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Original Research Article

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

Dejing Shi, Xiuhong Feng, Xuchen Ding*
Department of Ophthalmology, The Fourth Affiliated Hospital of Harbin Medical University, Harbin, China

For correspondence:* ***Email:* *xuchen_ding@126.com;* ***Tel:*** *+86-045182576576*

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Abstract

Purpose: *To investigate the expression of lncRNA MALAT1-targeting miR-570-3p and miR-34a and its effects on the invasion, proliferation, and apoptosis of human retinoblastoma cells.*
Methods: *MiR-34a, miR-570-3p, and lncRNA MALAT1 in a human normal retinal vascular endothelial cell line (ACBRI-181), human retinoblastoma cell line (SO-Rb50), human normal retinal tissue and human retinoblastoma tissue were determined. Luciferase assay was used to verify the targeting relationship between LncRNA MALAT1 and miR-570-3p and miR-34a. while cell invasion, cell apoptosis and cell proliferation were assessed by Transwell assay, flow cytometry, and tumor pellet-forming assay, respectively.*
Results: *LncRNA 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 ($p < 0.05$). Luciferase assay results showed that lncRNA MALAT1 targeted miR-570-3p and miR-34a. The invasion and proliferation of SO-Rb50 cells in the miR-570-3p inhibitor and miR-34a inhibitor groups were significantly increased, while the apoptosis of SO-Rb50 cells was significantly decreased ($p < 0.05$). However, the invasion and proliferation of SO-Rb50 cells in sh-MALAT1 group were significantly decreased, while apoptosis significantly increased. However, compared with sh-MALAT1 group alone, the invasion and proliferation of SO-Rb50 cells in co-transfected sh-MALAT1+miR-570-3p inhibitor + miR-34a inhibitor group w significantly increased, but apoptosis significantly decreased ($p < 0.05$).*
Conclusion: *LncRNA MALAT1 negatively regulates miR-570-3p and miR-34a to promote the invasion and proliferation of human retinoblastoma SO-Rb50 cells and inhibit apoptosis. These findings may be of significance in developing suitable therapies for human retinoblastoma*

Keywords: *Long non-coding RNA, microRNA, Human retinoblastoma, Cell proliferation, Apoptosis, Cell invasion*

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INTRODUCTION

Retinoblastoma is a common disease in the clinical oncology department, and it is a primary intraocular malignant tumor mostly prevalent in children. Strabismus and white band disease can occur in the early stage, and as the disease progresses, hyperopia, bulbous eye disease,

protrusion, etc. are manifested in the affected children. These diseases have a serious impact on their physical and mental health, as well as their family life, and also greatly increase their social and economic burden [1]. At present, the clinical pathogenesis is not clear. Further research to deepen the understanding of its pathogenesis as well as disease prevention, and treatment is ongoing.

Long-chain non-coding RNAs (lncRNAs) are RNAs with little or no protein-coding ability. However, lncRNAs are involved in cell migration, apoptosis, proliferation, and so on, which affect intracellular equilibrium. Lung adenocarcinoma metastasis-associated transcript 1 (MALAT1), is a core member of the lncRNA family and 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]. The MALAT1 is widely expressed in the 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 [3]. Studies have shown that MALAT1 promotes the occurrence and progression of retinoblastoma, but its underlying molecular mechanism needs further discussion [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 well-studied members of the miR-RNA family, miR-570-3p and miR-34a, 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 the Fourth Affiliated Hospital of Harbin Medical University from February to December 2020 were included in the study group. The tumor cells and normal adjacent tissues of the patients were obtained through surgery for routine specimen procedure.

Inclusion criteria

Patients who were diagnosed by histopathological examination and have not received radiotherapy or chemotherapy during the month before surgery were included in the study.

Exclusion criteria

Patients with severe cardiac, liver, and kidney dysfunction, combined with other malignant tumor diseases.

Ethical matters

The study was approved by the hospital's Medical Ethics Committee (19-HMU-021). The study was conducted by following the Declaration of Helsinki [7].

