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MTMR2 promotes the progression of NK/T cell lymphoma by targeting JAK1

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Abstract. – OBJECTIVE: The aim of this study was to investigate the expression characteristics of MTMR2 in NK/T cell lymphoma (NKTCL), and to further study its relationship with clinical parameters and the prognosis of patients with NKTCL. In addition, the potential mechanisms of MTMR2 promoting the progression of NKTCL was further explored.

MATERIALS AND METHODS: Quantitative Real Time-Polymerase Chain Reaction (qRT-PCR) was performed to examine MTMR2 level in peripheral blood of 45 patients with NK/T-cell lymphoma and 45 healthy volunteers. The interplay between MTMR2 expression and clinical indicators, as well as the prognosis of patients with NK/T-cell lymphoma was analyzed. Meanwhile, MTMR2 expression in NKTCL cell lines was verified by qRT-PCR. Subsequently, MTMR2 knockdown and the overexpression models were constructed using lentivirus in NKTCL cell lines, including SNK-6 and KHYG-1. Transwell invasion and cell wound healing assays were applied to analyze the effect of MTMR2 on the biological function of NKTCL cells. Finally, an in-depth study of the relationship between MTMR2 and JAK1 was conducted to explore the underlying mechanism.

RESULTS: QRT-PCR results showed that the expression level of MTMR2 in the serum of patients with NKTCL was remarkably higher than that of healthy volunteers, and the difference was statistically significant ($p<0.05$). Compared with patients with low expression of MTMR2, patients with high expression of MTMR2 exhibited significantly higher incidence of distant metastasis and lower overall survival rate ($p<0.05$). The metastasis ability of NKTCL SNK-6 cells was remarkably attenuated in MTMR2 knockdown group when compared with the negative control sh-NC group ($p<0.05$). Meanwhile, the metastatic ability of NKTCL KHYG-1 cells in MTMR2 overexpressing group was remarkably enhanced when compared with the control NC group ($p<0.05$). The Luciferase reporter gene assay confirmed that MTMR2 could target JAK1, thereby jointly regulating the malignant progression of NKTCL. In addition, cell recovery experiment verified that JAK1 could partially reverse the enhanced metastatic ability of NKTCL cells induced by the overexpression of MTMR2.

CONCLUSIONS: MTMR2 was highly expressed in NKTCL serum samples and cell lines, leading to high risk of distant metastasis and poor prognosis. In addition, MTMR2 might promote the malignant progression of NKTCL by regulating JAK1.

Key Words:
MTMR2, JAK1, NKTCL, Malignant progression.

Introduction

In recent years, the incidence of malignant lymphoma has been increasing year by year, which has become one of the major tumors seriously threatening human health and life[1-3]. NK/T-cell lymphoma is a type of non-Hodgkin lymphoma (NHL). It is a highly invasive type with corresponding clinical characteristics, such as rapid progression, short survival period, and poor prognosis[4,5]. So far, no standard first-line treatment has been developed for Natural Killer/T Cell Lymphoma (NKTCL) worldwide[5,6]. Currently, great advances have been made in the treatment of NK/T-cell lymphoma. For example, the use of Pegaspargase and gemcitabine-based regimens in the treatment of patients with advanced NK/T-cell lymphoma can receive an overall response rate of 87.5%, with small side effects. However, many patients become drug-resistant due to multi-drug resistance, resulting in poor efficacy[5-7]. The molecular pathogenesis of NKTCL has been explored for many years, however, it is still unclear[5-7].

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Abnormal expression of certain key factors and abnormal activation of signaling pathways are involved in the development of pathological types of lymphoma. Therefore, further in-depth study of key molecules and signaling pathways, exploration of the pathogenesis of NK/T-cell lymphoma, and the search for more effective targeted therapies can contribute to the advancement of the efficacy of NK/T-cell lymphoma chemotherapy and the improvement of patients' prognosis[8-11].

Myotubularin-related protein-2 (MTMR2) is a member of the muscle microtubule protein family. It encodes a tyrosine phosphatase and can also encode a tyrosine phosphatase. Current studies have reported that MTMR2 dephosphorylates the substrates PI-3-P and PI-3,5-P2 to phospholipid inositol and PI-S-P, respectively. Meanwhile, it plays an important role in the AKT pathway. MTMR2 overexpression inhibits the degradation of epidermal growth factor receptor (EGFR), thereby promoting sustained activation of AKT[12-14]. Through these functions, it is engaged in many life activities, such as signal transduction, cell cycle regulation, apoptosis, cell stress, etc. Therefore, it is of great significance to further study the function of MTMR2 in NK/T cell lymphoma and the underlying molecular mechanism[13-15]. Here, to explore how MTMR2 promoted the malignant progression of NKTCL, bioinformatics analysis was performed. The results showed that MTMR2 could interact with Janus Kinase 1 (JAK1) to jointly affect the occurrence and development of NKTCL. JAKs kinase mainly participates in the downstream signal transduction of cytokines and regulates gene expression through the JAK/STAT signaling pathway[16,17]. When a cytokine or growth factor binds to a receptor, dimerization of the receptor cytoplasmic domain binds to JAK kinase. Meanwhile, the tyrosine site of the receptor cytoplasmic region is phosphorylated by activation of JAK kinase, eventually recruiting STAT protein and phosphorylation. Next, two homologous or heterologous phosphorylated STAT proteins bind to form a dimer, to transport to the nucleus, and bind to DNA to regulate the target gene expression[18]. JAK1 has been confirmed to be involved in cell proliferation, differentiation, and immune regulation. Furthermore, abnormal activation of the JAK/STAT pathway has been found in many malignancies[19,20].

