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ORIGINAL ARTICLE

Effects of long non-coding RNA MALAT1 targeting miR-570-3p and miR-34a on invasion, proliferation and apoptosis of human retinoblastoma cells

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Summary

Purpose: *To investigate the expression of long non-coding RNA (LncRNA) MALAT1 targeting miR-570-3p and miR-34a and its effects on invasion, proliferation and apoptosis of human retinoblastoma cells.*

Methods: *qRT-PCR were used to detect the expression levels of miR-34a, miR-570-3p and Inc RNA MALAT1 in human normal retinal vascular endothelial cell line (ACBRI-181), human retinoblastoma cell line (SO-Rb50), human normal retinal tissue and human retinoblastoma tissue. The SO-Rb50 cell were divided into Control group, miR-570-3p Inhibitor transfection group, miR-34a Inhibitor transfection group, sh-MALAT1 alone transfection group, sh-MALAT1+miR-570-3p Inhibitor+miR-34a Inhibito co-transfection group. Luciferase assay was used to verify the targeting relationship between LncRNA MALAT1 and miR-570-3p and miR-34a. Transwell assay was used to detect cell invasion, flow cytometry was used to detect cell apoptosis, and tumor pellet-forming assay was used to detect cell proliferation.*

Results: *Compared with ACBRI-181 cell line and normal retinal tissue, the expression levels of lnc RNA MALAT1 in SO-Rb50 cell line and human retinoblastoma tissue line were significantly up-regulated, while the expression levels of miR-34a and miR-570-3p were significantly down-regulated. Luciferase assay showed that lncRNA MALAT1 could target miR-570-3p and miR-34a. Compared with the control group, the invasion and proliferation of SO-Rb50 cells in miR-570-3p Inhibitor group and miR-34a Inhibitor group were significantly increased, and the apoptosis rate of SO-Rb50 cells was significantly decreased; but the invasion and proliferation of SO-Rb50 cells in sh-MALAT1 group were significantly decreased, while the apoptosis rate was significantly increased. However, compared with the sh-MALAT1 group alone, the invasion and proliferation of SO-Rb50 cells in the co-transfected sh-MALAT1+miR-570-3p Inhibitor+miR-34a Inhibitor group were significantly increased, while the apoptosis rate was significantly decreased.*

Conclusions: *LncRNA MALAT1 can negatively regulate miR-570-3p and miR-34a to promote the invasion and proliferation of human retinoblastoma SO-Rb50 cells and inhibit apoptosis.*

Key words: *LncRNA MALAT1; miR-570-3p; miR-34a; Human retinoblastoma; Cell proliferation; Apoptosis; Cell invasion*

Introduction

Retinoblastoma is a common disease in clinical oncology department, which is a primary intraocular malignant tumor, mostly seen in children. Strabismus and white band disease can occur in the early stage of the disease. With the progress of the disease, the late children show hypoopia, bulbous eye disease, protrusion, etc., which has a serious impact on the physical and mental health and family life of children, and greatly increases the social and economic burden [1]. At present, the clinical

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pathogenesis is not completely clear, deepen the basic research to understand its pathogenesis, disease prevention, treatment and so on is of great importance. Long-chain non-coding RNAs (IncRNAs) are non-coding RNAs, although they have little or no protein-coding ability. However, Inc RNA is involved in cell migration, apoptosis, proliferation and so on, which affects intracellular equilibrium. Lung adenocarcinoma metastasis-associated transcript 1 (MALAT1), a core member of the Inc RNA family, is located on chromosome 11Q13. According to relevant reports, MALAT1 expression is upregulated in gastric cancer cells, and promotes cell metastasis, progression and invasion [2]. MALAT1 is widely expressed in human brain, spleen, liver and kidney, and is involved in the occurrence and development of various tumor diseases, such as cervical cancer and breast cancer. Studies have shown that MALAT1 promotes the occurrence and progression of retinoblastoma, but its underlying molecular mechanism needs further discussion [3,4]. A large number of studies have pointed out that lncRNAs can act as competitive endogenous Rnas (ceRNAs) to inhibit the expression and activity of miRNAs, thus regulating the expression of target mrnas [5,6]. As a well-studied miRNA, miR-570-3p and miR-34a, as members of the miR-RNA family, are reported to be down-regulated in Osteosarcoma cells and play a role in tumor suppression in the pathogenesis of Osteosarcoma [7].

