European Review for Medical and Pharmacological Sciences 2019; 23: 1176-1183

Correlations of mouse lymphoma xenografts with the expressions of MMP-9 and Bcl-2

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Abstract. – OBJECTIVE: To establish a mouse lymphoma xenograft model so as to investigate the correlation between the expression of matrix metallopeptidase-9 (MMP-9) and that of B-cell lymphoma 2 (Bcl-2) in lymphomas.

MATERIALS AND METHODS: Diffuse large Bcl (DLBCL) cells were cultured, and a mouse lymphoma xenograft model was established via the subcutaneous injection. Mouse lymphoma tissues were extracted, and the expressions of MMP-9 and Bcl-2 messenger ribonucleic acids (mRNAs) in the xenograft tumor were detected using Real-time polymerase chain reaction (PCR). Immunohistochemistry was used to detect the expression levels of MMP-9 and Bcl-2 proteins in lymphoma tissues and tumor-adjacent tissues. The consistency of MMP-9 expression and Bcl-2 expression was analyzed via Spearman's rank correlation analysis.

RESULTS: The expressions of MMP-9 and Bcl-2 in lymphoma tissues were increased. The expression levels of MMP-9 and Bcl-2 proteins in lymphoma tissues were higher than those in tumor-adjacent tissues. The expression levels of MMP-9 and Bcl-2 were correlated with weight loss degree of mice. The expression of MMP-9 was positively associated with that of BCL-2 in lymphoma.

CONCLUSIONS: MMP-9 and Bcl-2 are associated with the occurrence of DLBCL, and they are potential impact factors affecting the prognosis.

Key Words:
Lymphoma, MMP-9, BCL-2.

Introduction

Human non-Hodgkin's Lymphoma (NHL) is a heterogeneous tumor with a significant difference between clinical and pathophysiological manifestations. In recent years, the incidence rate of NHL has been increased year by year, especially for the aggressive and highly aggressive NHL[1]. Diffuse large b-cell lymphoma (DLBCL) is the most common NHL in the Western Hemisphere and China. According to the Revised European-American Lymphoma (REAL) and the World Health Organization (WHO) classifications, DLBCL accounts for about 30-40% of adult NHL cases. The histopathological type, location, stage and other prognostic factors of lymphoma are the basis for developing individualized treatment regimens for patients[4]. At present, R-CHOP regimen is taken as the treatment standard for patients with DLBCL, and the cure rate is about 70%. However, R-CHOP-based regimens do not result in satisfactory curative effects for all patients. The manageability of DLBCL has been influenced by risk factors including age, high international prognostic index score, germinal centromere phenotype, and extranodal-invasive and dual-protein expression variations[5-7]. DLBCL is characterized by different pathological subtypes, morphological changes and gene expression profiles. In tissues, there are no abnormally expressed apoptosis inhibitors and proliferation promoting factors. In clinical manifestations, genetic findings, responses to treatments and prognosis, DLBCL has no specific molecular targets. The application of gene expression profiling (GEP) in the study on DLBCL is an important progress in recent years. It further clarifies the heterogeneity of tumors and provides a theoretical basis for grouping patients. Currently, DLBCL cases are divided into germinal center B-cell like (GCB) and activated b-cell like (ABC) subtypes based on their cellular origins in the most prevalent system, yet about 10-15% of cases are unclassified[8,9]. Therefore, finding an effective driver and prognostic factor for DLBCL is of extremely important significance for the design of a precise medical solution.

Matrix metallopeptidases (MMPs) are a group of zinc and calcium-dependent endothelins that play a crucial role in the degradation of extracellular matrix collagens. MMPs and their tissue inhibitors of metallopeptidases (TIMPs) play important roles in the pathophysiology and

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clinical manifestations of human NHL. Among them, MMP-9 and TIMP-1 are the most important members of the MMP and TIMP families, and their overexpression is associated with poor clinical outcomes in NHL patients. Studies have shown that the high invasiveness and metastasis of NHL cells may be related to the expressions of MMP-9 and MMP-2 by NHL cells, the degradation of the extracellular matrix and basement membrane, and the assistance in the tumor cell diffusion to the extracellular matrix at the primary site. However, whether MMP-9 and MMP-2 are potential targets for the treatment of NHL remains to be further studied[10].