Cell lines and main reagents

Human retinoblastoma SO-RB50 cell line and human normal retinal vascular endothelial cell line ACBRI-181 were purchased from Shanghai Cell Bank, Chinese Academy of Sciences (Shanghai, China). TurboFect Transfection Regent, Fetal bovine serum, and RBM 1640 medium were purchased from Thermo Fisher Technologies (Waltham, MA, USA).

The RNA Extraction kits, (SYBR Premix Ex Taq™, and RNAiso Plus Reagent) were purchased from Dalian TaKaRa Company (Dalian, China). Annexin V/PI apoptosis detection kit was purchased from BD (Franklin Lakes, NJ, USA), and Transwell and Artificial basement membrane were purchased from Corning (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. The SO-RB50 cell line was divided into a 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.

The SO-RB50 cells were transfected with miR-570-3p Inhibitor, miR-34a Inhibitor, and sh-MALAT1 simultaneously or separately according to the instructions of the TurboFect Transfection reagent.

Quantitative real-time polymerase chain reaction (qRT-PCR)

The SO-RB50 and ACBRI-181 cells, human normal retinal tissue, and human retinoblastoma tissues were collected from each group, and total RNA was extracted from cells and tissues. The total RNA was reversely transcribed into cDNA using a TaKaRa Reverse transcription kit, and the reaction system was configured according to the manufacturers' instructions. Real-time quantitative PCR conditions are as follows: pre-denaturation temperature 94 °C for 3 min, denaturation temperature 94 °C for the 30s, annealing temperature 57.9 °C for 30 s, extension temperature 72 °C for 1 min, and extension temperature 72 °C for 5 min 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. The primers used are shown in Table 1.

Table 1: Primer sequences

Gene		Primer sequence (5′-3′)
LncRNA MALAT1	Forward	AAAGCAAGGTCTCCCCAC AG
	Reverse	GGTCTGTGCTAGTAC
miR-34a	Forward	GCAGATCTGGGTGAT
	Reverse	GCATCGATGTGCATGCT
miR-570-3p	Forward	CGAAAACAGCAATTACCT TTGC
	Reverse	TGGTGTCGTGGTAGTCG

Luciferase assay

After the culture medium in the plate was removed, PBS was added to 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 rpm. The supernatant was taken for luciferase detection, while strictly following the instructions of the instrument and kit to determine the luminescence value.

Tumor pellet-forming assay

The cells to be examined were digested with trypsin, then centrifuged for 5 min, the supernatant was removed, phosphate-buffered saline (PBS) was added into the cell fluid, repeated blowing and washing was done 3 times, and the medium was added to prepare single cell suspension (1×10^2 cells/mL). The cells were inoculated in 6-well plates and cultured for 4 h. 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

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

Transwell assay

Fetal bovine serum (1 %) was added into the cells to be tested in each group, and 1×10^6 cells/mL cultures were made. The prepared cell suspensions were added into the upper chamber covered with an 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 was observed under a light microscope.

Statistical analysis

Statistical Package for the Social Sciences (SPSS) 22.0 software (IBM, Armonk, NY, USA) was used for statistical analysis and the data expressed as mean ± standard deviation (SD). The *t*-test was used for data comparison between two groups, one-way ANOVA for comparison between multiple groups, and LSD *t*-test for pairwise comparison within a group. $P < 0.05$ was considered statistically significant.

RESULTS

LncRNA MALAT1 negatively regulated the expressions of miR-34a and miR-570-3p

PCR results showed that lncRNA MALAT1 levels in human retinoblastoma tissues were significantly up-regulated when compared with normal retinoblastoma tissues, while the expression levels of miR-34a and miR-570-3p were significantly down-regulated ($p < 0.05$). Similarly, the expression level of lncRNA MALAT1 in the SO-RB50 cell line was higher than that in the normal retinal vascular endothelial cell line ACBRI-181, while the expression levels of miR-34a and miR-570-3p were significantly lower than that in the normal retinal vascular endothelial cell line ACBRI-181 ($p < 0.05$). As shown in Figure 1 A and B.

Furthermore, miR-570-3p expression decreased significantly in the miR-570-3p inhibition group and increased significantly in the sh-MALAT1 group when 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 also decreased significantly in the miR-34a inhibition and increased significantly in the sh-MALAT1 group ($p < 0.05$). Compared with the sh-MALAT1 group, the expression level of miR-34a in the 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 Figures 1 C and D.