Considering the importance of miR-570-3p, miR-34a and MALAT1 in the pathogenesis of malignant tumors, this study investigated the effect of lncRNA-MALAT1 in human retinoblastoma SO-RB50 cells, and analyzed the relationship between lncRNA-MALAT1 and miR-34a and miR-570-3p, to provide evidence for clinical research.

Methods

Specimen Collection

Eight cases of human retinoblastoma patients admitted to our hospital from February to December 2020 were included as the research objects. The tumor cells and normal adjacent tissues of the patients were obtained by surgery for routine specimen processing. Inclusion criteria: radiotherapy and chemotherapy were not completed 1 month before surgery, knowledge of the study, and confirmed by histopathological examination. Exclusion criteria: patients with severe cardiac, liver and kidney dysfunction, combined with other malignant tumor diseases. The study was approved by our medical Ethics Committee.

Cell lines and main reagents

Human retinoblastoma SO-RB50 cell line and human normal retinal vascular vascular endothelial cell line ACBRI-181 were purchased from Shanghai Cell Bank, Chinese Academy of Sciences (Shanghai, China). TurboFect Transfection Regent, Fetal bovine serum, RBM 1640 medium were purchased from Thermo Fisher Technologies (Waltham, MA, USA). RNA Extraction kit, SYBR Premix Ex Taq™ Kit and RNAiso Plus Reagent kit were purchased from Dalian TaKaRa Company (Dalian, China). Annexin V/PI Apoptosis Detection Kit was purchased from BD (Franklin Lakes, NJ, USA); Transwell and Artificial basement membrane were purchased from Coring (Corning, NY, USA).

Cell culture and transfection

Conventional cell culture was carried out, digested with 0.25% trypsin and inoculated in 96 Wells for cell transfection. SO-RB50 cell line were divided into Control group, miR-570-3p Inhibitor group, miR-34a Inhibitor group, sh-MALAT1 alone transfection group, and miR-34a Inhibitor+miR-570-3p Inhibitor+sh-MALAT1 co-transfection group. SO-RB50 cells were transfected with miR-570-3p Inhibitor, miR-34a Inhibitor and sh-MALAT1 simultaneously or separately according to the instructions of TurboFect Transfection Regent reagent.

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

SO-RB50 and ACBRI-181 cells, human normal retinal tissue and human retinoblastoma tissues were collected from each group, and total RNA were extracted from cells and tissues. The total RNA was reversely transcribed into cDNA using TaKaRa Reverse transcription kit, and the reaction system was configured according to the instructions. Primers: LncRNA MALAT1 (Forward: 5'AAAGCAAGGTCTCCCCAC AG-3'; Reverse: 5'-GGTCTGTGCTAGTAC-3'); miR-34a (Forward: 5 '-GCAGATCTGGGTGAT-3'; Reverse: 5'-GCATCGATGTGCATGCT-3'); miR-570-3p (Forward: 5'-CGAAAACAGCAATTACCTTTGC-3'; Reverse 5 '-TGGTGTCGTGGTAGTCG-3'). Real-time quantitative PCR conditions: pre-denaturation temperature 94°C for 3 min, denaturation temperature 94°C for 30s, annealing temperature 57.9°C for 30 s, extension temperature 72°C for 1 min, and extension temperature 72°C for 5min after 30 cycles. The relative expression levels of LncRNA MALAT1, miR-570-3p and miR-34a in cells and tissues of each group were quantitatively analyzed.

Luciferase assay

After the culture medium in the culture plate was removed, PBS was added into the cell fluid for washing. After the treatment, 1× cell lysis solution was added into the well for cell lysis. Shaking was carried out for 5-10 min at room temperature, followed by 5 min centrifugation at 3000 r/min, and the supernatant was taken for luciferase detection. Strictly follow the instructions of the instrument and kit to determine the luminescence value.

Tumor pellet-forming assay

The cells to be examined were digested by trypsin, then centrifuged for 5min, the supernatant was re-

moved, phosphate buffered saline (PBS) was added into the cell fluid, repeated blowing and washing for 3 times, and medium was added to prepare single cell suspension (1×10^2 cells/mL); The cells were inoculated in 6-well plates and cultured for 4h. The proliferation of globular cells in each group was detected, and the number of tumor pellet-forming cells in each group was counted.

