCAT1 expression was associated with clinical stage and IPI score of DLBCL patients. Moreover, overexpression of PCAT1 promoted DLBCL cell proliferation, migration and invasion in vitro. Mechanistic investigation displayed that PCAT1 interplayed with miR-508-3p, while NFIB was a target gene of miR-508-3p. Further, miR-508-3p was in a downtrend while NFIB was increased in DLBCL tissues and cell lines. MiR-508-3p overexpression repressed DLBCL cell growth and metastasis, while PCAT1 overexpression reversed the inhibitory effect of miR-508-3p on the progression of DLBCL. Moreover, NFIB silencing suppressed DLBCL cell proliferation, migration and invasion, whereas PCAT1 vector or miR-508-3p knockdown destroyed the inhibitory of si-NFIB on the progression of DLBCL.

CONCLUSIONS: Taken together, our findings validated that PCAT1 acted as completive endogenous RNA by sponging miR-508-3p and upregulating NFIB to facilitate DLBCL cell proliferation, migration and invasion.

Key Words:
Diffuse large B-cell lymphoma, PCAT1, MiR-508-3p, NFIB.

Introduction

Lymphoma is a malignant tumor originated from the lymphatic hematopoietic system. It presents mainly as painless lymphadenopathy, hepatosplenomegaly, accompanied by fever, night sweat, emaciation, itching and other systemic symptoms. Diffuse large B-cell lymphoma (DLBCL) is the most common lymphoid system tumor in adults, accounting for about 30% to 40% of all non-Hodgkin's lymphomas. The 5-year survival rate of DLBCL is about 50%. At present, the etiology of lymphoma is not clear. It is generally believed that it may be related to gene mutation, virus and other pathogens infection, radiation, chemical drugs, combined with systemic immune disease.

Recent studies have shown that lncRNAs participate in a variety of important regulatory processes such as x chromosome silencing, genomic imprinting and chromatin modification, transcriptional activation, transcriptional interference, and intracellular transport. Emerging studies have proved that LncRNAs exert crucial roles in the tumorigenesis and development in DLBCL. MALAT1 was proved to enhance DLBCL cell proliferation, migration and immune escape by inhibiting miR-195[1]. Qian et al[2] detected that NEAT1 accelerated cell proliferation and lymphomagenesis by miR-34b-5p/ GLI1

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axis in DLBCL. Moreover, SMAD5-AS1 was found to be down regulated in DLBCL and repress cell proliferation via inhibiting miR-135b-5p while up-regulating APC[3]. Prostate cancer associated ncRNA transcript 1 (PCAT1) was first identified through a global transcriptomic sequencing study of prostate cancer[4]. In hepatocellular carcinoma, PCAT1 was validated to be upregulated and promote migration and invasion by sponging miR-129-5p and upregulating HMGB1 expression[5]. Moreover, PCAT1 was also proved to be a carcinogen in non-small cell lung cancer[6] and myeloma[7]. Although the expression and function of PCAT1 have been explored in various human tumors, the role of PCAT1 in DLBCL is still scarce.

MiRNAs are involved in a series of important processes in life, including early development, cell proliferation, apoptosis, cell death, fat metabolism, and cell differentiation[8]. For example, miR-155 was discovered to be high expressed in DLBCL tissues, and the depletion of miR-155 suppressed DLBCL cell proliferation, migration and invasion[9]. On the contrary, miR-16-1 might be a tumor-inhibiting factor in DLBCL[10]. Moreover, miR-214 was down expressed and induced cell apoptosis but repressed cell growth and invasion[11]. MiR-508-3p was first found to be significantly down-regulated in renal cell carcinoma, and to have a significant inhibitory effect on cell metastasis[12]. Furthermore, in ovarian cancer (OC), miR-508-3p was down regulated and might be a new biomarker for OC treatment[13]. To our knowledge, the role of miR-508-3p in DLBCL is still not clear.

In this research, we investigated the expression pattern of PCAT1 in DLBCL, and indicated the effect of PCAT1 on the development of DLBCL. Simultaneously, we found that PCAT1 regulating DLBCL cell progression by modulating miR-508-3p/NFIB.

Patients and Methods

Tissue Samples

In our study, 48 DLBCL tissues and adjacent normal lymph gland tissues were gathered from Qingdao Hospital of Traditional Chinese Medicine (Qingdao Hiser Hospital). All patients had not received preoperative radiotherapy, chemotherapy, or other related treatment. After surgical resection, the tissues were immediately cryopreserved at -80°C for future experiments. DLBCL patients were selected according to the diagnostic criteria published by the World Health Organization in 2008. The human experiment was compliant with the principles of the Helsinki Declaration. Our experiments were approved by the Ethics Committee of Qingdao Hospital of Traditional Chinese Medicine (Qingdao Hiser Hospital), and all patients have written the informed consent.

Cell Lines and Cell Culture

DLBCL cell lines (OCI-LY-7, OCI-LY-7, TMD8 and U2932) were obtained from the Shanghai JingKang Bioengineering CO., LTD (Shanghai, China). Human peripheral blood B-lymphocyte (IM-9) was purchased from BeNa Culture Collection (Beijing, China). All cells were grown in 90% Roswell Park Memorial Institute-1640 (RPMI-1640) medium with 10% fetal bovine serum (FBS) supplemented with penicillin G and streptomycin, L-glutamine and HEPES. The cells were cultured in an incubator at 37 °C and 5% CO_2.

Cell Transfection

Small interfering RNA downregulating PCAT1 (si-PCAT1), pcDNA3.1-PCAT1, negative control (NC) small interfering RNA (si-NC), NC miRNA mimic, NC inhibitor, miR-508-3p mimic, miR-508-3p inhibitor were purchased from GenePharma (Shanghai, China). All were transfected into OCI-LY-7 cells by Lipofectamine 3000 (Invitrogen, Carlsbad, CA, USA).

RNA Isolation, Reverse Transcription and RT-qPCR

The total RNA was isolated from DLBCL tissues and cells by the TRIzol® Reagent (Invitrogen, Carlsbad, CA, USA). GoScript Reverse Transcription System was used to reverse RNA transcription into cDNA. Then, LightCycle 96 thermocycle (Roche, Basel, Switzerland) was adopted to quantify the expression level of PCAT1, miR-508-3p and NFIB. PCAT1 and NFIB were standardized to GAPDH, while U6 was normalized to miR-508-3p. The sequences of primers were listed in Table I.