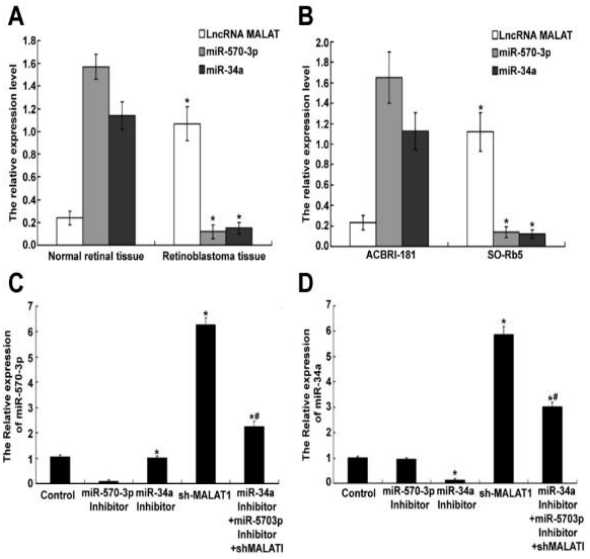

Figure 1: Expression levels of proteins. (A) Changes in the expression levels of lncRNA MALAT1, miR-34a, and miR-570-3p in normal retinal tissues and human retinoblastoma tissues. (B) Changes in the expression levels of lncRNA MALAT1, miR-34a and miR-570-3p in human normal retinal vascular endothelial cell line ACBRI-181 and human retinoblastoma cell line SO-RB50. (C) Changes in miR-570-3p expression levels in each transfected cell group (D): Changes in miR-34A expression levels in each transfected cell group (compared with normal retinal tissue, $*p < 0.05$ (A); compared with the control group, $*p < 0.05$ (B); compared with the sh-MALAT1 group, $^{\#}p < 0.05$ (C and D)

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

The luciferase activity assay data showed that the luciferase activity of lncRNA MALAT1 wild-type cells was significantly decreased when miR-570-3p mimics and miR-34a mimics were added ($p < 0.05$). 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 ($p > 0.05$). This experiment demonstrated that lncRNA MALAT1 had a targeting relationship with miR-570-3p and miR-34a, as shown in Figure 2.

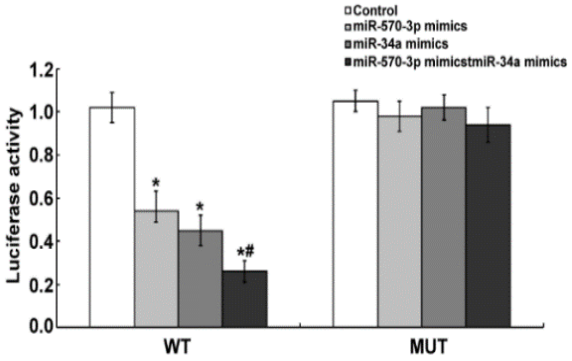

Figure 2: Targeting relationship between lncRNA MALAT1 and miR-34a, miR-570-3p was detected by luciferase activity assay (compared with the control group, $*p < 0.05$; compared with the miR-570-3p mimics group and the miR-34a mimics group, $^{\#}p < 0.05$)

sh-MALAT1 inhibit SO-Rb50 cell proliferation

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 regulated cell proliferation through miR-34a and miR-570-3p.

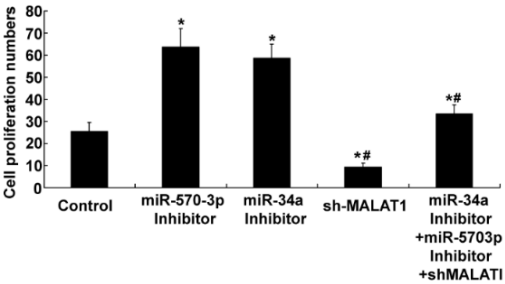

Figure 3: Proliferation of SO-Rb50 cells in each group were determined using tumor pellet-forming experiment (compared with control group, $*p < 0.05$; compared with sh-MALAT1 group, $^{\#}p < 0.05$)