Based on the above characteristics, the aim of this study was to prove whether MTMR2 exerted the potential to be a serological marker for early diagnosis of tumors and whether it could provide a possible option for target gene therapy of tumors. In addition, we wondered whether MTMR2 was involved in the malignant progression of NK-TCL cells *via* targeting JAK1.

Patients and Methods

Patients and NK/T-Cell Lymphoma Samples

Peripheral blood of 45 patients with NK/T-cell lymphoma and 45 healthy volunteers were collected. No patient received any radiotherapy or chemotherapy before surgery. Pathological typing and staging criteria for NK/T-cell lymphoma were performed according to the Union for International Cancer Control (UICC, Geneva, Switzerland) lymphoma staging criteria. Informed consent was obtained from patients and their families before the study. Our research has been approved by the Ethics Oversight Committee of of The Second Affiliated Hospital of Xi'an Jiaotong University.

Cell Lines and Reagents

Human NK/T-cell lymphoma cell lines (KHYG-1, NK-92, HANK-1, SNK-1, SNK-6), and normal NK cell line were purchased from American Type Culture Collection (ATCC; Manassas, VA, USA). F-12k medium, 1640 medium, and fetal bovine serum (FBS) were purchased from American Life Technologies (Gaithersburg, MD, USA). All cells were cultured in F-12k medium and 1640 medium containing 10% fetal bovine serum in a 37° C, 5% CO_2 incubator.

Cell Transfection

The control group (NC or sh-NC) and MTMR2 (MTMR2 or sh-MTMR2) containing the MTMR2 lentiviral sequence were purchased from Shanghai Jima Company (Shanghai, China). The cells were first seeded into 6-well plates and grown to a density of 40%. Lentiviral transfection was performed according to the manufacturer's instructions. After 48 h, the transfected cells were collected for quantitative Real Time-Polymerase Chain Reaction (qRT-PCR), Western Blot analysis, and cell function experiments.

Transwell Cell Migration and Invasion Assay

After 48 h of transfection, the cells were trypsinized and resuspended in the serum-free medium. The density of cells was adjusted to 2.0×10^5/

ml. Transwell chambers containing Matrigel and no Matrigel were placed into 24-well plates. 200 μl of cell suspension was added in the upper chamber. Meanwhile, 500 μl of medium containing 10% FBS was added to the lower chamber. After incubation in a 37° C incubator for 48 hours, the chamber was removed. Then, the cells were fixed with 4% paraformaldehyde for 30 minutes and stained with crystal violet for 15 minutes. Subsequently, the cells were washed with PBS, and the inner surface of the basement membrane of the chamber was carefully cleaned to remove the inner layer cells. Perforated cells stained in the outer layer of the basement membrane of the chamber were finally observed under the microscope. 5 fields of view were randomly selected for each sample.

Cell Wound Healing

Transfected cells for 48 hours were digested, centrifuged, and re-suspended in the medium without FBS. Cell density was adjusted to 5 x 10^5 cells/mL. The density of plated cells was determined according to the size of cells (the majority of the number of cells plated was set to 50,000 cells/well). The confluency of the cells reached 90% or more the next day. After stroke, the cells were rinsed gently with phosphate-buffered saline (PBS) for 2-3 times and observed again after 24 hours of incubation with low-concentration serum medium (such as 1% FBS).

Quantitative Real Time-Polymerase Chain Reaction (qRT-PCR)

Total RNA was extracted from NKTCL cell lines and tissues using TRIzol reagent (Invitrogen, Carlsbad, CA, USA). Extracted RNA was then reversely transcribed into cDNA using PrimeScript RT Reagent (TaKaRa, Otsu, Shiga, Japan). QRT-PCR reactions were performed using SYBR® Premix Ex Taq™ (TaKaRa, Otsu, Shiga, Japan), and StepOne Plus Real-time PCR system (Applied Biosystems, Foster City, CA, USA). Primers used for qPCR reaction were as follows: MTMR2: forward: 5'-TGAGCCCCAGAACTGAGAAG-3', reverse: 5'-GCGCTACACTGACATTGGAG-3'; JAK1: forward: 5'-TGAGCCCCAGAACTGAGAAG-3', reverse: 5'-GCGCTACACTGACATTGGAG-3'; β-actin: forward: 5'-CCTGGCACCCAGCACAAT-3', reverse: 5'-TGCCGTAGGTGTCCCTTTG-3'. Data analysis was performed using ABI Step One software, and the relative expression levels of mRNAs were calculated using the $2^{-\Delta\Delta Ct}$ method.