Dual-Luciferase Reporter Assay

In this article, bioinformatics website RegRNA 2.0 was used to search miRNAs which bound to PCAT1 with putative binding sites. The binding sequences of PCAT1 or NFIB containing the

Table I. Real time PCR primers.

Gene		Primers5′-3′
PCAT1	Forward	5'-CCTCTAAGTGCCAGTGCAGG-3'
	Reverse	5'-ACCCTTTGACCCTTGGCATT-3'
miR-508-3p	Forward	5'-CAAGCATGATTGTAGCCTTTTG-3'
	Reverse	5'-TATCGTTGTACTCCAGACCAAGAC-3'
NFIB	Forward	5'-ACACACATGGTCGGCTCG-3'
	Reverse	5'-TCAAGGTTACAGCCCCAAGC-3'
GAPDH	Forward	5'-GCTCTCTGCTCCTCCTGTTC-3'
	Reverse	5'-CCATGGTGTCTGAGCGATGT-3'
U6	Forward	5'-CTCGCTTCGGCAGCACA-3'
	Reverse	5'-AACGATTCACGAATTTGCGT-3'

miR-508-3p binding sites and mutant binding sites were inserted into pmirGLO Luciferase plasmids to construct PCAT1-wt or NFIB-wt and PCAT1-mut or NFIB-mut reporter vectors. Then, all reporter vectors were co-transfected with miR-NC or miR-508-3p mimic into OCI-LY-7 cells. Cells were cultured in the incubator at 37°C, 5% CO_2, and 95% humidity. After 48 hours, the Luciferase activity was tested by the Dual-Luciferase reporter assay kit.

Cell Counting Kit-8 (CCK-8) Assay

The 100 μl inoculated cell suspension was cultured in a 96-well plate in an incubator at 37°C and 5% CO_2 saturated humidity. Added 10 μl of CCK-8 reagent to each well and continue to culture in the incubator for 0-96 hours. Finally, the absorbance was measured at 450 nm.

Transwell Assay

OCI-LY-7 cells (1×10^5 /well) were cultured in the transwell chambers (8 μm, Millipore, Billerica, MA, USA). Unlike cell migration, 50 μl Matrigel was added to the upper chamber to assess cell invasion. The culture medium containing 10% FBS was added to the lower chamber. After cultured for 24 h, wiped off the matrix glue and cells in the upper chamber with a cotton swab. Then, fixed with 4% glutaraldehyde, and stained with 0.1% crystal violet for 20 min. In the end, the number of migrated and invasive cells in 5 random fields was counted under the light microscope.

Western Blot Assay

Total proteins samples were isolated by 10% sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) and then transferred to the NC membrane. After incubation with 5% skimmed milk, the membrane was incubated with specific antibodies. Finally, the protein signals were detected by enhanced chemiluminescence (ECL) Western Blotting Substrate.

Statistical Analysis

Our data were presented as mean ± SD and analyzed by SPSS Statistics 17.0 (SPSS, Chicaco, IL, USA). Differences between two groups were tested by Student's *t*-test. One-way ANOVA and Tukey's post-hoc test were adopted to analyze the differences of multiple groups. Pearson's correlation analysis was used to explore the relationship between PCAT1, miR-508-3p and NFIB. Statistical significance was set as $p<0.05$.

Results

The Dysregulation of PCAT1 and MiR-508-3p was Found in DLBCL

The expression of PCAT1 and miR-508-3p was detected by RT-qPCR assay. Our results displayed that there was an uptrend of PCAT1 in DLBCL tissues (Figure 1A). Moreover, PCAT1 was higher expressed in DLBCL cell lines (OCI-LY-7, TMD8, OCI-LY-10 and U2932) than in IM-9 cells (Figure 1B). On the contrary, miR-508-3p was lower expressed in DLBCL tissues than in normal tissues (Figure 1C). Next, we noticed that miR-508-3p was notably down regulated in DLBCL cell lines compared with IM-9 cells (Figure 1D). Our results indicated that PCAT1 was high expressed, while miR-508-3p was down regulated in DLBCL.

Overexpression of PCAT1 Enhanced Cell Proliferation, Migration and Invasion in DLBCL

