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LINC00665 facilitates the progression of osteosarcoma *via* sponging miR-3619-5p

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Abstract. – **OBJECTIVE: Long non-coding RNAs (lncRNAs) play vital roles in the pathogenesis and development of multiple cancers, including osteosarcoma (OS). The present study aims to investigate the role of LINC00665 in OS progression.**

PATIENTS AND METHODS: The expression levels of LINC00665 and miR-3619 were assessed by RT-qPCR. The correlation between LINC00665 and miR-3619 expression was evaluated by Pearson's correlation analysis. The interaction between LINC00665 and miR-3619 was predicted by starBase, which was further confirmed by Luciferase reporter assay and RIP assay. The viability, invasion, and migration of OS cells were analyzed by CCK-8 and transwell assays.

RESULTS: LINC00665 expression was upregulated in OS tissues and cell lines, and the high level of LINC00665 was associated with poor prognosis in OS. Moreover, LINC00665 knockdown attenuated the viability, invasion, and migration of OS cells. In addition, miR-3619 was demonstrated to be a target of LINC00665. Overexpression of miR-3619 inhibited OS progression, while this effect was abolished by the upregulation of LINC00665.

CONCLUSIONS: We demonstrated that LINC 00665 accelerated OS development by targeting miR-3619. These findings might provide potential treatment strategies for patients with OS.

Key Words:
LINC00665, MiR-3619-5p, Osteosarcoma.

Introduction

Osteosarcoma (OS) is one of the most common malignant bone tumor in adolescents and young adults[1-3]. Although great progress has been made in the treatment of OS patients, the overall survival rate is still dissatisfactory[4,5]. Until now, the pathomechanism underlying the tumorigenesis and development of OS has not been well studied. Therefore, it is necessary to explore the pathogenesis of OS to improve the prognosis of OS patients. Long non-coding RNAs (lncRNAs) are transcripts longer than 200 nucleotides in length, without the protein-coding ability[6,7]. Growing evidence indicates that lncRNAs are dysregulated in various tumors, such as cervical cancer[8], breast cancer[9], and colorectal cancer[10]. Multiple lncRNAs have also been determined to play a vital role in OS development. LncRNA ASB16-AS1 promoted the development of OS by competitively binding with miR-760 and upregulating HDGF expression in OS[11]

LncRNA HULC sponging miR-372 facilitated OS progression by upregulating HMGB1[12]. LncRNA GAS6-AS2 promoted the tumorigenesis of OS by regulating miR-934/BCAT1 axis[13] (Albany NY. However, the biological role of LINC00665 in OS remains unknown.

MicroRNAs (miRNAs) are another type of endogenous non-coding RNAs (ncRNAs) with a length of 22-25 nucleotides[14-16]. MiRNA has been reported to be involved in the occurrence and development of OS[17]. Wan et al[18] showed that miR-181b promoted OS cell proliferation through inhibiting p53 expression. Ma et al[19] indicated that miRNA-29c suppressed OS cell proliferation by targeting PIK3R3. Yu et al[20] demonstrated that miRNA-744 facilitated the proliferation of OS cells by regulating PTEN. Shekhar et al[21] showed that miR-424 and miR-449 inhibited OS by regulating Cyclin A2. Up to date, researches on miR-3619 in OS are rarely reported.

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In this study, we assessed LINC00665 expression in OS tissues and cells. In addition, we explored the function of LINC00665 in the development of OS cells. To further observe the molecular mechanism of LINC00665 in OS, the downstream target of LINC00665 was predicted. Finally, the effect of the target miRNA on LINC00665 inducing OS cell progression was investigated.

Patients and Methods

Tissue Samples

Thirty-three paired osteosarcoma tissues and adjacent normal bone tissues were obtained from patients in Shuyang Hospital Affiliated to Xuzhou Medical University. All tissues were affirmed by pathological examinations. Inclusion criteria: (1) patients were diagnosed with osteosarcoma, (2) patients understood and agreed to cooperate with the researcher. Exclusion criteria: (1) patients with other malignancies, (2) patients who do not agree to work with researchers, (3) patients who have been treated before admission. This study was approved by the Ethics Committee of the Shuyang Hospital Affiliated to Xuzhou Medical University. All patients provided informed consent for their participation in the study.