Western Blot

Transfected cells were lysed using cell lysis buffer, shaken on ice for 30 minutes, followed by centrifugation at 14,000 x g for 15 minutes at 4°C. Total protein concentration was determined by the protein assay kit (Pierce, Rockford, IL, USA). Extracted proteins were separated by 10% sodium dodecyl sulphate-polyacrylamide gel electrophoresis (SDS-PAGE) gel and transferred onto polyvinylidene difluoride membranes (Millipore, Billerica, MA, USA). Western blot analysis was performed according to standard procedures. Primary antibodies against MTMR2 and glyceraldehyde 3-phosphate dehydrogenase (GAPDH) and the corresponding secondary antibodies were all purchased from Cell Signaling Technology (Danvers, MA, USA).

Dual-Luciferase Reporter Assay

HEK293T cells were seeded into 24-well plates and co-transfected with JAK1 mimetic/NC and pMIR Luciferase reporter plasmids. Before, the plasmid was paired with the MTMR2 mutation binding site 3'UTR by insertion of other wild-type MTMR2. The mutation binding site was then constructed into pMIR. Subsequently, the plasmid was transfected into cells according to the manufacturer's protocol of Lipofectamine 2000 (Thermo Fisher Scientific, Waltham, MA, USA). After 48 hours of transfection, the reporter Luciferase activity was normalized to control the firefly Luciferase activity using a Dual-Luciferase reporter assay system (Promega, Madison, WI, USA).

Statistical Analysis

Statistical analysis was performed using GraphPad Prism 5 V5.01 software (La Jolla, CA, USA). The differences between the two groups were analyzed by using the Student's *t*-test. One-way ANOVA was applied to compare the differences among different groups, followed by post-hoc test (Least Significant Difference). Independent experiments were repeated for at least three times. Experimental data were expressed as mean ± standard deviation (± s). There were three levels of $p<0.05$, $p<0.01$ and $p<0.001$ at the significance level, and $p<0.05$ was considered statistically significant.

Results

MTMR2 Was Highly Expressed in Serum of NK/T-Cell Lymphoma Patients

To determine the role of MTMR2 in NK/T-cell lymphoma, 45 patients with NK/T-cell lymphoma and healthy volunteers were enrolled in this study. The expression of MTMR2 in the serum of these subjects were examined by qRT-PCR. As a result, MTMR2 expression was significantly elevated in serum of NK/T-cell lymphoma patients when compared with healthy volunteers (Figure 1A), suggesting that MTMR2 might act as a tumor-promoting gene in NK/T-cell lymphoma.