Flow cytometry experiment

The cells in each group were mixed with PBS buffer to form 1×10^6/mL suspension. 5 μL propidium iodide (PI) and 10 μL FITC-labeled Annexin V antibody were added and incubated at room temperature for 30 min against light. Then, after washing with PBS once, cell apoptosis in each group was detected by BD Canto flow cytometry.

Transwell assay

1% fetal bovine serum was added into the cells to be tested in each group for culture, and 1×10^6 cells/mL were made. The prepared cell suspensions were added into the upper chamber covered with artificial basement membrane Transwell, and the medium containing 20% fetal bovine serum was added into the lower chamber. The cells at the bottom of the upper chamber were stained with 0.5% crystal violet, and the cells at the side of the upper chamber were removed with cotton swabs. The number of cells with invasion and metastasis in each group were observed under microscope.

Statistical Analysis

Statistical Product and Service Solutions (SPSS) 22.0 software (IBM, Armonk, NY, USA) was used for statistical analysis of all data, which was expressed as ($\bar{x}\pm s$). *t*-test was used between two groups, *one-way ANOVA* was used between multiple groups, and LSD-t test was used for pairwise comparison within the group. When $p<0.05$, the difference was considered statistically significant.

Results

LncRNA MALAT1 negatively regulates the expression of miR-34a and miR-570-3p

qRT-PCR showed that the level of lncRNA MALAT1 in human retinoblastoma tissues was significantly up-regulated compared with normal retinoblastoma tissues, while the expression levels of miR-34a and miR-570-3p were significant-