Cell Lines

The human OS cell lines (143B, U2OS, MG-63 and Saos-2), normal human osteoblast cell line (hFOB1.19) and 293T cells were obtained from the American Type Culture Collection (ATCC, Manassas, VA, USA). All cells were cultured in Dulbecco's Modified Eagle's Medium (DMEM; Gibco, Rockville, MD, USA), and supplemented with 10% fetal bovine serum (FBS; Gibco, Rockville, MD, USA) in a humidified atmosphere containing 5% CO_2 at 37°C.

Cell Transfection

Small interfering RNA (siRNA) targeting LINC00665 (si-LINC00665#1, si-LINC00665#2, si-LINC00665#3) with control (si-NC), miR-3619 mimic with control (NC mimics), and miR-3619 inhibitor with control (NC inhibitor) were synthesized by Genepharma (Shanghai, China). LINC00665 was subcloned into pcDNA3.1 (GenePharma, China) for LINC00665 overexpression. The cell transfection was conducted with Lipofectamine 2000 (Invitrogen, Carlsbad, CA, USA).

RT-qPCR

Total RNA was extracted from tissues and cell lines by using TRIzol (Invitrogen, Carlsbad, CA, USA). The RNAs were reverse transcribed to cDNAs using a reverse transcriptase kit (TaKaRa, Dalian, China). RT-qPCR was used on the ABI 7500 Detection System by using the SYBR-Green PCR Master Mix kit (TaKaRa, Dalian, China). GAPDH and U6 were employed as internal controls. The mRNA level was detected using the $2^{-\Delta\Delta Cq}$ method. The following sequences of primers were used: LINC00665 forward, 5' -GGTGCAAAGTGGGAAGTGTG-3', reverse, 5'-CGGTGGACGGATGAGAAACG-3'; miR-3619-5p forward, 5'-UCAGCAGGCAGGCUGGUGCAGC-3', reverse, 5'- GCUGCACCAGCCUGCCUGCUGA-3'; U6 forward, 5'-GCTTCGGCAGCACATATACTAAAAT-3', reverse, 5'- CGCTTCACGAATTTGCGTGTCAT-3'; GAPDH forward, 5'-AGCCACATCGCTCAGACAC-3', reverse, 5'-GCCCAATACGACCAAATCC-3'.

Transwell

For migration assay, transfected cells (1×10^5) in medium without serum were placed in the upper chamber. The culture medium was added to the lower chamber. After 24h culture, and the cells in the lower chamber were fixed with methanol and dyed with crystal violet (Sangon Biotechnology, Shanghai, China). For invasion assay, the insert was coated with Matrigel (BD Biosciences, Bedford, MA, USA). Besides that, all other steps are the same. Migrated and invaded cells were recorded under an inverted microscope (Olympus Corp., Tokyo, Japan).

CCK-8 Assay

Cell viability was assessed by Cell Counting Kit-8 (Dojindo Laboratories, Kumamoto, Japan) assay. 143B and U2OS cells were seeded into 96-well plates. After 24 h, 48 h and 72 h of incubation at 37°C. CCK-8 reagent was added to each well and cells continuously incubated for 4 hours at 37°C. The absorbance at 450 nm was recorded through the microplate reader (Bio-Rad, Hercules, CA, USA).

Luciferase Reporter Assay

Wild-type LINC00665 (LINC00665-WT) and mutant LINC00665 (LINC00665-Mut) were synthesized and cloned into the pGL3 Luciferase reporter vectors (Promega, Madison, WI, USA). Then, miR-3619 mimics or NC mimics were also

co-transfected with above reporters into 293T cells using Lipofectamine 2000 (Invitrogen, Carlsbad, CA, USA). Luciferase activity was analyzed in each group using Luciferase reporter assay kit (Promega, Madison, WI, USA) after 48 h of the transfection.

RNA Immunoprecipitation (RIP) Assay

EZMagna RIP kit (EZ-Magna, Millipore, Billerica, MA) was performed to conduct the RIP assay. The 143B and U2OS cells were transfected with NC mimics or miR-3619 mimics for 48 h and then incubated with Ago2 or IgG antibody. RT-qPCR was used to measure the enrichment expressions of LINC00665 and miR-3619.