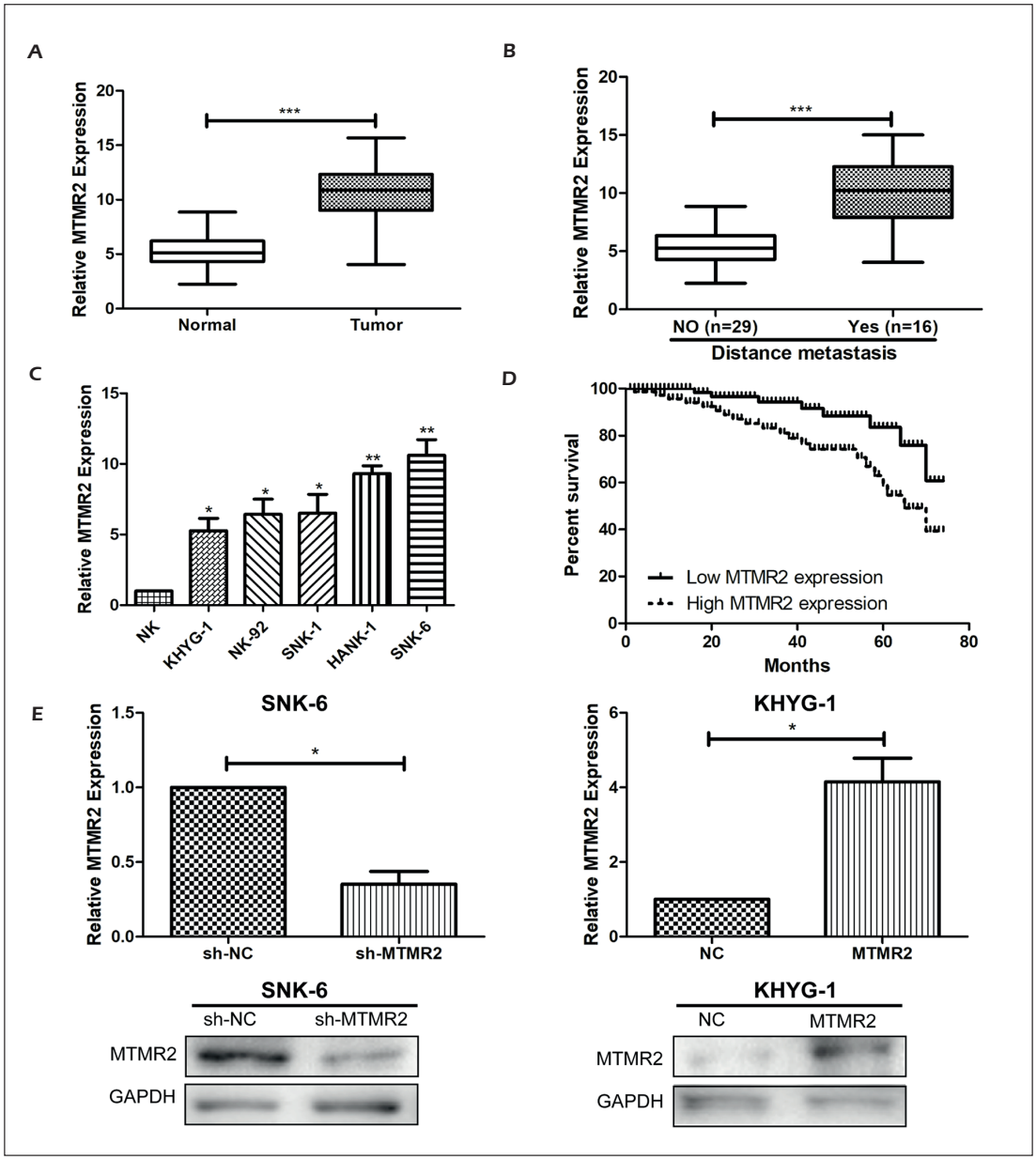

Figure 1. MTMR2 is highly expressed in the serum samples of NK/T cell lymphoma patients and in cell lines. **A,** QRT-PCR was used to detect the differential expression of MTMR2 in peripheral blood of patients with NK/T-cell lymphoma and healthy volunteers. **B,** QRT-PCR was used to detect the differential expression of MTMR2 in peripheral blood of patients with NK/T cell lymphoma. **C,** QRT-PCR was used to detect the expression level of MTMR2 in NK/T cell lymphoma cell lines. **D,** Kaplan Meier survival curve of patients with NK/T cell lymphoma based on MTMR2 expression was shown. The prognosis of patients with high expression was significantly worse than that of those with low expression. **E,** QRT-PCR and Western Blotting demonstrated the expression efficiency of MTMR2 after transfection of MTMR2 overexpression/knockdown vector in NK/T cell lymphoma SNK-6 and KHYG-1 cell lines. Data were expressed as mean ± SD, *$p<0.05$, **$p<0.01$, ***$p<0.001$.

In addition, we found that MTMR2 expression was significantly higher in patients with distant metastasis than those without distant metastasis (Figure 1B). Meanwhile, the expression level of MTMR2 in NKTCL cell lines was remarkably higher than that of normal lymphocytes as well, especially in SNK-6 and KHYG-1 cell lines. Therefore, these two cell lines were selected for subsequent experiments (Figure 1C).

MTMR2 Expression Was Correlated with Clinical Stage and Overall Survival of NK/T-Cell Lymphoma Patients

According to qRT-PCR results, all patients were divided into two groups, including high and low expression groups. The number of patients in each group was counted. Chi-square test was performed to analyze the interplay between MTMR2 expression and age, gender, pathological stage, and the condition of distant metastasis of NKTCL patients. As shown in Table I, high expression of MTMR2 was positively correlated with the incidence of distant metastasis of NKTCL patients. To further explore the relationship between MTMR2 level and prognosis, the Kaplan-Meier survival curve was plotted. The results demonstrated that that high expression of MTMR2 was remarkably associated with poor prognosis of NK/T-cell lymphoma. Higher level of MTMR2 indicated significantly worse prognosis ($p<0.05$; Figure 1D).

MTMR2 Promoted Invasiveness and Migration Abilities of NK/T-Cell Lymphoma Cells

To explore the effect of MTMR2 on the invasiveness and migration ability of NKTCL cells, MTMR2 overexpression and knockdown models were successfully constructed, respectively. Transfection efficiency was verified by qRT-PCR and Western Blot (Figure 1E). The impact of MTMR2 on invasiveness and migration ability of NKTCL cells (SNK-6 and KHYG-1 cell lines) was analyzed by transwell and cell wound healing assays. The results revealed that in SNK-6 cell line, the cell metastatic ability of MTMR2 knockdown group decreased remarkably when compared with negative control sh-NC group. Conversely, in KHYG-1 cell line, cell metastatic ability of MTMR2 overexpression group was remarkably enhanced when compared with control NC group (Figure 2A, 2B).

Knockdown of MTMR2 Decreased the Expression of JAK1

QRT-PCR showed that in SNK-6 cell line, the mRNA expression level of JAK1 was remarkably downregulated after overexpression of MTMR2. However, in KHYG-1 cell line, the mRNA expression of JAK1 was remarkably upregulated after silencing MTMR2 (Figure 3A). In addition, qRT-PCR results revealed that the expression of JAK1 in the serum of patients with NKTCL was remarkably lower than that of healthy volunteers, and the difference was statistically significant (Figure 3B). Similarly, JAK1 was lowly expressed in NKTCL cell line when compared with normal cell line, and the difference was statistically significant (Figure 3C). Luciferase reporter gene assay demonstrated that MTMR2 could directly bind to JAK1 (Figure 3D, 3E). Furthermore, qRT-PCR results indicated that the mRNA expression of MTMR2 was negatively correlated with JAK1 expression in peripheral blood of NKTCL patients (Figure 3F).