Based on the mean expression value of PCAT1, 48 cases of DLBCL patients were di-

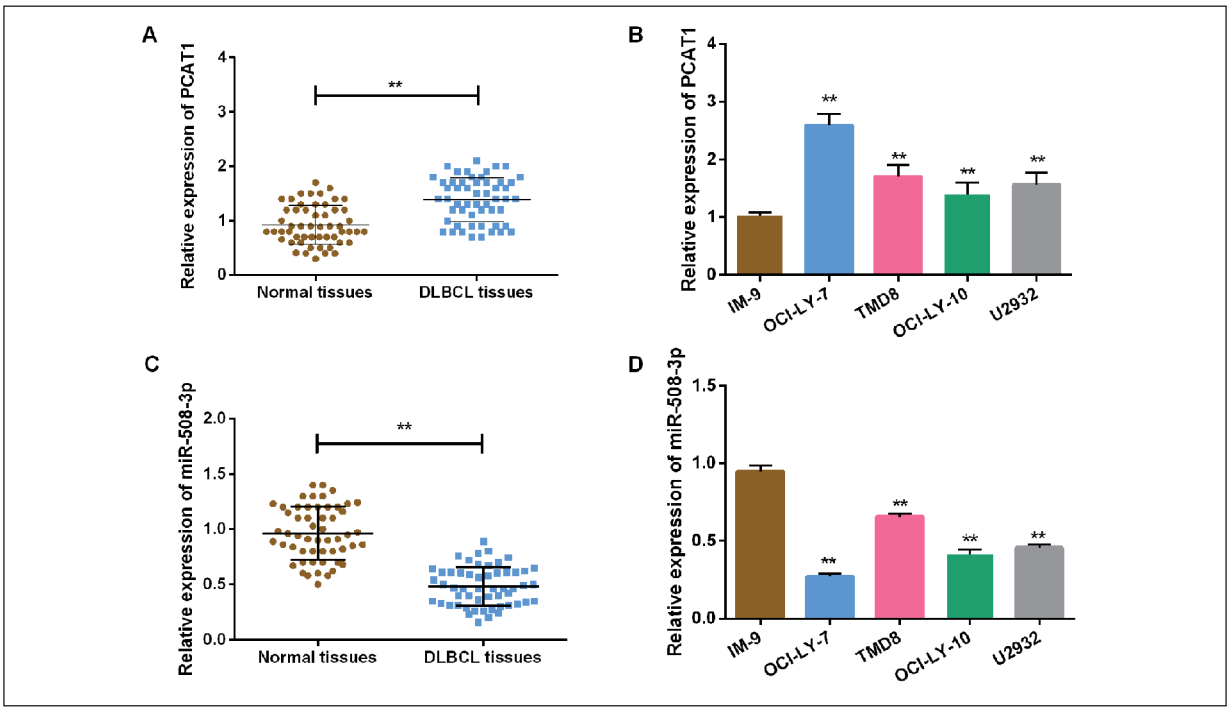

Figure 1. PCAT1 was high expressed, while miR-508-3p was down expressed in DLBCL. **A**, PCAT1 was higher expressed in DLBCL tissues than in normal tissues. **B**, PCAT1 was higher regulated in DLBCL cell lines (OCI-LY-7, TMD8, OCI-LY-10 and U2932) than in IM-9 cells. **C**, Downexpression of miR-508-3p was found in DLBCL tissues. **D**, Downexpression of miR-508-3p was found in DLBCL cell lines (OCI-LY-7, TMD8, OCI-LY-10 and U2932). $^{**}p<0.01$.

vided into two groups (low PCAT1 expression group and high PCAT1 expression group). We noticed that PCAT1 expression was closely related with clinical stage and IPI score (Table II). To explore the function of PCAT1 on DLBCL cell progression, we transfected PCAT1 vector into

Table I. Correlation between the expression level of UCA1 and clinical characteristics of DLBCL patients (n=48).

Clinical characteristics	No. of cases n = 48	UCA1 expression		*p*-value
		Low (n = 21)	High (n = 27)	
Age (years)				0.536
≥ 55	25	12	13	
< 55	23	9	14	
Gender				0.683
Male	29	12	17	
Female	19	9	10	
Ann Arbor stage				0.202
I-II	18	10	8	
III-IV	30	11	19	
Clinical stage				0.014*
I-II	16	11	5	
III-IV	32	10	22	
LDH ratio				0.422
≤ 1	26	10	16	
> 1	22	11	11	
IPI score				0.030*
0-2	31	10	21	
3-5	17	11	6	

*$p < 0.05$, the difference is significant. LDH: Lactate dehydrogenase; IPI: International prognostic index.

OCI-LY-7 cells. Results displayed that the expression of PCAT1 was significantly increased by PCAT1 vector (Figure 2A). Next, CCK-8 assay and transwell assay were used to assess cell proliferation, migration and invasion viability. As shown in Figure 2B, PCAT1 overexpression was found to enhance cell proliferation. Moreover, PCAT1 overexpression increased the number of migrated and invaded cells (Figure 2C, D). Taken together, PCAT1 overexpression was revealed to enhance cell proliferation, migration and invasion in DLBCL, and be strong connected with clinical stage and IPI score.

PCAT1 Acted as a Molecular Sponge of MiR-508-3p in DLBCL

LncRNAs were reported to act as sponges of miRNAs in the tumorigenesis and development of human tumors. We found that there were special binding sites between PCAT1 and miR-508-3p (Figure 3A). Next, Luciferase reporter assay revealed that miR-508-3p mimic lowered the Luciferase activity of PCAT1-wt, rather than PCAT1-mut (Figure 3B). Moreover, RT-qPCR assay was carried out to assess the relationship between PCAT1and miR-508-3p. Accordingly, we noticed that miR-508-3p mimic suppressed the expression of PCAT1, while miR-508-3p inhibitor increased the expression of PCAT1 of OCI-LY-7 cells (Figure 3C). Furthermore, the expression of miR-508-3p was inhibited by PCAT1 vector but increased by depletion of PCAT1 (Figure 3D). To research PCAT1/miR-508-3p axis in the progression of DLBCL, we transfected miR-508-3p mimic or PCAT1 vector into OCI-LY-7 cells. As shown in Figure 3E, miR-508-3p mimic accelerated the expression of miR-508-3p, while PCAT1 vector lessened the expression of miR-508-3p in OCI-LY-7 cells. Functionally, the cell proliferation was found to