Bcl-2 is one of the most important oncogenes in the study on apoptosis. The intracellular apoptotic pathway is mediated by the Bcl-2 family[11]. Proteins in the Bcl-2 family control cell death primarily through the direct binding, and regulate mitochondrial outer membrane permeabilization (MOMP), thus leading to the irreversible release of space proteins in the membrane, which in turn activates apoptotic processes[12,13]. The affinity and relative abundance of Bcl-2 family proteins determine the dominant roles in regulating the anti-apoptotic and pro-apoptotic Bcl-2 family proteins that regulate MOMP. Disorders in these processes not only impair normal development, but also lead to tumor development and drug resistance. Although there are a large number of reports on the expressions of MMP-9 and Bcl-2 in various malignant tumors and their relationship with the occurrence, development and invasion of the tumor, the current research is still insufficient. In this study, the expression of MMP-9 and Bcl-2 in DLBCL was studied by establishing a mouse lymphoma xenograft model, the possible related mechanisms of their influences on the occurrence, development, treatment and prognosis of DLBCL were explored, thus providing bases for further clinical application in lymphomas so as to bring greater survival benefits to patients.

Materials and Methods

Cell Culture

DLBCL cell line SU-DHL-4 cells were purchased from Cell Bank of Chinese Academy of Sciences (Wuhan, China), cultured in Roswell Park Memorial Institute (RPMI)-1640 medium containing 10% fetal bovine serum (FBS), and supplemented with 100 μg/mL streptomycin and 100 IU/mL penicillin. Cell culture flasks were placed in an incubator with 5% CO_2 and 95% humidity at 37°C.

Feeding, Processing and Grouping of Animals

Female severe combined immunodeficiency (SCID) mice aged 6-8 weeks old with uniform body weight were purchased from Shanghai SLAC Laboratory Animal Co., Ltd., Chinese Academy of Sciences (Shanghai, China). The mice were fed in an animal laminar flow room with barrier facilities at the feeding temperature of 25±2°C, the daily temperature difference of 2°C, the relative humidity of 40-60%. Natural illumination was adopted, and the feed was sterilized. One week later, 24 mice were randomly divided into the lymphoma group (n=12) and the control group (n=12). This study was approved by to the Animal Ethics Committee of Qingdao Center Hospital (Qingdao, China).

Establishment of a Mouse Lymphoma Xenograft Model

DLBCL cell line SU-DHL-4 cells were cultured, and cells in the logarithmic growth phase were taken after passage and amplification. The cell density was adjusted to 6×10^6 mL, and the cells were collected by centrifugation and resuspended using serum-free Roswell Park Memorial Institute (RPMI)-1640 medium. 0.2 mL cell suspension was injected subcutaneously into the back of mice. The long and short diameters of the tumor were measured once every 3 days, and the volume was calculated. After the volume reached 150 mm^3, the cells were used for subsequent experiments.

Real-Time Quantitative Polymerase Chain Reaction (qPCR)

Gene sequences of the target gene and β-actin were obtained by GenBank. The design software Primer-Blast on the National Center for the Biotechnology Information (NCBI) website was applied for designing primers. The primers were synthesized by Sangon Biotech Service Co., Ltd., (Shanghai, China). The specific primer sequences are as follows: Bcl-2: forward: 5'-AGGAGCAGGTGCCTACAAGA-3' and reverse: 5'-GCATTTTCCCACCACTGTCT-3', and MMP-9: forward: 5'-GCTGGACTCGGTCTTTGAGGATC-3' and reverse: 5'-TTGAGCCTCCTTGACTGATGGG-3'. The reaction system was 25 μL and the reaction conditions are as follows: pre-denaturation at 95°C for 2 min, followed by 40 cycles, including 95°C for 20 s and sequential reaction at

60°C for 60 s. After template denaturation, annealing, primer extension and other stages, deoxyribonucleic acids (DNAs) were synthesized into the single-stranded chain complementary to the template chain, and the semi-retained replication could magnify genes to be amplified millions of times. After the reaction, the melting curve was a single peak curve, indicating the specificity of qPCR products. After the amplification of genes was complete, the amplification curve reached the plateau. The relative messenger ribonucleic acid (mRNA) expression level was calculated as follows: $2^{-\Delta Ct}$ [ΔCt = Ct (β-actin)], and the fold change in different treatments was calculated using $2^{-\Delta\Delta CT}$ where ΔΔCT = ΔCT (experimental group) - ΔCT (control group).