sh-MALAT1 promoted the apoptosis of SO-Rb50 cells

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

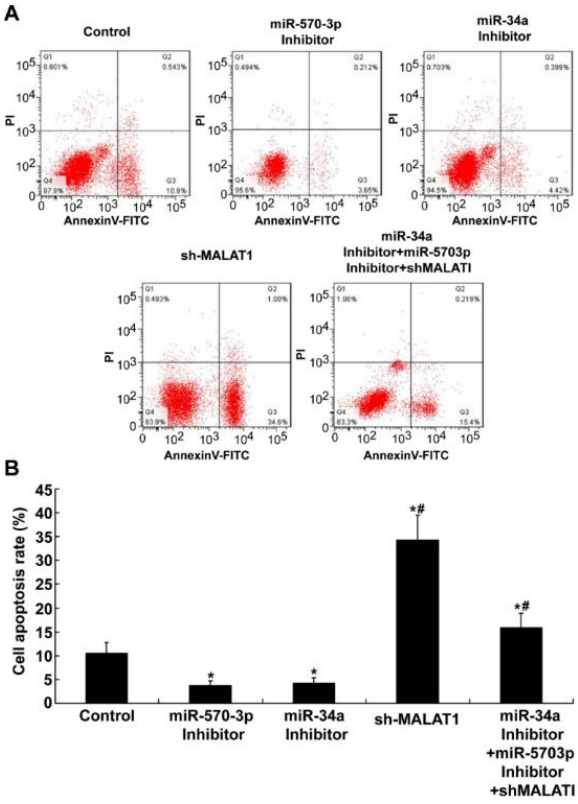

Figure 4: The apoptosis of SO-Rb50 cells in each group detected by flow cytometry. (A) Cell apoptosis as detected by flow cytometry. (B): Statistics of SO-Rb50 apoptosis rate in each group (*$p < 0.05$, vs. control group; #$p < 0.05$ vs. sh-MALAT1 group)

sh-MALAT1 inhibited SO-Rb50 cell invasion

Transwell assay showed that compared with the control group, the number of cell invasions in the miR-34a inhibitor group and miR-570-3p inhibitor group were significantly increased, while the number of cell invasions in the sh-MALAT1 group was significantly decreased ($p < 0.05$). Compared with the sh-MALAT1 group alone, the number of cell invasions 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 (Figure 5).

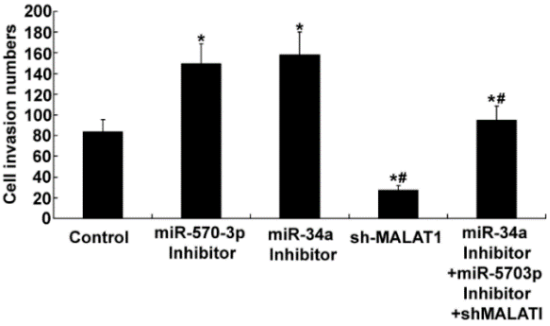

Figure 5: Invasion of SO-Rb50 cells in each group was detected by the Transwell experiment (*$p < 0.05$, vs. control group; #$p < 0.05$ vs. sh-MALAT1 group)

DISCUSSION

Retinoblastoma is a common clinical malignant tumor disease, most common in infants and young children, and about 60 % of children with tumor cell metastasis [8]. Although there are many 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 regulated retinoblastoma by changing the expression of β-catenin [13,14]. Overexpression of MALAT1 promotes cell metastasis and reduces e-cadherin levels by associating with zeste homolog 2 enhancer [15]. Meanwhile, some scholars have pointed out that MALAT1 is a carcinogenic lncRNA that can activate the phosphoinositol 3-kinase/Akt signaling pathway and promote tumor metastasis and growth [16].

A large number of literature 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, as well as promote their apoptosis [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 lncRNA MALAT1 levels were significantly up-regulated ($p < 0.05$). The expression of miR-34a and miR-570-3p in the SO-Rb50 cell line 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 the sh-MALAT1 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 the lncRNA MALAT1 level and the miR-34a and miR-570-3p.