Statistical Analysis

All data were assessed by SPSS 16.0 (SPSS Inc., Chicago, IL, USA) and presented as mean ± standard deviation (SD) based on three independent times. Kaplan-Meier analysis was used to analyze the overall survival rate of OS patients. Student's *t*-test or ANOVA followed by Dunnett's test was conducted for comparisons between groups. Kaplan-Meier analysis and the log-rank test were used to estimate survival curves. $p < 0.05$ was considered a statistically significant difference.

Results

LINC00665 Expression Was Upregulated in OS

RT-qPCR was used to assess the expression of LINC00665 in OS tissues and normal tissues, and the results illustrated that LINC00665 was upregulated in OS tissues (Figure 1A). Besides, the LINC00665 level was upregulated in OS cell lines (143B, U2OS, MG-63, and Saos-2 cells) compared with hFOB1.19 cell line (Figure 1B). In addition, patients with high LINC00665 expression had a shorter overall survival time than patients with low LINC00665 expression (Figure 1C). Taking together, LINC00665 level was upregulated in OS, and the upregulation of LINC00665 was associated with poor prognosis of OS patients.

Knockdown of LINC00665 Suppressed the Development of OS Cells

To further explore the biological role of LINC00665 in OS, three siRNAs against LINC00665 (si-LINC00665#1, si-LINC00665#2, si-LINC00665#3) and si-NC were transfected into 143B and U2OS cells. The transfection efficiencies were confirmed by RT-qPCR assay (Figure 2A). CCK-8 assay showed that knockdown of LINC00665 inhibited the viability of OS cells (Figure 2B). A similar result has occurred in transwell assay, in which LINC00665 knockdown suppressed invasion and migration in OS cells (Figure 2C and D). All these data indicated that LINC00665 silencing inhibited the OS cell progression.

MiR-3619 Was a Target of LINC00665

With the assistance of starBase, the binding site of miR-3619 on LINC00665 was predicted (Figure 3A). As shown in figure 3B, miR-3619 mimics restrained the luciferase activity of LINC00665-WT, but not that of the LINC00665-Mut. In ad-

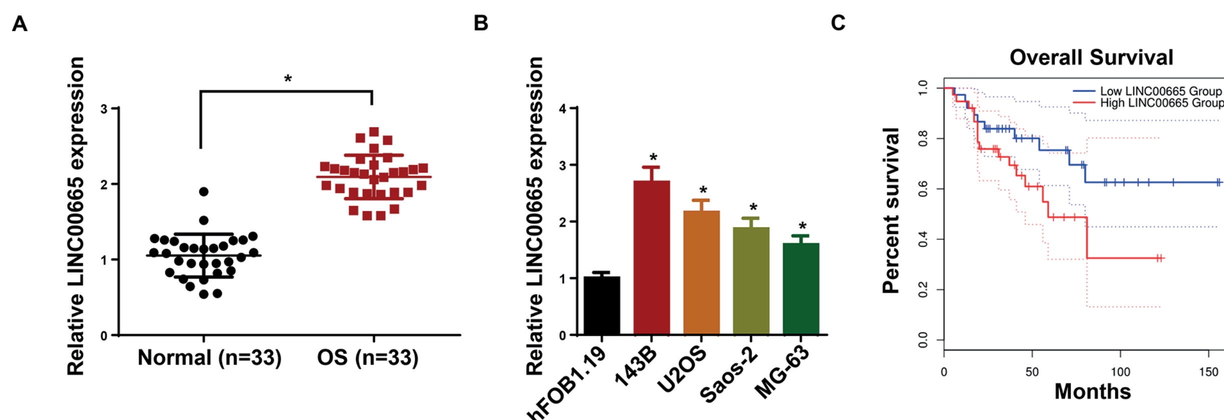

Figure 1. LINC00665 expression was upregulated in OS. **A**, The expression of LINC00665 was measured in OS tissues and normal samples by RT-qPCR. **B**, The level of LINC00665 was detected in OS cell lines (143B, U2OS, MG-63 and Saos-2 cells) and normal human osteoblast cell line (hFOB1.19) by RT-qPCR. **C**, The survival rate of OS patients was analyzed in high or low LINC00665 expression group. The data were presented as mean ± SD (*$p < 0.05$).