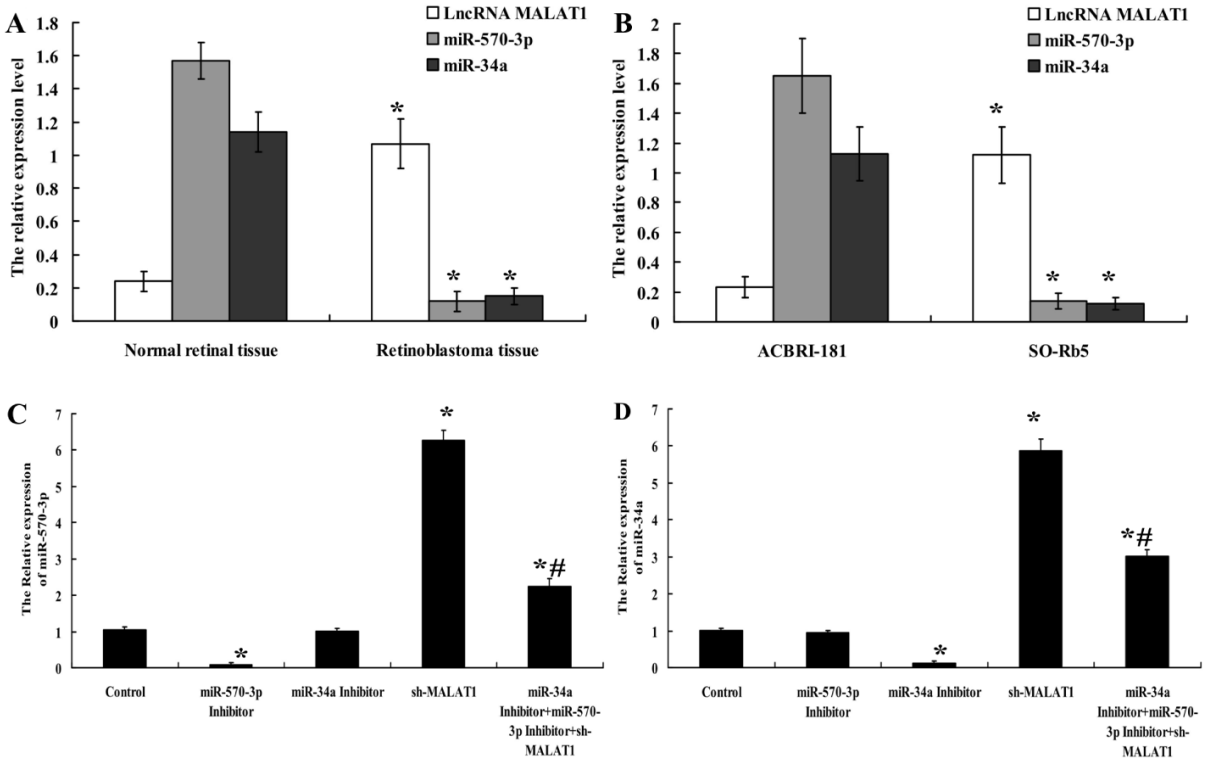

Figure 1. The detection results of qRT-PCR. **A:** Changes in the expression levels of lncRNA MALAT1, miR-34a and miR-570-3p in normal retinal tissues and human retinoblastoma tissues (* compared with normal retinal tissues, $p < 0.05$). **B:** Changes in the expression levels of lncRNA MALAT1, miR-34a and miR-570-3p in human normal retinal vascular endothelial cell line ACBRI-181 and human retinoblastoma cell line SO-RB50 (* compared with normal retinal tissue, $p < 0.05$). **C:** Changes in miR-570-3p expression levels in each transfected cell group (* compared with the Control group, $p < 0.05$; # compared with sh-malat1 group, $p < 0.05$). **D:** Changes in miR-34A expression levels in each transfected cell group (* compared with the Control group, $p < 0.05$; # compared with sh-MALAT1 group, p<s0.05).

ly down-regulated, with statistical significance (p<0.05). Similarly, the expression level of lnc RNA MALAT1 in SO-RB50 cell line was higher than that in normal retinal vascular endothelial cell line ACBRI-181, while the expression level of miR-34a and miR-570-3p was lower than that in normal retinal vascular endothelial cell line ACBRI-181, the difference was significant (p<0.05). As shown in the Figure 1A and Figure 1B.

At the same time, qRT-PCR showed that miR-570-3p expression were decreased significantly in the miR-570-3p Inhibiton group and increased significantly in the sh-MALAT1 group compared with the control group (p<0.05). But compared with sh-MALAT1 group, miR-570-3p expression level in miR-34a Inhibitor+miR-570-3p Inhibitor+sh-MALAT1 group was significantly decreased (p<0.05). Compared with the control group, miR-34a expression were also decreased significantly in the miR-34a Inhibiton group, and increased significantly in the sh-MALAT1 group (p<0.05).

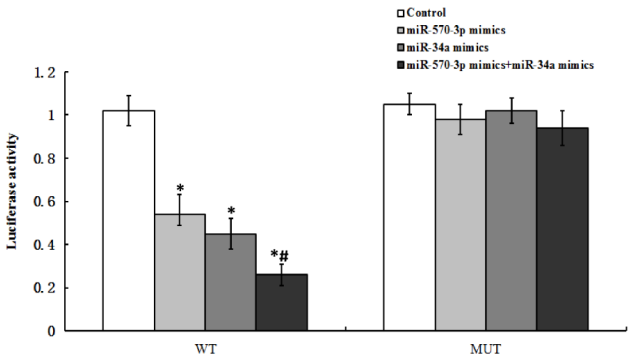

Figure 2. The targeting relationship between lncRNA MALAT1 and miR-34a, miR-570-3p were detected by luciferase activity assay (* compared with Control group, p<0.05; # compared with miR-570-3p mimics group and miR-34a mimics group, p<0.05).

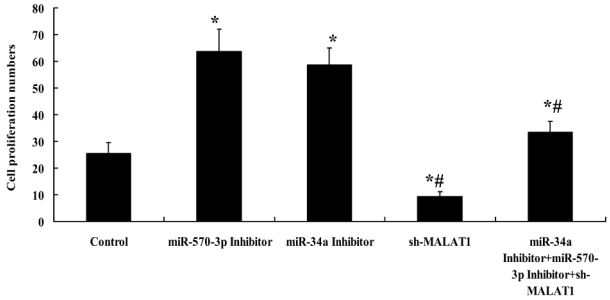

Figure 3. The proliferation of SO-Rb50 cells in each group were detected by tumor pellet-forming experiment (* compared with Control group, p<0.05; # compared with sh-MALAT1 group, p<0.05).

Compared with the sh-MALAT1 group, the expression level of miR-34a in miR-34a Inhibitor+miR-570-3p Inhibitor+sh- MALAT1 group was also significantly decreased (p<0.05). This result indicates that lncRNA MALAT1 negatively regulates Mir-34a and Mir-570-3p, as shown in Figure 1C and Figure 1D.