Table I. Association of MTMR2 expression with clinicopathologic characteristics of NK/T-cell lymphoma.

Parameters	No. of cases	MTMR2 expression		*p*-value
		Low (%)	High (%)	
Age (years)				0.500
< 60	20	12	8	
≥ 60	25	13	12	
Gender				0.671
Male	15	9	6	
Female	30	16	14	
T stage				0.894
T1-T2	22	12	10	
T3-T4	23	13	10	
Distance metastasis				0.015
No	29	20	9	
Yes	16	5	11	

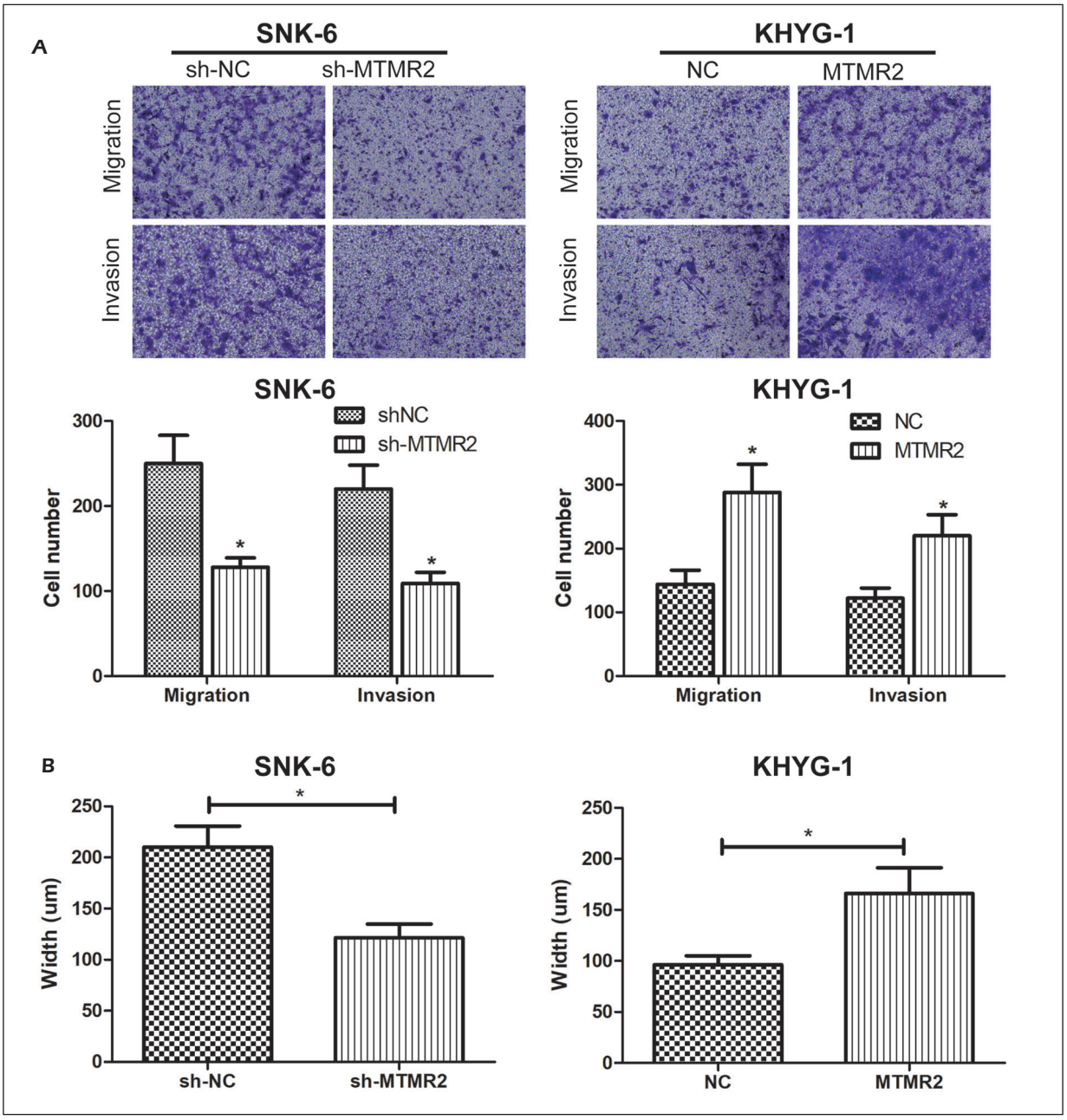

Figure 2. Overexpression/silencing of MTMR2 promotes/inhibits NK/T cell lymphoma cell metastatic ability. **A,** Transwell invasion and migration assay detected the invasion and migration of NK/T cell lymphoma cells after transfection of MTMR2 in SNK-6 and KHYG-1 cell lines (magnification: 40×). **B,** Cell scratch assay detected the ability of NK/T cell lymphoma cells to crawl after transfection of MTMR2 in SNK-6 and KHYG-1 cell lines. Data were expressed as mean ± SD, *$p<0.05$.