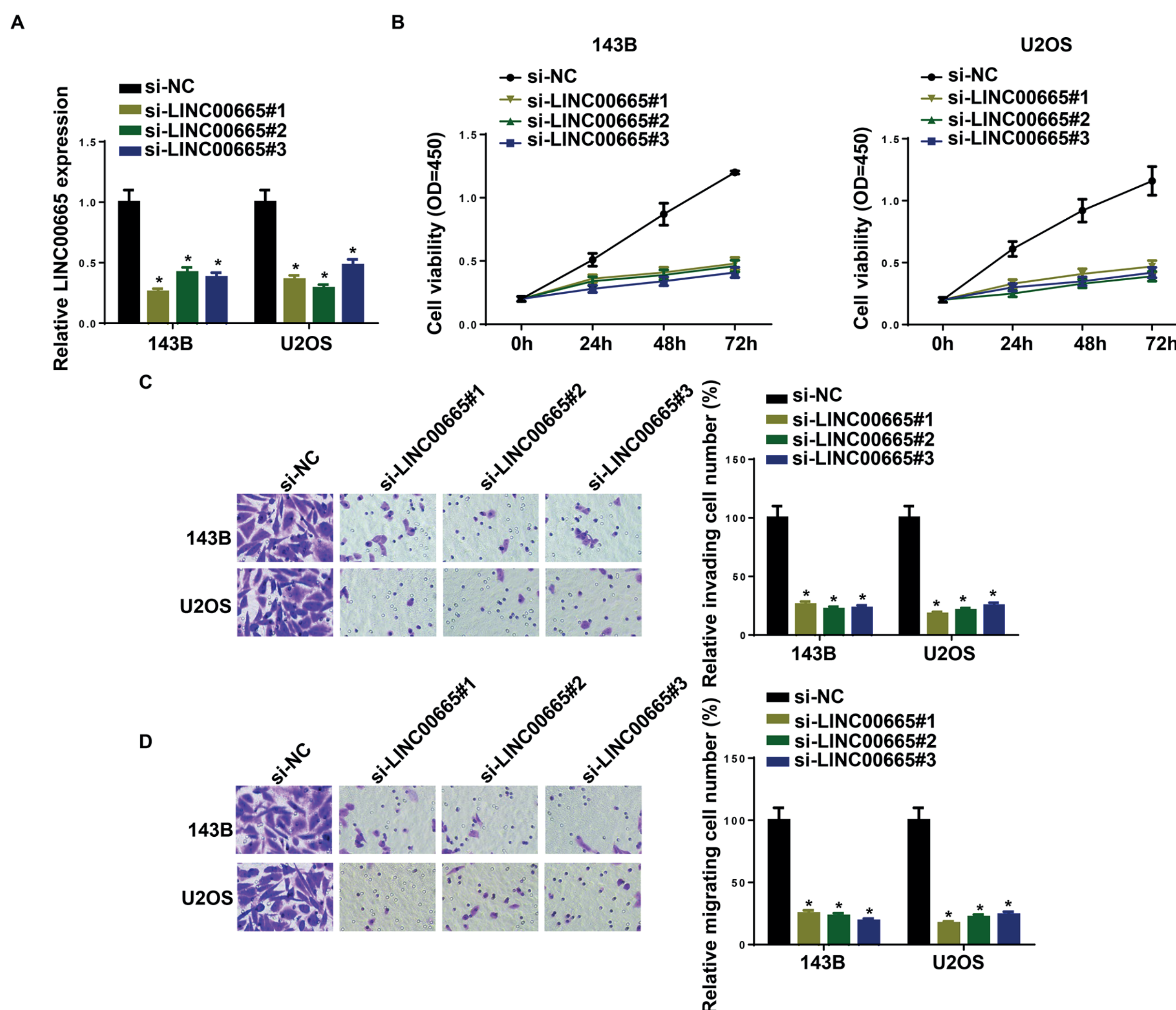

Figure 2. Knockdown of LINC00665 suppressed the development of OS cells. **A**, Transfection efficacy of si-LINC00665#1, si-LINC00665#2 and si-LINC00665#3 was detected in 143B and U2OS cells by RT-qPCR. **B**, CCK-8 assay measured proliferation of 143B and U2OS cells after transfection of si-LINC00665#1, si-LINC00665#2, si-LINC00665#3 and si-NC. **C-D,** Transwell assay detected invasion and migration of 143B and U2OS cells after transfection of si-LINC00665#1, si-LINC00665#2, si-LINC00665#3 and si-NC (magnification ×40). The data were presented as mean ± SD (*$p < 0.05$).