LncRNA MALAT1 targets miR-34a and miR-570-3p

The luciferase activity assay showed that the luciferase activity of lncRNA MALAT1 wild-type cells were significantly decreased when miR-570-3p mimics and miR-34a mimics were added (all p<0.05). When miR-570-3p mimics+ miR-34a mimics were added simultaneously, luciferase activity in lncRNA MALAT1 wild-type cells was decreased more significantly (p<0.05). There was no significant change in luciferase activity in lncRNA MALAT1 mutant cells (all p>0.05). This experiment demonstrated that lncRNA MALAT1 had a targeting relationship with miR-570-3p and miR-34a, as shown in Figure 2.

sh-MALAT1 inhibits SO-Rb50 cell proliferation by miR-570-3p and miR-34a

Tumor pellet-forming assay revealed that sh-MALAT1 inhibited so-RB50 cell proliferation through miR-570-3p and miR-34a, as shown in Figure 3. Compared with the Control group, cell proliferation of miR-34a inhibitor group and miR-570-5p inhibitor group were significantly increased, and the proliferation number of sh-MALAT1 group was significantly decreased (p<0.05). Compared with sh-MALAT1 group, cell proliferation was increased in sh-MALAT1+miR-570-5p inhibitor+miR-34a inhibitor group (p<0.05). Therefore, in human retinoblastoma SO-Rb50 cells, sh- MALAT1 can regulate cell proliferation through miR-34a and miR-570-3p.

sh-MALAT1 promotes apoptosis of SO-Rb50 cell through miR-570-3p and miR-34a

Flow cytometry showed that, compared with the Control group, the apoptosis rate of miR-34a inhibitor group and miR-570-3p inhibitor group were significantly decreased (p<0.05), while the apoptosis rate of sh-MALAT1 group was significantly increased (p<0.05). However, compared with the sh-MALAT1 group alone, the apoptosis rate of s sh-MALAT1+miR-570-3p inhibitor+miR-34a inhibitor combined group was significantly decreased (p<0.05). These results suggest that sh-MALAT1 can regulate miR-34a and miR-570-3p to promote the apoptosis of SO-Rb50 cells, as shown in Figure 4.

sh-MALAT1 inhibits SO-Rb50 cell invasion by miR-570-3p and miR-34a

Transwell assay showed that compared with the control group, the number of cell invasion in miR-34a inhibitor group and miR-570-3p inhibitor group were significantly increased, while the number of cell invasion in sh-MALAT1 group was significantly decreased ($p<0.05$). Compared with the sh-MALAT1 group alone, the number of cell invasion was significantly increased in the sh-MALAT1+miR-570-3p inhibitor+miR-34a inhibitor combined group. These results suggest that sh-MALAT1 can regulate the increase of miR-34a and miR-570-3p levels and inhibit the invasion of SO-RB50 cells.

Discussion

Retinoblastoma is a common clinical malignant tumor disease, most common in infants and young children, and about 60% of children with tumor cells metastasis [8]. Although there are many