Detection via Western Blotting

Mouse lymphoma tissues were sheared and homogenized, and then the lysate was added, followed by centrifugation at 20,000 g in ice for 30 min at 4°C. The total protein concentration was determined using the bicinchoninic acid assay (BCA) Protein Assay Kit (Pierce Biotechnology, Waltham, MA, USA). Next, the samples were subjected to sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) and membranes were transferred onto a polyvinylidene difluoride (PVDF) membrane. Next, bands were incubated with Bcl-2 monoclonal antibody, MMP-9 monoclonal antibody, primary antibody glyceraldehyde-3-phosphate dehydrogenase (GAPDH) (diluted 1:2,000, No.: sc-32233, Santa Cruz Biotechnology, CA, USA) overnight at 4°C, respectively. After that, the bands were incubated with horseradish peroxidase (HRP)-conjugated secondary antibody (Shanghai Beyotime Biotechnology Co., Ltd., Shanghai, China) after washing for 1 h, and the band images of the enhanced chemiluminescence (ECL) mixture was observed via fluorescence imaging technique.

Immunohistochemistry

Lymphoma tissues and the corresponding tumor-adjacent normal tissues were fixed with formaldehyde and embedded in paraffin. Bcl-2 monoclonal antibody (purchased from Abcam, Cambridge, USA, diluted at 1:50) and MMP-9 monoclonal antibody (purchased from Zhongshan Biotech Co., Ltd., Zhongshan, Guangdong, diluted at 1:200) were stained using immunohistochemical streptavidin-peroxidase (SP) method. Positive control: the detection showed that tissues containing test antigens could be strongly positively expressed according to the official websites of Abcam (Cambridge, USA) and Zhongshan Biotech Co., Ltd., (Zhongshan, Guangdong, China). Negative control: the primary antibody was replaced by phosphate-buffered saline (PBS) solution, and results were negative. Positive signals were yellow, brown or medium brown. Five high-magnification fields (10×40) were randomly observed under an electron microscope. The proportion of positive cells with yellow, brown or tan signals and the intensity of signals were taken as criteria for determination.

Statistical Analysis

Statistical Product and Service Solutions (SPSS) 22.0 (IBM, Armonk, NY, USA) was used for statistical analysis. All test methods were bilateral, and $p<0.05$ represented that the difference was statistically significant.

Results

Establishment of a Mouse Lymphoma Xenograft Model

Two weeks after the injection of SU-DHL-4 cells, mice gradually developed a stagnant body weight gain and showed states of emaciation, energielos, vertical hair and sluggish activity. At 10.7 (9.5±11.2) days after injection, the mice suffered from paralysis of both hindlimbs, so they had to crawl relying on the forelimbs on both sides. Their emaciation was obvious, the average body weight was decreased to (15.1±0.7) g, and they died at about 7.5 days after paralysis. After the onset, the mice were sacrificed and dissected, and the infiltration appeared in a large number of lymphoma cells in the mice bone marrow (Figure 1).

Detection of the Expression Levels of MMP-9 and Bcl-2 in Xenografts by Reverse Transcription (RT)-PCR

The mRNA levels of MMP-9 and BCL-2 in tumor tissues of lymphoma mice and control mice were quantitatively detected via RT-PCR. The results revealed that the mRNA levels of MMP-9 and Bcl-2 in the lymphoma group were significantly increased compared with those in the control group ($p<0.05$), and the differences in the mean value were 4.75 times and 2.09 times, respectively ($p<0.05$) (Figure 2).