dition, RIP assay revealed that LINC00665 and miR-3619 were markedly enriched in Anti-Ago2, which proved that LINC00665 might be related to miR-3619 (Figure 3C). Subsequently, RT-qPCR showed that miR-3619 was lowly expressed in OS tissues and cells (Figure 3D and E), and the levels of miR-3619 had a negative correlation with the levels of LINC00665 (Figure 3F). Patients with low levels of miR-3619 possessed a lower survival rate compared with patients with high expression levels of miR-3619 (Figure 3G). In addition, LINC00665 silencing increased miR-3619 expression (Figure 3H). These results showed that LINC00665 interacted with miR-3619 and inhibited the expression of miR-3619.

LINC00665 Promoted OS Tumorigenesis by Targeting MiR-3619

To validate whether LINC00665 promoted OS progression via miR-3619, gain-of-function experiments were carried out. First, the upregulation of miR-3619 caused by miR-3619 mimics was reversed by LINC00665 overexpression in OS cells (Figure 4A). Subsequently, it was found that the upregulation of miR-3619 inhibited cell viability, while this effect was abrogated by

LINC00665 overexpression (Figure 4B). Similarly, overexpression of LINC00665 counteracted the repressive effect of miR-3619 overexpression on invasion and migration of OS cells (Figure 4C and D). Overall, LINC00665 accelerated OS cell progression by absorbing miR-3619.

Discussion

OS is a common and highly invasive bone tumor, and its morbidity and mortality rates are still the highest among primary bone tumors[22,23]. The malignant phenotype of tumor cells is the main cause of OS-related death[24,25]. Therefore, it is particularly vital to explore the potential molecular mechanisms that block the malignant phenotypes of OS.

The significance of lncRNAs in various biological processes of disease, especially in carcinogenesis, has attracted a lot of attention from researchers[26,27]. Several studies have illustrated that LINC00665 functioned as an oncogene in the development of various cancers. So, Ji et al[28] showed that LINC00665 overexpression accelerated breast cancer development via miR-379/LIN28B axis.