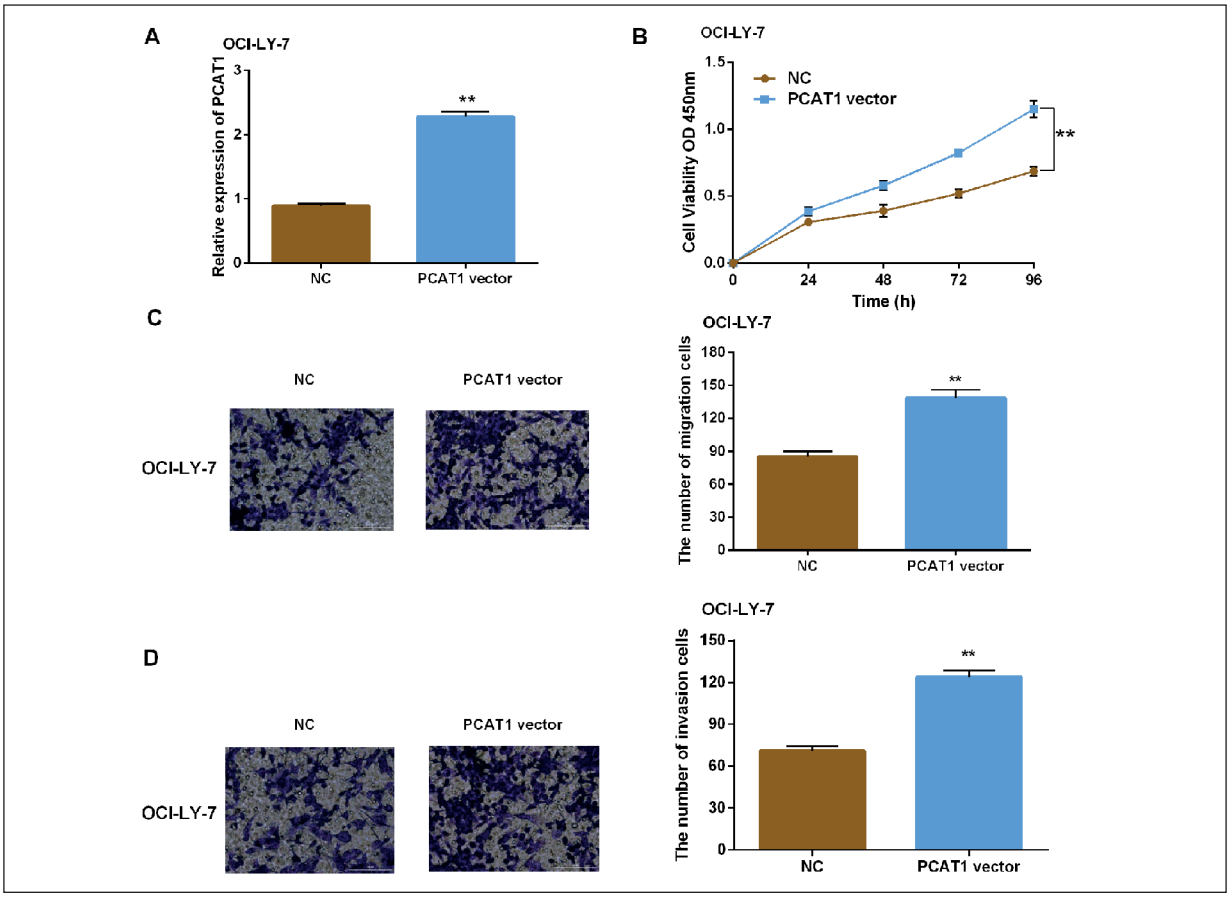

Figure 2. Upregulation of PCAT1 promoted cell proliferation, migration and invasion of OCI-LY-7 cells. **A**, The expression of PCAT1 was increased by PCAT1 vector. **B**, CCK-8 assay revealed that PCAT1 overexpression promoted cell proliferation of OCI-LY-7 cells. **C, D**, Transwell assay displayed that PCAT1 overexpression increased the number of migrated and invade cells of OCI-LY-7 cells (scale bar=100 μm). $^{**}p<0.01$.

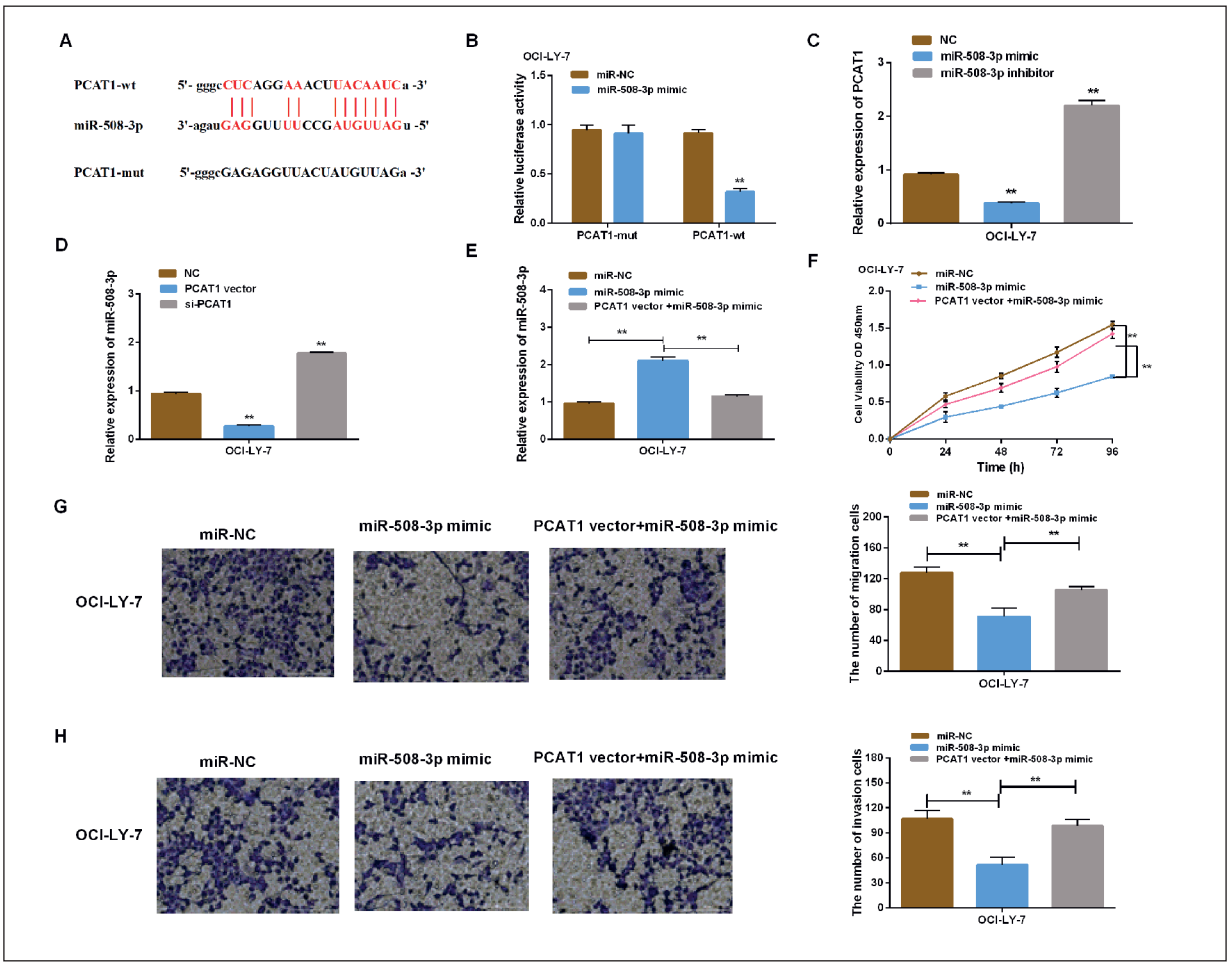

Figure 3. PCAT1 acted as a molecular sponge of miR-508-3p in DLBCL. **A**, There were binding sites between PCAT1 and miR-508-3p. **B**, The Dual-Luciferase reporter assay was assessed the Luciferase activity of PCAT1-mut and PCAT1-wt. **C**, The impact of miR-508-3p mimic or miR-508-3p inhibitor on PCAT1 expression. **D**, The impact of PCAT1 vector or PCAT1 knockdown on miR-508-3p expression. **E**, The expression of miR-508-3p was detected in OCI-LY-7 cells transfected PCAT1 vector with miR-508-3p mimic. **F**, MiR-508-3p mimic inhibited OCI-LY-7 cell proliferation, while PCAT1 vector destroyed the suppression effect of miR-508-3p mimic. **G, H**, PCAT1 vector reversed the inhibitor effect of miR-508-3p mimic on OCI-LY-7 cell migration and invasion (scale bar=100 μm). $^{**}p<0.01$.