JAK1 Reversed MTMR2 Induced Carcinogenesis

To further explore the interaction between MTMR2 and JAK1 in NKTCL cells, we first constructed MTMR2 and JAK1 co-transfected cell models. Transfection efficiency was verified by qRT-PCR (Figure 4A). Subsequently, the migration ability of cells was examined using transwell and cell wound healing assays. The results illustrated that silencing JAK1 reversed the metastasis ability of NKTCL SNK-6 cells in MTMR2 knockdown group. Meanwhile, in KHYG-1 cell line, the overexpression of JAK1 reversed the enhanced metastatic ability induced by MTMR2 overexpression (Figure 4B, 4C).

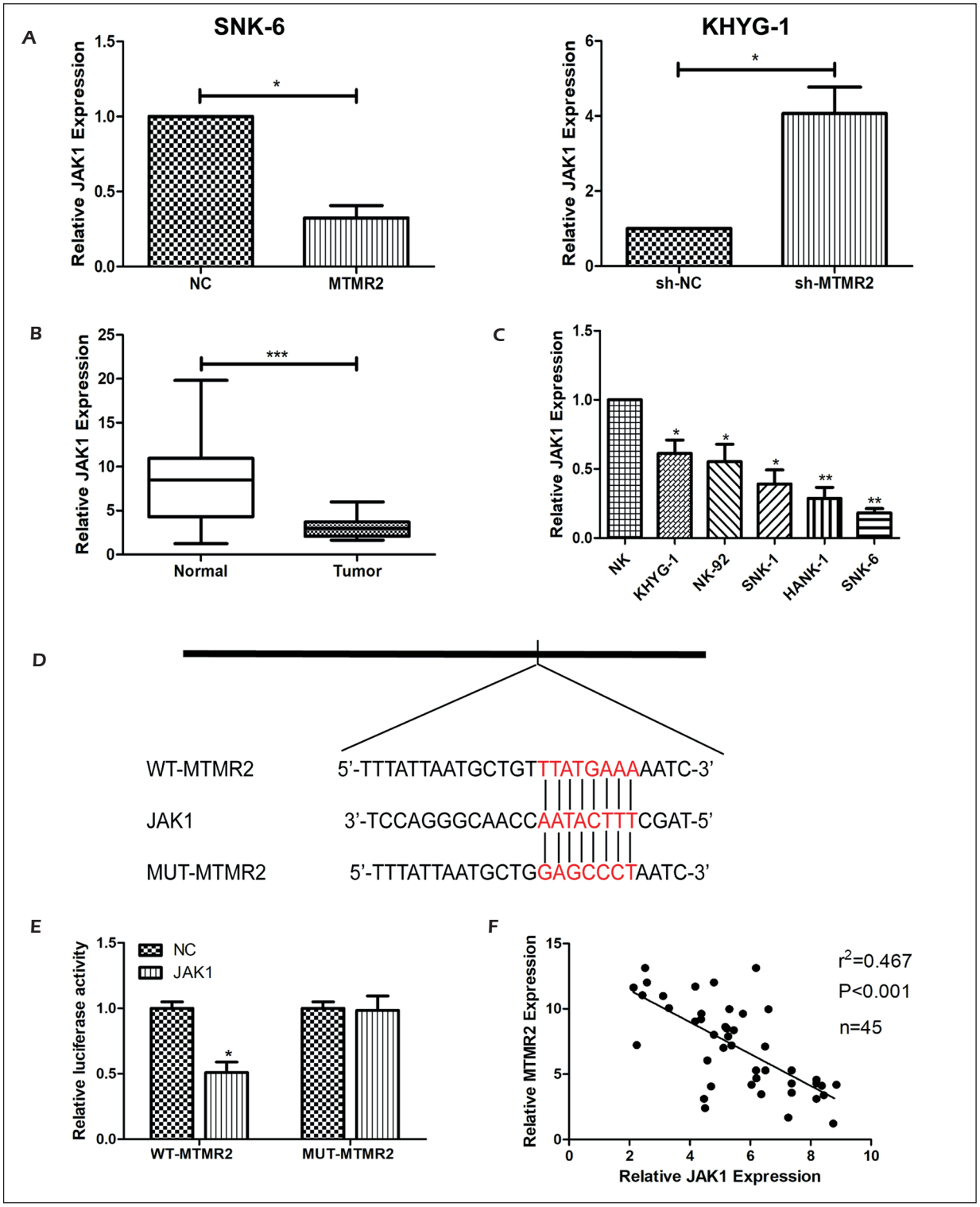

Figure 3. MTMR2 can targeted bind to JAK1. **A,** QRT-PCR verified the mRNA expression of JAK1 after transfection of MTMR2 overexpression and knockdown vectors in SNK-6 and KHYG-1 cell lines. **B,** QRT-PCR was used to detect the difference in JAK1 expression in serum of NK/T cell lymphoma patients and healthy volunteers. **C,** QRT-PCR was used to detect the expression level of JAK1 in NK/T cell lymphoma cell lines. **D,** The predicted binding site of MTMR2 and JAK1 was shown. **E,** Dual-Luciferase reporter gene assay demonstrated the direct targeting of MTMR2 and JAK1. **F,** QRT-PCR was used to detect the difference in the expression of MTMR2 and JAK1 in serum of NK/T cell lymphoma. Data were expressed as mean ± SD, *p<0.05, **p<0.01, ***p<0.001.