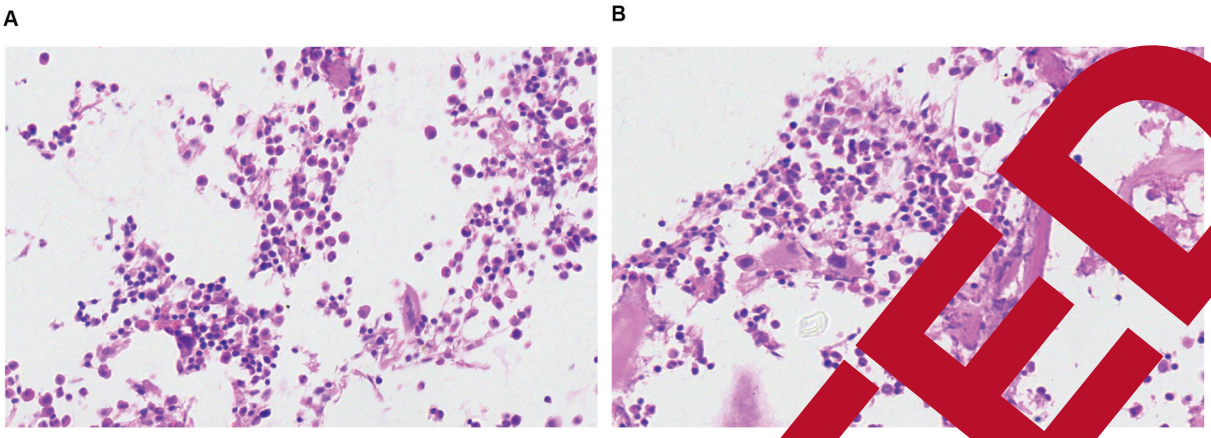

Figure 1. Infiltration degree of lymphoma cells in th ne marrow.

Detection of the Expression Levels of MMP-9 and Bcl-2 Proteins Using Immunohistochemistry

MMP-9 and Bcl-2 were all expressed in the cytoplasm, manifested as yellow, pale brown or medium brown signals. In the lymphoma group, MMP-9 was highly expressed in t raffin-embedded tissue sections in 9 o cases, with a positive rate of 75%. In the c ol group, MMP-9 was highly expressed in th raffin-embedded tissue sections in 1 out of cases, with a positive rate of 8.3% (Table I). the lymphoma group, Bcl-2 expres- sed in paraffin-embedded de se ns in 2 o ases, with a pos ve rate of 66.7%. In control group, Bcl-2 was highly expressed he paraffin- edded tissue sections in 1 of 12 cases th a positive rate of 16.7% (II). Wi xon rank-sum test demonstra ifferences in the expressions of MMP and Bcl-2 in lymphoma tissues and mor-adjacent tissues were statistically signi- ure 3).

Correlations of MMP-9 and Bcl-2 with the Body Weight of Mice

The expression levels of MMP-9 and Bcl-2 were correlated with the degree of body weight

Table I. Expression le MMP-9 p in lymphoma tissues and tumor-adjacent tissues.

	MM protein expression		
	w expression [n (%)]	High expression [n (%)]	*p*
Lymph issues	(25)	9 (75)	0.011
Tum acent ti	11 (91.7)	1 (8.3)	
N	15	7	
Yes	11	32	

Expres s of Bcl-2 protein in lymphoma tissues and tumor-adjacent tissues.

	Bcl-2 protein expression		
	Low expression [n (%)]	High expression [n (%)]	*p*
L a tissues	4 (33.3)	8 (66.7)	0.003
Tum djacent tissues	10 (83.7)	2 (16.7)	

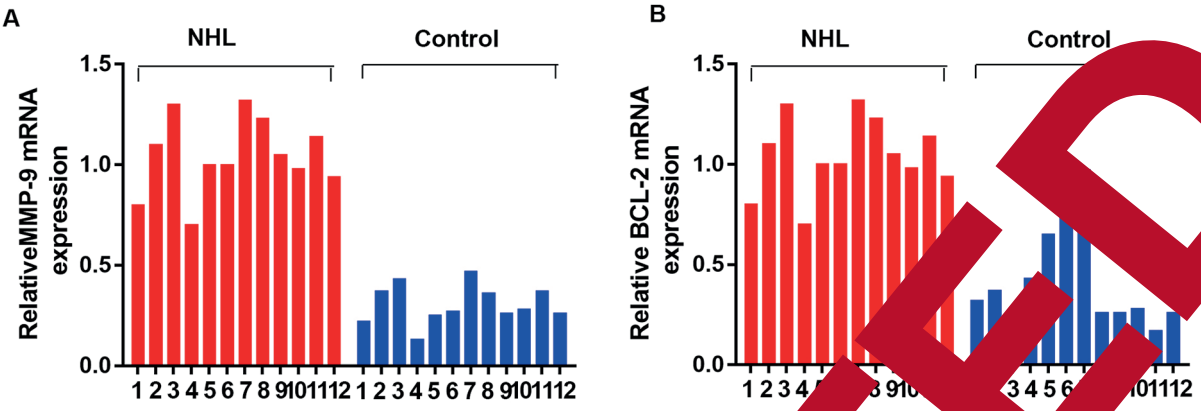

Figure 2. The expression levels of MMP-9 and Bcl-2 in the lymph[illegible]up and the co[illegible].