be repressed by miR-508-3p mimic transfection, while PCAT1 vector destroyed the suppression effect of miR-508-3p mimic in OCI-LY-7 cells (Figure 3F). Moreover, PCAT1 overexpression had the same effect on cell migration and invasion of OCI-LY-7 cells (Figure 3G, H). Combined with our results, PCAT1 was manifested to interplay with miR-508-3p in DLBCL.

MiR-508-3p Directly Interacted with NFIB 3'UTR in DLBCL

Based on the Targetscan, there were binding sites between miR-508-3p and NFIB (Figure 4A). Dual-Luciferase reporter assay was adopted to verify this topic (Figure 4B). Then, we discovered that NFIB was higher regulated in DLBCL tissues than in normal tissues (Figure 4C). Moreover, there was an uptrend expression of NFIB in DLBCL cell lines (Figure 4D). RT-qPCR assay and Western blot assay were used to explore the expression of NFIB. The results revealed that the mRNA expression and protein expression of NFIB was restricted by miR-508-3p mimic, while increased by miR-508-3p inhibitor (Figure 4E, F). In addition, there was a negative correlation between miR-508-3p and NFIB in DLBCL patients (Figure 4G). Our findings indicated that miR-508-3p interacted with NFIB in DCBCL.

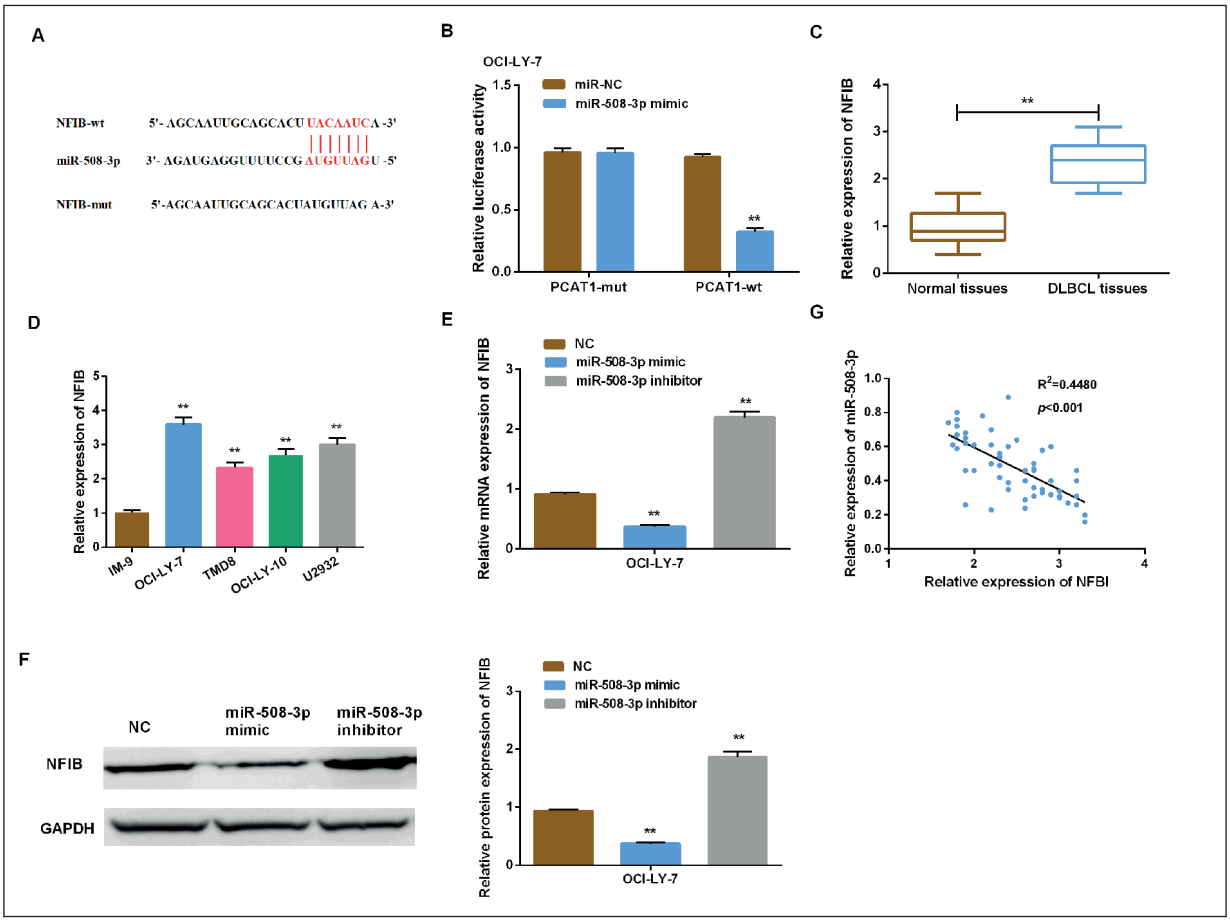

Figure 4. MiR-508-3p directly interacted with NFIB 3'UTR in DLBCL. **A**, NFIB had special binding sites with miR-508-3p. **B**, The relative Luciferase activity of NFIB-mut or NFIB-wt. **C**, NFIB was up expressed in DLBCL tissues. **D**, NFIB was up expressed in DLBCL cell lines. **E**, **F**, The mRNA and protein expression of NFIB was reduced by miR-508-3p mimic, while increased by miR-508-3p inhibitor. **G**, There was a negative correlation between miR-508-3p and NFIB. $^{**}p<0.01$.