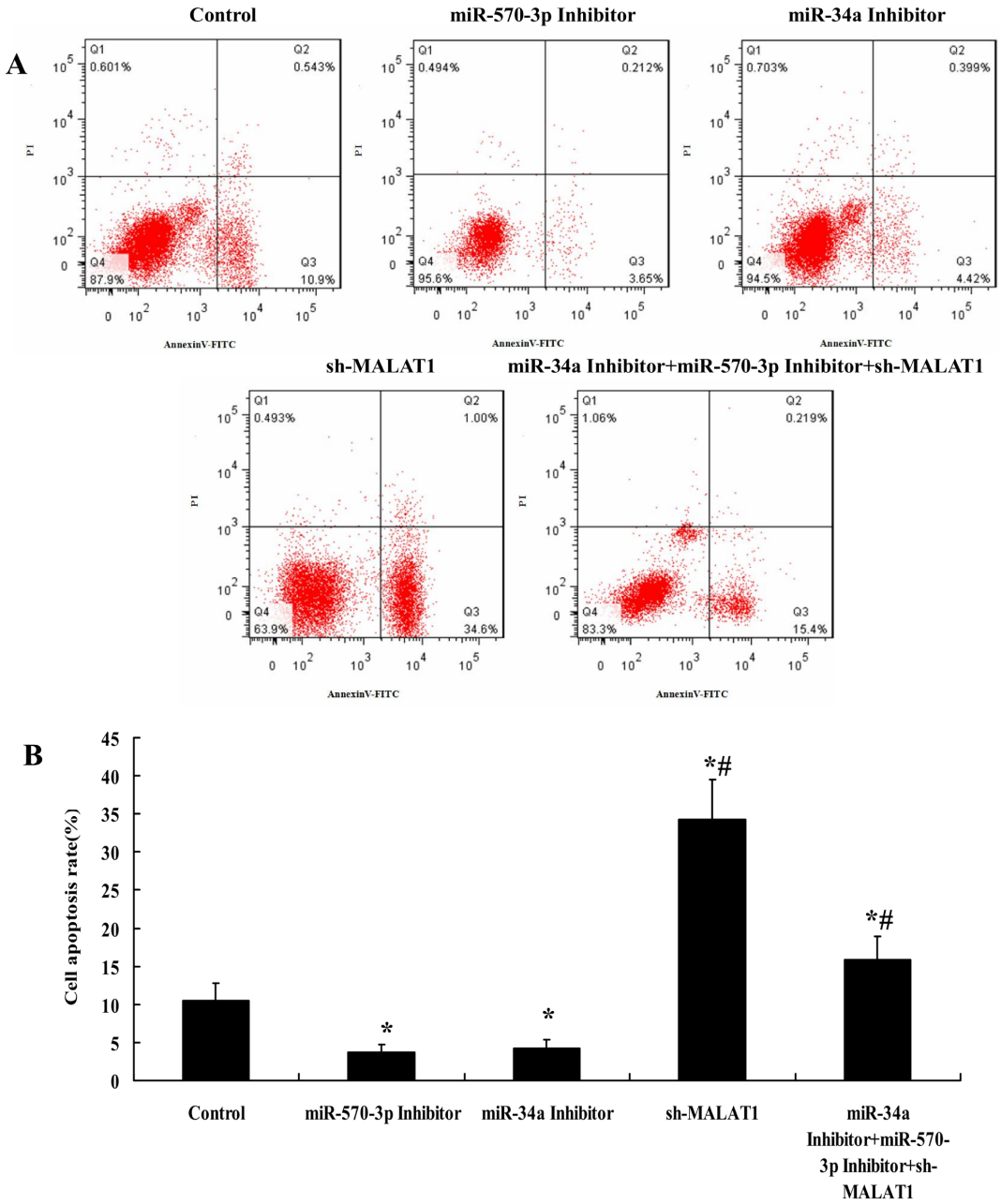

Figure 4. The apoptosis of SO-Rb50 cells in each group were detected by flow cytometry. **A:** Cell apoptosis were detected by flow cytometry. **B:** Statistics of SO-Rb50 apoptosis rate in each group (* compared with Control group, $p < 0.05$; # compared with sh- MALAT1 group, $p<0.05$).

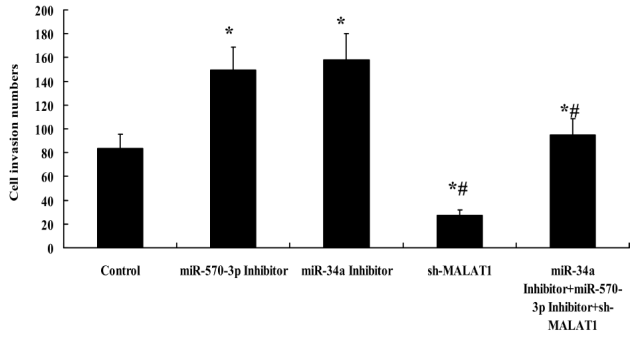

Figure 5. The invasion of SO-Rb50 cells in each group were detected by Transwell experiment (* compared with Control group, p<0.05; # compared with sh-MALAT1 group, p<0.05).

clinical treatment measures for it at present, such as vitreous chemotherapy combined with ocular arterial chemosurgery, laser photocoagulation, systemic chemotherapy, etc., these methods have limited efficacy and some defects [9,10]. Therefore, it is of great significance to investigate the pathogenesis of retinoblastoma in clinical practice, and to treat, prevent and diagnose retinoblastoma.