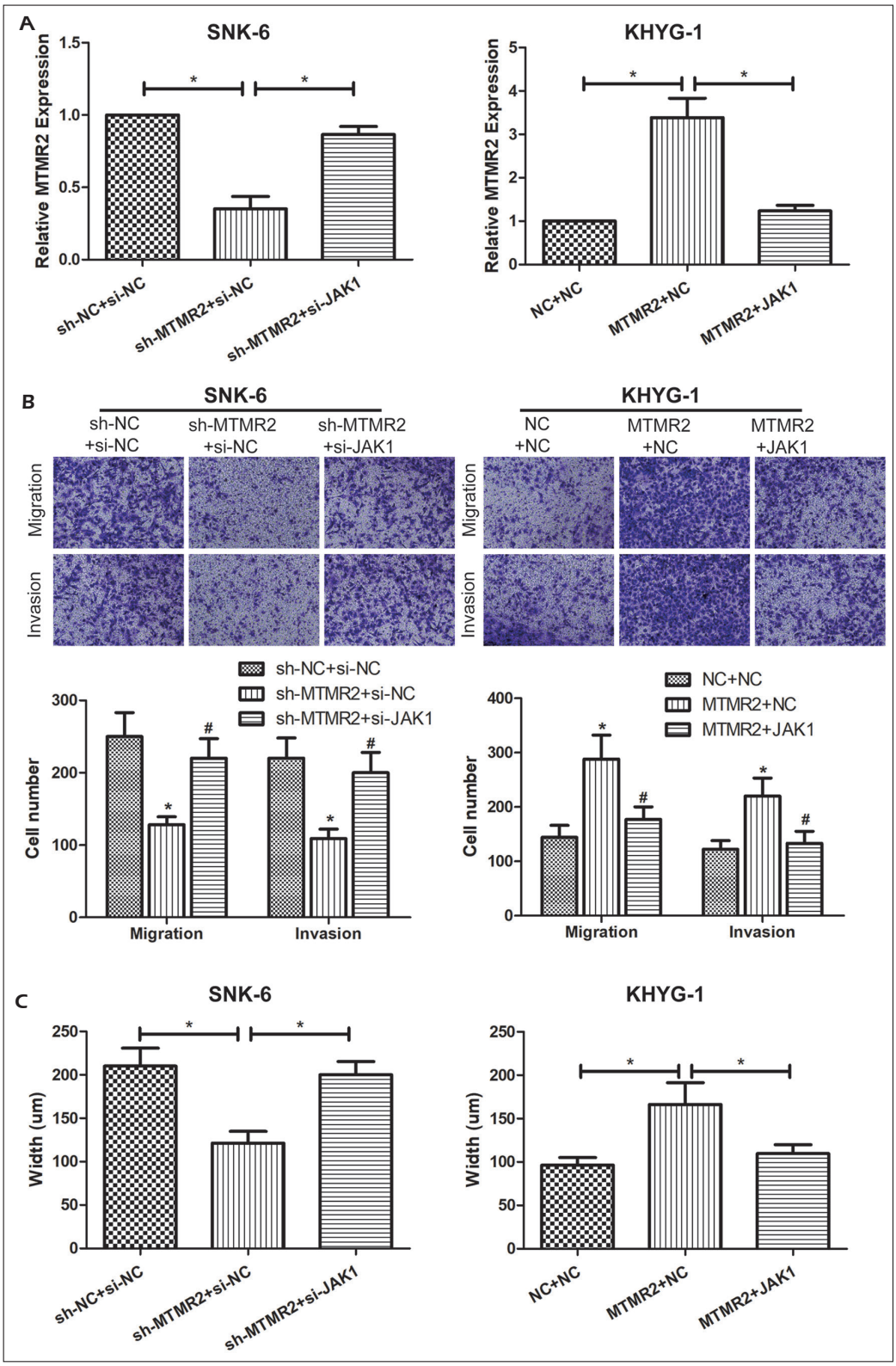

Figure 4. MTMR2 regulates the expression of JAK1 in NK/T cell lymphoma cell lines. **A,** The expression level of MTMR2 in SNK-6 and KHYG-1 cell lines co-transfected with MTMR2 and JAK1 was detected by qRT-PCR. **B,** Transwell invasion and migration assays detected the invasion and migration of NK/T cell lymphoma cells (SNK-6 and KHYG-1) after co-transfection of MTMR2 and JAK1 (magnification: 40×). **C,** Cell scratch assay detected the migration ability of NK/T cell lymphoma cells (SNK-6 and KHYG-1) after co-transfection of MTMR2 and JAK1. Data were expressed as mean ± SD, $*^{\#}p<0.05$.