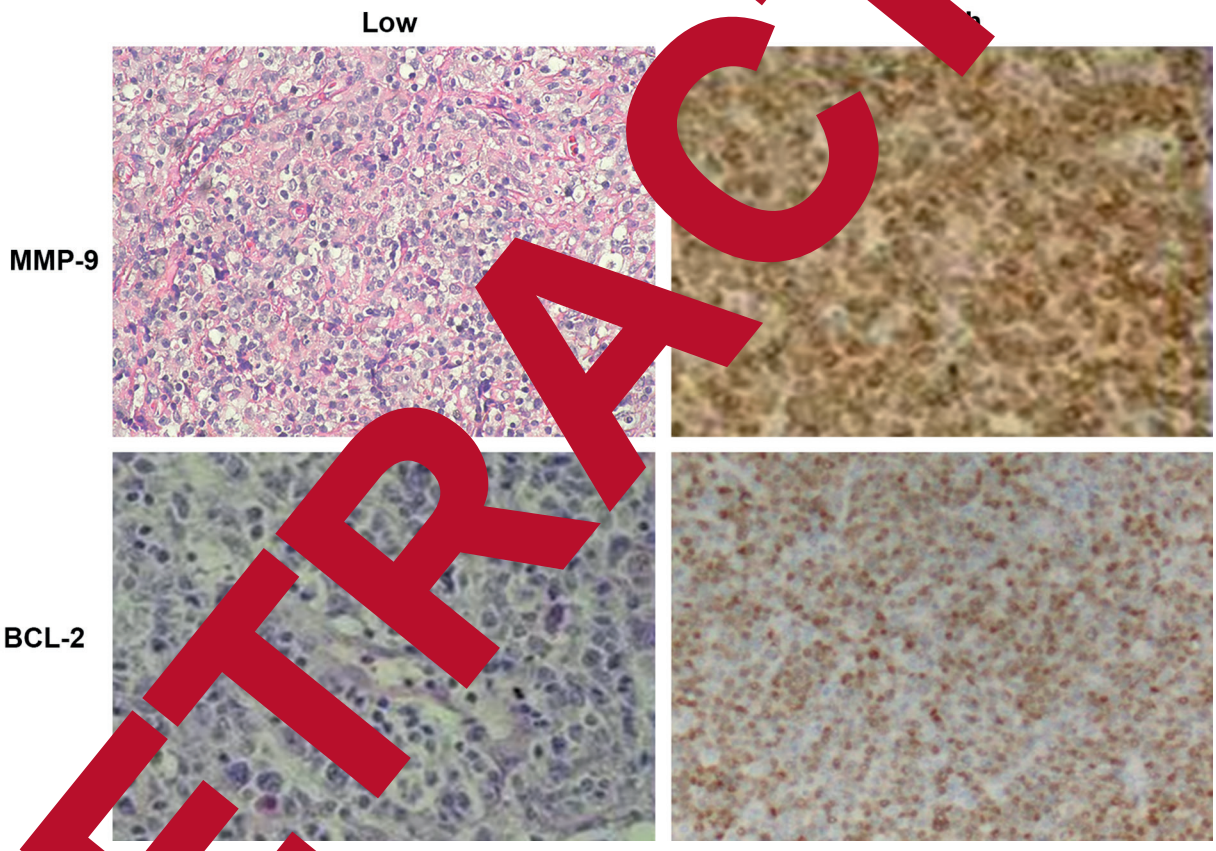

Figure 3. [illegible]w and high expressions of MMP-9 and Bcl-2 proteins in lymphoma tissues.

loss [illegible]mice. The [illegible]ody weight loss of mice with th[illegible]ions of MMP-9 and Bcl-2 was [illegible]r than [illegible]at of mice with the low expres-[illegible]ns of MMP-9 and Bcl-2. Besides, the body [illegible]t loss was the most obvious in mice at ab[illegible]9 days after the injection of tumor cells (Figure 4).

Correlation Between MMP-9 Expression and Bcl-2 Expression in the Body of Lymphoma

Spearman's rank correlation analysis showed that there was a good consistency and a positive correlation between MMP-9 expression and BCL-2 expression (r=0.472, p=0.001) (Table III).