PCAT1/miR-508-3p Axis Regulated DLBCL Progression by Modulating NFIB

To explore the effect of PCAT1/miR-508-3p/NFIB on DLBCL cell progression, PCAT1 knockdown or miR-508-3p inhibitor was transfected into OCI-LY-7 cells. We discovered that the mRNA expression of NFIB was reduced by PCAT1 silencing and increased by miR-508-3p inhibitor, while co-transfection PCAT1 silencing and miR-508-3p inhibitor reversed the effect of si-PCAT1 on NFIB expression (Figure 5A). Similarly, miR-508-3p inhibitor destroyed the inhibition effect of NFIB protein expression stimulated by si-PCAT1 (Figure 5B). Functionally, we found that cell proliferation was suppressed by si-PCAT1, while promoted by miR-508-3p inhibitor, and PCAT1 silencing with miR-508-3p inhibitor alleviated the suppressive effect of si-PCAT1 (Figure 5C). Furthermore, miR-508-3p inhibitor had the same reversion effect on cell migration and invasion affected by si-PCAT1 (Figure 5D, E). In addition, we revealed that PCAT1 was inversely correlated with miR-508-3p, while PCAT1 was positively correlated with NFIB (Figure 5 F, G). Consequently, we demonstrated that PCAT1 regulated cell progression by modulating miR-508-3p-mediated NFIB expression in DLBCL.

Discussion

In recent years, lncRNAs have become a hot topic in scientific research. Although the exact role of lncRNAs in physiological processes is still unclear, a large amount of data has revealed their key role in various stages of tumorigenesis and metastasis. PCAT1 was indicated to act as a carcinogen in many human tumors, such as epi-

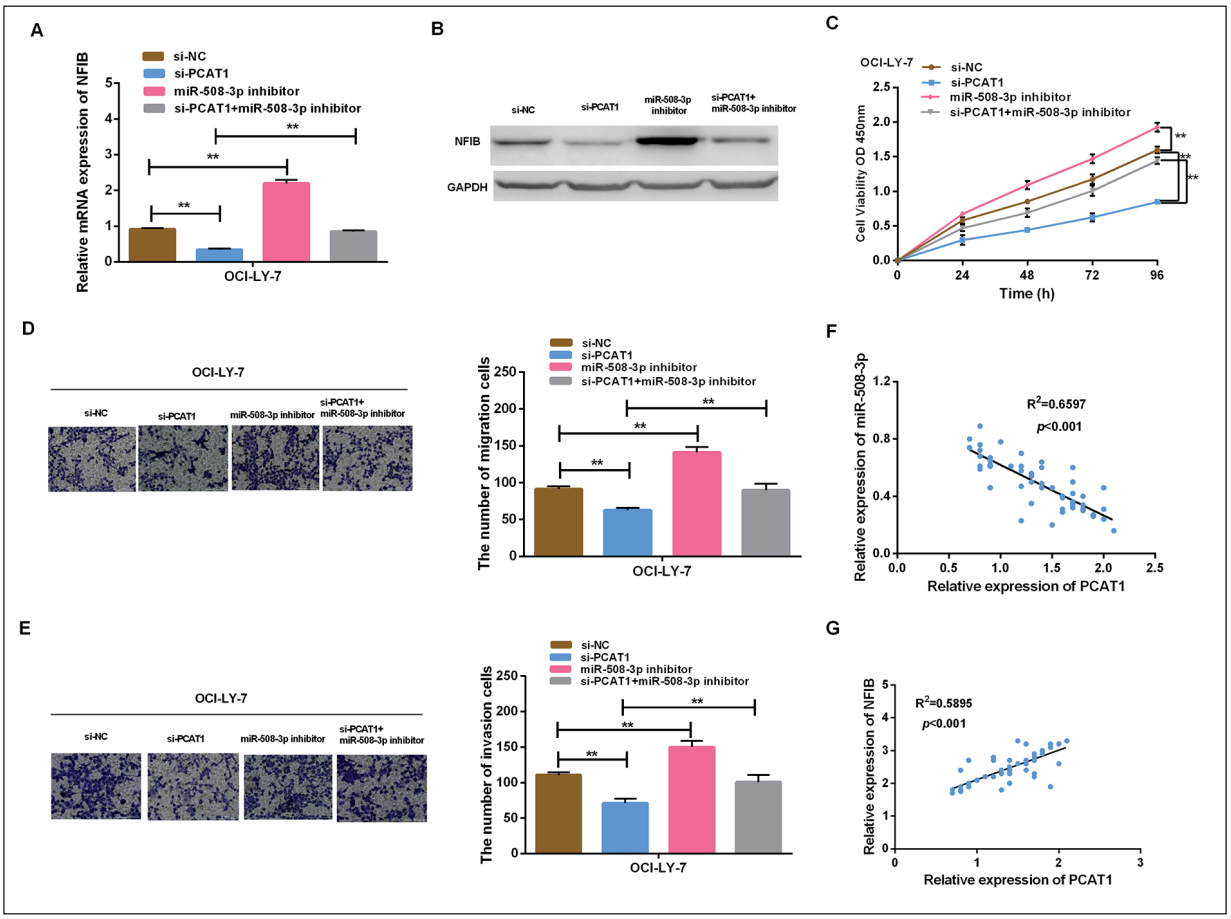

Figure 5. PCAT1/miR-508-3p axis regulated DLBCL progression by modulating NFIB. **A**, **B**, The mRNA and protein expression of NFIB in OCI-LY-7 cells transfection with si-PCAT1 or miR-508-3p inhibitor. **C**, **D**, **E**, MiR-508-3p inhibitor reversed the suppression effect of si-PCAT1 on cell proliferation, migration and invasion (scale bar=100 μm). **F**, There was a negative correlation between miR-508-3p and PCAT1 in DLBCL tissues. **G**, NFIB was found to be positively correlated with PCAT1 in DLBCL tissues. $^{**}p<0.01$.

thelial ovarian cancer[14], osteosarcoma[15] and cervical cancer[16]. In our research, PCAT1 was found to be higher expressed in DLBCL tissues and cell lines than that in control groups. Functionally, elevated PCAT1 expression enhanced cell proliferation, migration and invasion of DLBCL cells. Consistent with our findings, PCAT1 was also found to promote cell progression in gastric cancer[17]. More importantly, we discovered that high PCAT1 expression was closely associated with clinical stage and IPI score of DLBCL patients. Similarly, the elevated PCAT1 expression was related with lymph node metastasis, TNM stage, distant metastasis and depth of infiltration[18].