Discussion

Natural Killer/T Cell Lymphoma (NKTCL) is a kind of non-Hodgkin Lymphoma with high invasive ability, special morphology, immune phenotype, and biological behavior. The clinical characteristics of NKTCL includes rapid progression, short survival period, and poor prognosis[1-4]. In China, it accounts for 5%-10% of all lymphomas, ranking first in the incidence of T-cell lymphomas[3-5]. The 5-year survival rate of patients with NKTC is 32%, with a median survival of 8 months[2-5]. Currently, there is no standard optimal treatment scheme for NKTCL. Meanwhile, the molecular pathogenesis of NKTCL is still unclear[4,5]. Some traditional views hold that the activation of proto-oncogenes and the inactivation of tumor suppressor genes are closely related to the occurrence of tumors[3,6,7]. In recent years, many investigations[21,22] have suggested a new view that the related products of proto-oncogenes and tumor suppressor genes are members of signal transduction involved in cell proliferation and differentiation. Moreover, the occurrence of cell canceration is due to abnormal signal transduction, leading to abnormal cell proliferation and differentiation. Previous researches[12,15,17,20] on multiple gene expression profiles have shown that the activation of MTMR2, JAK1, and other factors can promote the occurrence and development of malignant tumors. Some studies[5,10] have shown that abnormal expression and activation of certain key signaling pathway factors can lead to the pathological occurrence and development of a variety of lymphomas. All these findings suggest that the further exploration of NKTCL signaling pathways and key molecules may be a potential direction to improve the efficacy of targeted therapy and the prognosis of patients.

Mutations in MTMR2 gene can lead to progressive fat osteomyelitis, which is an autosomal recessive demyelination neuropathy. It has also been reported[12] that this protein may be associated with DNA damage repair. The 14-3-3 protein family is widely expressed and highly conserved in eukaryotic cells. It binds to target proteins by recognizing phosphorylated threonine/serine[12-14]. At present, abnormal expression of MTMR2 has been found[14,15] in a variety of tumors with different organs in the body, which may be related to malignant progression of tumors. In this study, a large number of clinical NKTCL specimens were collected for the first time to explore the role of MTMR2 in the development of NKTCL. MTMR2 expression level at the transcription level in fresh NKTCL surgical specimens and NKTCL cell lines was detected. Our results found that MTMR2 level in the serum of NKTCL patients was significantly higher than that of healthy volunteers. At the same time, MTMR2 expression in NKTCL cell lines remarkably increased when compared with normal cells. Therefore, we concluded that MTMR2 played an extremely important role in the occurrence and development of NKTCL. To verify the role of MTMR2 in NKTCL cell function, we performed transwell invasion and cell scratch assays after knockdown or overexpression of MTMR2. The results indicated that MTMR2 promoted the metastatic ability of NK/T cell lymphoma, playing a significant role in NK/T cell lymphoma. However, its specific molecular mechanism still remained elusive.

Many members of the type I and II cytokine receptor families do not have kinase catalytic activity. They need to form complexes with specific JAK family members, depending on their tyrosine kinase activity to activate the downstream signals. When a cytokine or growth factor binds to a receptor, the cytoplasmic region of the receptor is dimerized and binds to JAK kinase. Activated JAK kinase phosphorylates the tyrosine site in the cytoplasmic region of the receptor, forming an anchor site connecting the effector protein containing SH2 domain downstream[16-18]. Target genes involved in the regulation of the JAK/STAT pathway include those engaged in cell proliferation, differentiation, and immune regulation, such as MYC, cyclinD1, survivin, and Bcl2. Therefore, abnormal activation of the JAK/STAT pathway has been considered an important mechanism for the occurrence of some malignant tumors[19,20]. In this study, to prove whether MTMR2 promoted the development of NKTCL by regulating JAK1, qRT-PCR was used to detect the changes in JAK1 expression after MTMR2 overexpression/knockdown. The results demonstrated that the mRNA expression level of JAK1 was remarkably upregulated after MTMR2 knockdown. This suggested that MTMR2 played a pivotal role in promoting malignant progression in NKTCL *via* regulating JAK1. Furthermore, Luciferase reporter gene assay suggested that MTMR2 and JAK1 could be directly targeted. Subsequent experiments demonstrated that JAK1 could reverse the relevant cellular functional changes induced by MTMR2. With the deepening of research, further understanding of the biological functions

of genes and their roles in the process of tumor development would be more conducive to the diagnosis, treatment and prognosis evaluation of tumors.

Conclusions

In summary, MTMR2 was highly expressed in NKTCL and was closely correlated with the incidence of distant metastasis and poor prognosis of NKTCL patients. In addition, MTMR2 might promote the metastasis ability of NKTCL *via* regulating JAK1.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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