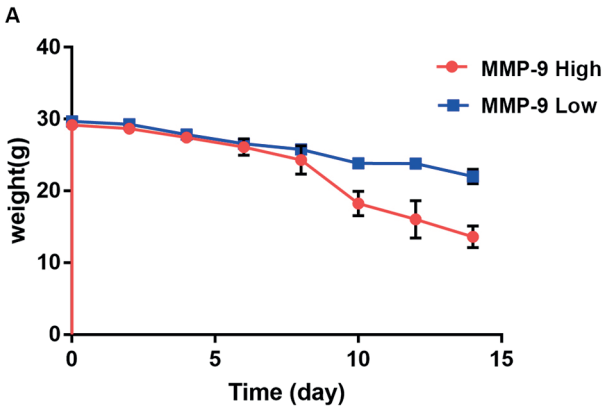

Figure 4. Correlations of the expression levels of MMP-9 and Bcl- the body weigh

Table III. Correlation between MMP-9 expression and Bcl-2 expressio phoma tissues mal tissues.

		MMP-9			
		Low expression	h expressio	*r*	*p*
Bcl-2	Low expression	7	4	0.472	0.001
	High expression	3			

Discussion

A large number of genetic mutations in DL CL are of values, including mutati of MYD8 XCR4, EZH2, CD79A, CD79 D11 [14,15]. These genes are of importa gnifica for the diagnosis of DLBCL and instru in the use of novel targeted dr rapi a family of highly co ved pendent endoproteolytic enzy that can de most of the proteins on t ement mem and extracellular mat ral, all types MMPs share the follo g cha istics: 1) a zinc atom is structur located at t ve center of enzymes; MPs are often sy sized as inactive zy ens, an an become active proteinases afte out 80 o acids at the N-terminal are clea primary ucture often includes two hig served ions, namely, the N-terprop n and the middle of the ca c stru omain, and the C-terminal stru al domai varies greatly; 4) the enzyme ac exclusively inhibited by tissue i itor o metalloproteinase (TIMP). Studies e confirmed the important roles of the MMP in solid tumors such as gastric cancer, breast er and bladder cancer, which has been considered as a new indicator for invasion, metd prognosis[16-18]. However, the value of MM in the lymphoma research field, especially in DLBCL, still needs to be further explored. It was found in this study through the establishment of a mouse lymphoma xenograft model that the expression of MMP-9 was associated with the occurrence and development of lymphomas, thus providing a theoretical basis for follow-up studies. In the development of malignant tumors, impaired apoptosis plays a central role in understanding the antagonism of Bcl-2 protein family on apoptosis and its structure. Combating a variety of pro-life members by mimicking their natural inhibitors is of great importance for the development of new anticancer drugs. Nearly 30 years ago', it was realized for the first time that anti-apoptotic Bcl-2 not only prevents malignant cells from apoptosis, but also prevents the apoptosis of normal cell lines[19-21]. This important observation has evolved from simply identifying new members of the Bcl-2 family to understanding how their biochemical reactions trigger the process of cell death and the pharmacological inhibition of anti-apoptotic Bcl-2 function in the disease[22,23]. In this report, the mouse lymphoma xenograft model revealed that the expression of Bcl-2 was closely related to the development of lymphomas and was consistent with the expression of MMP-9. This will lay the

foundation for further exploring how the two factors interact and participate in the occurrence and development of DLBCL.

Conclusions

The discovery and exploration of the driving factors and prognostic factors of lymphomas is the hotspot and difficulty of the current study. The results of this study will provide evidence for follow-up studies in this field and provide new insights into the molecular biology of NHL. MMP-9 and Bcl-2, as new targets for the treatment and efficacy prediction of DLBCL, have potential clinical significance.

Conflict of Interest

The Authors declare that they have no conflict of interest.

Funding

This work was funded by the program "The impact of pre-transplantation PET/CT on non-Hodgkin lym[illegible] patients undergoing autologous stem cell transpl[illegible] (2013WS0022).

Availability of data and materi[illegible]

The datasets used and/or analyzed d[illegible]rent study are available from the correspond[illegible]uthor [illegible]asonable request.

Authors' contribu[illegible]s

CS wrote the manu[illegible]d helped with [illegible]ture. XZ feed and treated t[illegible]established mo[illegible] lymphoma xenograft m[illegible]LS pe[illegible]d qPCR. LW was responsible for Wes[illegible]n blotting. A[illegible]s read and approved the final m[illegible]ript.

Ethi[illegible]or[illegible] and c[illegible]ent to participate

The study [illegible]proved [illegible]e Ethics Committee of Qing[illegible]nter H[illegible](Q[illegible]o, China).

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