In recent years, more and more studies believe that MALAT1 is positively correlated with the occurrence and development of retinoblastoma [11,12]. For example, silencing MALAT1 can regulate retinoblastoma by changing the expression of β-catenin. Overexpression of MALAT1 promotes cell metastasis and reduces e-cadherin levels by associating with zeste homolog 2 enhancer [13,14]. Meanwhile, some scholars have pointed out that MALAT1 is a carcinogenic lncRNA that can activate phosphoinositol 3-kinase/Akt signaling pathway and promote tumor metastasis and growth [15,16]. A large number of literatures have shown that lncRNA MALAT1 can negatively regulate a variety of miRNAs, such as miR-125b, miR-205 and miR-200s, in bladder cancer, kidney cancer, breast cancer and clear cell carcinoma of the kidney [17,18]. Studies have pointed out that miR-34a can target the autophagy, metastasis and proliferation of tumor cells in pediatric neuroblastoma [19]. Meanwhile, it has been reported that the increased expression of miR-570-3p in human retinoblastoma can inhibit the proliferation and invasion of tumor cells and promote the apoptosis of tumor cells [20].

This study showed that compared with normal retinal tissues and cell lines, the expression levels of miR-34a and miR-570-3p in human retinoblastoma tissues were significantly down-regulated by qRT-PCR, while the level of lncRNA MALAT1 was significantly up-regulated (p<0.05). The expression of miR-34a and miR-570-3p in cell line SO-Rb50 was lower than that in normal retinal vascular endothelial cell line ACBRI-181, while the expression of lncRNA MALAT1 was higher than that in cell line ACBRI-181, indicating a significant difference. Meanwhile, when the expression level of lncRNA MALAT1 in SO-Rb50 cells of shMALAT1 group was significantly inhibited, the expression levels of miR-34a and miR-570-3p were significantly increased. These results suggest that lncRNA MALAT1 level in human retinoblastoma tissues and cell lines SO-RB50 is negatively correlated with the expression of miR-34a and miR-570-3p. In this luciferase experiment, when miR-34a mimics and miR-570-3p mimics were transfected into lncRNA MALAT1 wild-type SO-Rb50 cells, the luciferase activity was significantly decreased. The above study confirmed the targeting relationship between lncRNA MALAT1 level and miR-34a and miR-570-3p.

miR-34a is considered to be a direct transcriptional target of the tumor suppressor p53, and reduced expression of miR-34a in tumors is necessarily associated with p53 inactivation mutations [21]. As a new prognostic biomarker, it is correlated with tumor stage and size, and shows low expression in various tumor tissues. Some scholars believe that MALAT1, as a molecular sponge of miR-34a, can actively regulate the expression of CCND1 in human retinoblastoma [22]. As a member of the cyclin family, CCND1 is closely associated with tumor metastasis and occurrence, and the overexpression of CCND1 partially reverses MALAT1 silencing regulation of tumor cell viability, invasion and migration [23]. Some studies have also shown that miR-34a may be independent of MALAT1 through RNA drop-down analysis, which is mainly related to the dilution of miR-34a by adding cell lysates and surfactants, resulting in false negative in immunoprecipitation [24]. miR-570-3p has been shown to inhibit some tumor invasiveness and reduce the risk of tumor death. Studies have shown that miR-570-3p can exert an inhibitory effect on tumor immune-related factors and participate in lymph node metastasis, cell invasion and tumor differentiation of gastric cancer [25]. In order to further clarify the potential mechanism of MALAT1 in the human retinoblast pathway, the functional role of MALAT1 as miRNA bait for miR-34a and miR-570-3p was proposed.

In this study, sh-MALAT1 can inhibit cell proliferation, promote cell apoptosis and weaken cell invasion in human retinoblastoma SO-Rb50 cell line. However, the effect of SH-MALAT1 can be reversed by targeting the expression of miR-34a and miR-570-3p. This study suggested that up-regulation of miR-34a and miR-570-3p could inhibit the proliferation and invasion of SO-Rb50

cells and enhance the effect of apoptosis. In this process, MALAT1 acts as a molecular sponge to inhibit miR-34a and miR-570-3p.

Conclusions

In summary, this study found that lncRNA MALAT1 can regulate the invasion, proliferation and apoptosis of human retinoblastoma tumor cells by targeting miR-570-3p and miR-34a.

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Conflict of interests

The authors declare no conflict of interests.

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