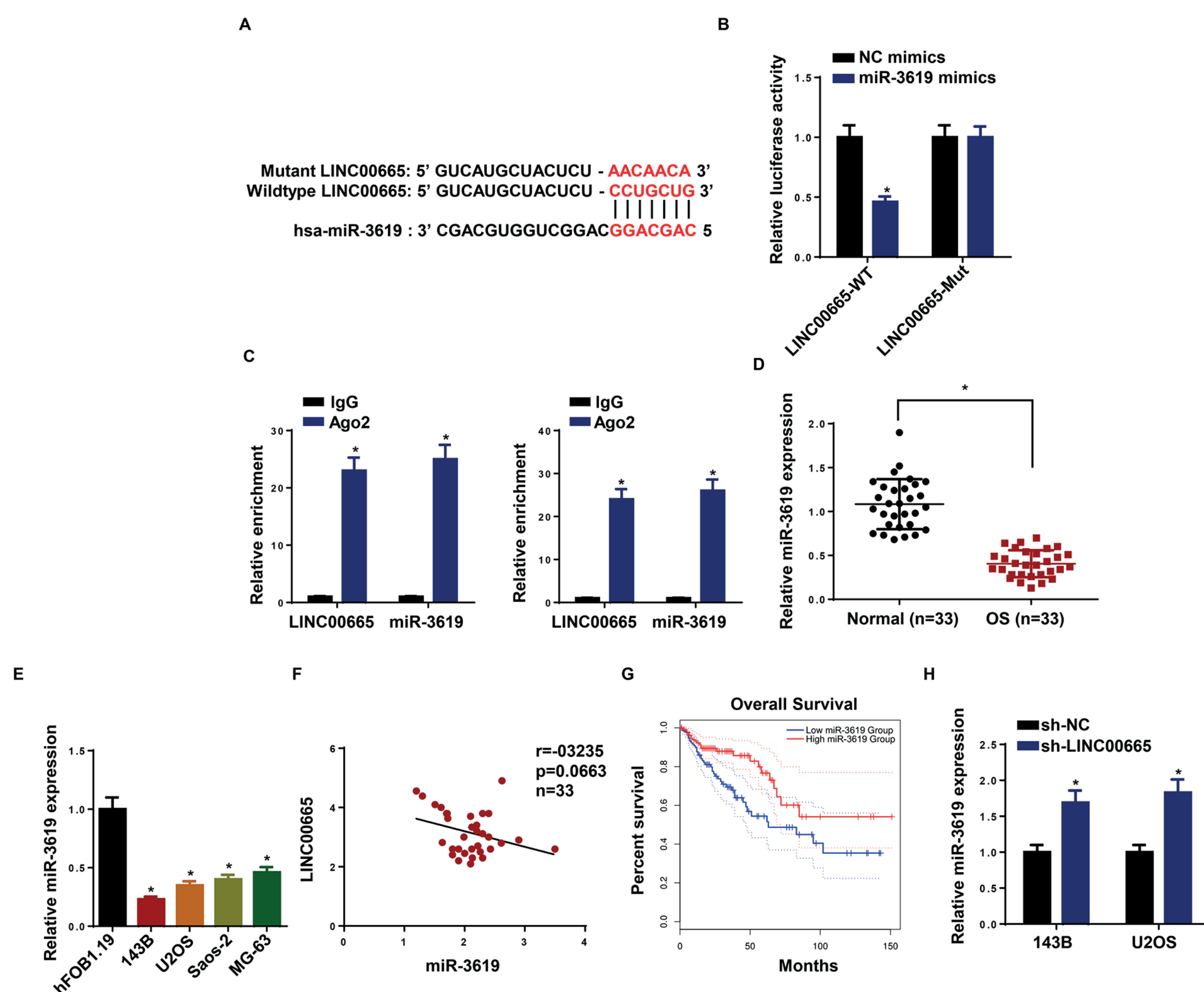

Figure 3. MiR-3619 was regulated by LINC00665 in OS cells. **A**, The potential binding sites of LINC00665 and miR-3619. **B**, Luciferase activity was measured in 293T cells co-transfected with miR-3619 mimics or NC mimics and LINC00665-WT or LINC00665-Mut. **C**, RIP assay was performed to determine the enrichment of LINC00665 and miR-3619 in Anti-IgG and Anti-Ago2. **D, E,** The expression of miR-3619 was detected in OS tissues and cell lines by RT-qPCR. **F**, The correlation between LINC00665 and miR-3619 levels was analyzed in OS patients. **G**, The survival rate of OS patients was analyzed in high or low miR-3619 expression group. **H**, The level of miR-3619 was measured in 143B and U2OS cells transfected with si-NC or si-LINC00665 by qRT-PCR. The data were presented as mean ± SD (*$p < 0.05$).

Chen et al[29] suggested that LINC00665 enhanced prostate cancer development by regulating miR-1224. Qi et al[30] indicated that LINC00665 participated in gastric cancer progression by modulating miR-149 expression. In the present study, we first explored the biological role of LINC00665 in OS development. We found that LINC00665 expression was upregulated in OS tissues and cell lines. Moreover, OS patients with a high level of LINC00665 had a shorter overall survival time than those with a low level of LINC00665. In addition, loss-of-function assays demonstrated that LINC00665 silencing impeded OS cell viability, migration and invasion.

LncRNAs could serve as a competing endogenous RNA (ceRNAs) to indirectly modulate the level of miRNAs target genes[17]. In our study, miR-3619 was predicted as a potential target of LINC00665 by starBase, and the interaction between LINC00665 and miR-3619 was further confirmed by Luciferase reporter and RIP assays. MiR-3619 served as a tumor suppressor in several cancers, such as papillary thyroid carcinoma[31], infantile hemangioma[32], retinoblastoma[33], and bladder carcinoma[34]. Consistent with the previous study, RT-qPCR results revealed that miR-3619 was downregulated in OS cells, and patients with low miR-3619 expression had a shorter overall