LncRNAs can interact with miRNAs to participate in the expression regulation of target genes and play an important role in the formation and development of tumors. Differentially expressed miRNAs play a role similar to proto-oncogenes or tumor suppressor genes by regulating different target genes, and are closely related to the occurrence, development, treatment and prognosis of tumors[19-21]. In DLBCL, miR-21, miR-155, miR146b-5p, miR-224 and miR-17/92 clusters might have predictive value in the treatment response to DLBCL chemotherapy[22]. In colorectal cancer, PCAT1 was validated to be a sponge of miR-149-5p, and knockdown of PCAT1 inhibited cell growth and metastasis by modulating miR-149-5p expression[23]. In our study, we validated that PCAT1 was a sponge of miR-508-3p in DLBCL. Moreover, miR-508-3p was found to be down expressed in DLBCL tissues and cell lines. In gastric cancer, miR-508-3p was also discovered to be in the same downtrend[24]. Functional experiments demonstrated that miR-508-3p

mimic remarkably retarded DLBCL cell growth, migration and invasion, while PCAT1 vector mitigated the suppressive effect of miR-508-3p mimic. Similar with our results, Zang et al[25] verified that PCAT1 was a competing endogenous RNA of miR-508-3p and regulated the progression of esophageal squamous cell carcinoma by inhibiting miR-508-3p and regulating ANXA10.

NFIB has been reported to act as a tumor promoter in various human cancers. For example, NFIB overexpression was found to facilitate glioma cell proliferation and colony formation[26]. Additionally, NFIB drove the cell progression in colorectal cancer[27] and gastric cancer[28]. We demonstrated that NFIB was a target gene of miR-508-3p and was up regulated in DLBCL tissues and cell lines. In line with our findings, Wu et al[29] discovered that NFIB was high expressed in gastric cancer tissues and cell lines, and NFIB overexpression enhanced cell migration, invasion and growth. Interestingly, NFIB played as a tumor inhibitor in osteosarcoma[30]. Next, we noticed that PCAT1 silencing inhibited the expression of NFIB, while miR-508-3p inhibitor transfection alleviated the suppressive effect of NFIB by si-PCAT1. Functionally, we validated that PCAT1 regulated cell progression by interplayed with miR-508-3p-mediated NFIB expression in DLBCL.

Conclusions

We first discovered that PCAT1 was upregulated in DLBCL, and promoted cell proliferation, migration and invasion by modulating miR-508-3p/NFIB in DLBCL. Our findings demonstrated that PCAT1 might be a diagnostic, prognostic biomarker and a potential therapeutic target in DLBCL.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Authors' Contribution

The Authors declare that they have no conflict of interests.

References

1) Wang QM, Lian GY, Song Y, Huang YF, Gong Y. LncRNA MALAT1 promotes tumorigenesis and immune escape of diffuse large B cell lymphoma by sponging miR-195. Life Sci 2019; 231: 116335.
2) Qian CS, Li LJ, Huang HW, Yang HF, Wu DP. MYC-regulated lncRNA NEAT1 promotes B cell proliferation and lymphomagenesis via the miR-34b-5p-GLI1 pathway in diffuse large B-cell lymphoma. Cancer Cell Int 2020; 20: 87.
3) Zhao CC, Jiao Y, Zhang YY, Ning J, Zhang YR, Xu J, Wei W, Kang-Sheng G. Lnc SMAD5-AS1 as ceRNA inhibit proliferation of diffuse large B cell lymphoma via Wnt/beta-catenin pathway by sponging miR-135b-5p to elevate expression of APC. Cell Death Dis 2019; 10: 252.
4) Prensner JR, Iyer MK, Balbin OA, Dhanasekaran SM, Cao Q, Brenner JC, Laxman B, Asangani IA, Grasso CS, Kominsky HD, Cao X, Jing X, Wang X, Siddiqui J, Wei JT, Robinson D, Iyer HK, Palanisamy N, Maher CA, Chinnaiyan AM. Transcriptome sequencing across a prostate cancer cohort identifies PCAT-1, an unannotated lincRNA implicated in disease progression. Nat Biotechnol 2011; 29: 742-749.
5) Zhang D, Cao J, Zhong Q, Zeng L, Cai C, Lei L, Zhang W, Liu F. Long noncoding RNA PCAT-1 promotes invasion and metastasis via the miR-129-5p-HMGB1 signaling pathway in hepatocellular carcinoma. Biomed Pharmacother 2017; 95: 1187-1193.
6) Zhao B, Hou X, Zhan H. Long non-coding RNA PCAT-1 over-expression promotes proliferation and metastasis in non-small cell lung cancer cells. Int J Clin Exp Med 2015; 8: 18482-18487.
7) Shen X, Shen P, Yang Q, Yin Q, Wang F, Cong H, Wang X, Ju S. Knockdown of long non-coding RNA PCAT-1 inhibits myeloma cell growth and drug resistance via p38 and JNK MAPK pathways. J Cancer 2019; 10: 6502-6510.
8) Zhang J, Duy Le T, Liu L, He J, Li J. Identifying miRNA synergistic regulatory networks in heterogeneous human data via network motifs. Mol Biosyst 2016; 12: 454-463.
9) Han B, Gao ZD, Wang HX, Wang ZH, Fan CB, Liu JL, Tian M, Zhao HG. Expression of MiR-155 in Tissue of Patients with Diffuse Large B-Cell Lymphoma and Its Effect on Cell Biological Characteristics. Zhongguo shi yan xue ye xue za zhi 2019; 27: 445-451.
10) Tuncer SB, Akdeniz D, Celik B, Kilic S, Sukruoglu O, Avsar M, Ozer L, Ekenel M, Ozel S, Yazici H. The expression levels of miRNA-15a and miRNA-16-1 in circulating tumor cells of patients with diffuse large B-cell lymphoma. Mol Biol Rep 2019; 46: 975-980.
11) Sun JR, Zhang X, Zhang Y. MiR-214 prevents the progression of diffuse large B-cell lymphoma by targeting PD-L1. Cell Mol Biol Lett 2019; 24: 68.

12) Zhai Q, Zhou L, Zhao C, Wan J, Yu Z, Guo X, Qin J, Chen J, Lu R. Identification of miR-508-3p and miR-509-3p that are associated with cell invasion and migration and involved in the apoptosis of renal cell carcinoma. Biochem Biophys Res Commun 2012; 419: 621-626.

13) Zhao L, Wang W, Xu L, Yi T, Zhao X, Wei Y, Vermeulen L, Goel A, Zhou S, Wang X. Integrative network biology analysis identifies miR-508-3p as the determinant for the mesenchymal identity and a strong prognostic biomarker of ovarian cancer. Oncogene 2019; 38: 2305-2319.

14) Ding C, Wei R, Rodriguez RA, Del Mar Requena Mullor M. LncRNA PCAT-1 plays an oncogenic role in epithelial ovarian cancer by modulating cyclinD1/CDK4 expression. Int J Clin Exp Pathol 2019; 12: 2148-2156.

15) Huang J, Deng G, Liu T, Chen W, Zhou Y. Long noncoding RNA PCAT-1 acts as an oncogene in osteosarcoma by reducing p21 levels. Biochem Biophys Res Commun 2018; 495: 2622-2629.

16) Ma TT, Zhou LQ, Xia JH, Shen Y, Yan Y, Zhu RH. LncRNA PCAT-1 regulates the proliferation, metastasis and invasion of cervical cancer cells. Eur Rev Med Pharmacol Sci 2018; 22: 1907-1913.

17) Bi M, Yu H, Huang B, Tang C. Long non-coding RNA PCAT-1 over-expression promotes proliferation and metastasis in gastric cancer cells through regulating CDKN1A. Gene 2017; 626: 337-343.

18) Liang C, Qi Z, Ge H, Liang C, Zhang Y, Wang Z, Li R, Guo J. Long non-coding RNA PCAT-1 in human cancers: a meta-analysis. Clin Chim Acta 2018; 480: 47-55.

19) Sui J. MiRNA-30 Play an Important Role in Non-Small Cell Lung Cancer (NSCLC). Clin Lab 2020; 66.

20) Fang QY, Deng QF, Luo J, Zhou CC. MiRNA-20a-5p accelerates the proliferation and invasion of non-small cell lung cancer by targeting and down-regulating KLF9. Eur Rev Med Pharmacol Sci 2020; 24: 2548-2556.

21) Buruiană A, Florian ȘI, Florian AI, Timiș TL, Mihu CM, Miclăuș M, Oșan S, Hrapșa I, Cataniciu RC, Farcaș M, Șușman S. The Roles of miRNA in Glioblastoma Tumor Cell Communication: Diplomatic and Aggressive Negotiations. Int J Mol Sci 2020; 21: 1950.

22) Ting CY, Liew SM, Price A, Gan GG, Bee-Lan Ong D, Tan SY, Bee PC. Clinical significance of aberrant microRNAs expression in predicting disease relapse/refractoriness to treatment in diffuse large B-cell lymphoma: A meta-analysis. Crit Rev Oncol Hematol 2019; 144: 102818.

23) Wang AH, Fan WJ, Fu L, Wang XT. LncRNA PCAT-1 regulated cell proliferation, invasion, migration and apoptosis in colorectal cancer through targeting miR-149-5p. Eur Rev Med Pharmacol Sci 2019; 23: 8310-8320.

24) Huang T, Kang W, Zhang B, Wu F, Dong Y, Tong JH, Yang W, Zhou Y, Zhang L, Cheng AS, Yu J, To KF. miR-508-3p concordantly silences NFKB1 and RELA to inactivate canonical NF-kappaB signaling in gastric carcinogenesis. Mol Cancer 2016 ; 15: 9.

25) Zang B, Zhao J, Chen C. LncRNA PCAT-1 Promoted ESCC Progression via Regulating ANXA10 Expression by Sponging miR-508-3p. Cancer Manag Res 2019; 11: 10841-10849.

26) Li Y, Xu J, Zhang J, Zhang J, Zhang J, Lu X. MicroRNA-346 inhibits the growth of glioma by directly targeting NFIB. Cancer Cell Int 2019; 19: 294.

27) Sun L, Fang Y, Wang X, Han Y, Du F, Li C, Hu H, Liu H, Liu Q, Wang J, Liang J, Chen P, Yang H, Nie Y, Wu K, Fan D, Coffey RJ, Lu Y, Zhao X, Wang X. miR-302a Inhibits Metastasis and Cetuximab Resistance in Colorectal Cancer by Targeting NFIB and CD44. Theranostics 2019; 9: 8409-8425.

28) Zhang W, Zhan F, Li D, Wang T, Huang H. RGMB-AS1/miR-22-3p/NFIB axis contributes to the progression of gastric cancer. Neoplasma 2020; 67: 484-491.

29) Wu C, Zhu X, Liu W, Ruan T, Wan W, Tao K. NFIB promotes cell growth, aggressiveness, metastasis and EMT of gastric cancer through the Akt/Stat3 signaling pathway. Oncol Rep 2018; 40: 1565-1573.

30) Mirabello L, Koster R, Moriarity BS, Spector LG, Meltzer PS, Gary J, Machiela MJ, Pankratz N, Panagiotou OA, Largaespada D, Wang Z, Gastier-Foster JM, Gorlick R, Khanna C, de Toledo SR, Petrilli AS, Patiño-Garcia A, Sierrasesúmaga L, Lecanda F, Andrulis IL, Wunder JS, Gokgoz N, Serra M, Hattinger C, Picci P, Scotlandi K, Flanagan AM, Tirabosco R, Amary MF, Halai D, Ballinger ML, Thomas DM, Davis S, Barkauskas DA, Marina N, Helman L, Otto GM, Becklin KL, Wolf NK, Weg MT, Tucker M, Wacholder S, Fraumeni JF Jr, Caporaso NE, Boland JF, Hicks BD, Vogt A, Burdett L, Yeager M, Hoover RN, Chanock SJ, Savage SA. A Genome-Wide Scan Identifies Variants in NFIB Associated with Metastasis in Patients with Osteosarcoma. Cancer Discov 2015; 5: 920-931.