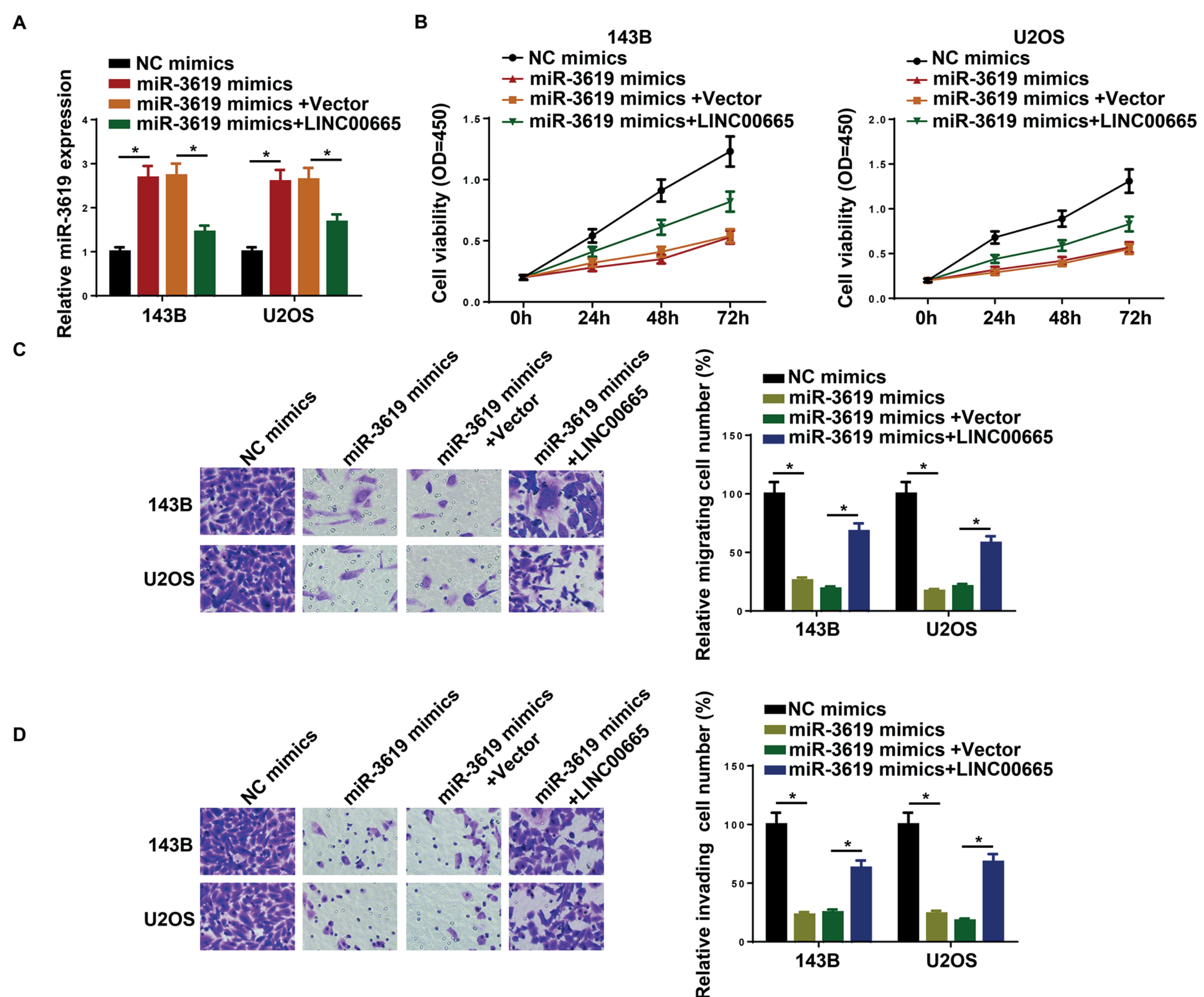

Figure 4. LINC00665 promoted OS tumorigenesis by targeting miR-3619. **A**, The level of miR-3619 was measured in143B and U2OS cells transfected with NC mimics, miR-3619 mimics, miR-3619 mimics+pcDNA3.1, miR-3619 mimics+LINC00665. **B**, Cell viability of the 143B and U2OS cells transfected with NC mimics, miR-3619 mimics, miR-3619 mimics+pcDNA3.1, and miR-3619 mimics+LINC00665 was measured by CCK-8. **C-D,** Transwell assay was used to examine the invasion and migration of transfected 143B and U2OS cells (magnification ×40). The data were presented as mean ± SD (*$p < 0.05$).

survival time. Furthermore, the upregulation of LINC00665 neutralized the suppressive effect of miR-3619 overexpression on proliferation, migration, and invasion of OS cells, indicating that LINC00665 regulated OS development by sponging miR-3619.

Conclusions

We summarized the therapeutic role of LINC00665 silencing on OS progression, possibly by sponging miR-3619. This study indicated a new potential mechanism of LINC00665 in the progression and therapeutic of OS.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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