The miR-34a is considered to be a direct transcriptional target of the tumor suppressor p53, and the 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, thus silencing the regulation of tumor cell viability, as well as 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 via the addition of cell lysates and surfactants, resulting in a false negative in immunoprecipitation [24]. The 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 participates 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 retinoblastoma pathway, the functional role of MALAT1 as miRNA bait for miR-34a and miR-570-3p was proposed.

In this study, sh-MALAT1 inhibited cell proliferation, promoted cell apoptosis and weakened cell invasion in human retinoblastoma SO-Rb50 cell line. However, the effect of sh-MALAT1 was reversed by targeting the expressions of miR-34a and miR-570-3p. This study suggests that the 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 the process, MALAT1 acts as a molecular sponge to inhibit miR-34a and miR-570-3p.

CONCLUSION

This study has demonstrated that lncRNA MALAT1 regulates the invasion, proliferation, and apoptosis of human retinoblastoma tumor cells by targeting miR-570-3p and miR-34a. These results provide a new insight into the diagnosis and potential treatment of human retinoblastoma.

DECLARATIONS

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Funding

None provided.

Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest is associated with this work. This article was previously published in the Journal of BUON (https://jbuon.com/archive/26-6-2623.pdf) but was retracted as per our request

(See the retraction notice here: https://jbuon.com/archive/26-6-2623-retraction-notice.pdf). We requested to retract this paper as we were not informed of the decision made by Web of Science that J BUON was delisted by SCIE. The editor-in-chief of JBUON agreed with the retraction request and informed us that we are free to submit this paper elsewhere.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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REFERENCES

1. *Chen Y, Peng J, Cao S. Bauerenol inhibits proliferation, migration and invasion of retinoblastoma cells via induction of apoptosis, autophagy and cell cycle arrest. Trop J Pharm Res 2022; 21(7):1377-1382 doi: 10.4314/tjpr.v21i7.3*
2. *Arun G, Spector DL. MALAT1 long non-coding RNA and breast cancer. RNA Biol 2019; 16(6): 860-863.*
3. *YiRen H, YingCong Y, Sunwu Y, Keqin L, Xiaochun T, Senrui C, Ende C, XiZhou L, Yanfan C. Long noncoding RNA MALAT1 regulates autophagy associated chemoresistance via miR-23b-3p sequestration in gastric cancer. Mol Cancer 2017; 16(1): 174.*
4. *Goyal B, Yadav S, Awasthee N, Gupta S, Kunnumakkara AB, Gupta SC. Diagnostic, prognostic, and therapeutic significance of long non-coding RNA MALAT1 in cancer. Biochim Biophys Acta Rev Cancer 2021; 1875(2): 188502.*
5. *Sun J, Li G, Zhang L, Xie Y, Chen C, He J, et al. LncRNA NBAT-1 inhibits the progression of hepatocellular carcinoma by interacting with CYLD. Trop J Pharm Res 2021; 20(8):1585-1591 doi: 10.4314/tjpr.v20i8.6*
6. *Zheng S, Jiang F, Ge D, Tang J, Chen H, Yang J, Yao Y, Yan J, Qiu J, Yin Z, et al. LncRNA SNHG3/miRNA-151a-3p/RAB22A axis regulates invasion and migration of osteosarcoma. Biomed Pharmacother 2019; 112: 108695.*
7. *Stockhausen K. The Declaration of Helsinki: revising ethical research guidelines for the 21st century. Med J Aust 2000; 172(6): 252-253.*
8. *Chen R, Liu Y, Zhuang H, Yang B, Hei K, Xiao M, Hou C, Gao H, Zhang X, Jia C, et al. Quantitative proteomics reveals that long non-coding RNA MALAT1 interacts with DBC1 to regulate p53 acetylation. Nucleic Acids Res 2017; 45(17): 9947-9959.*
9. *Gutschner T, Hammerle M, Eissmann M, Hsu J, Kim Y, Hung G, Revenko A, Arun G, Stentrup M, Gross M, et al. The noncoding RNA MALAT1 is a critical regulator of the metastasis phenotype of lung cancer cells. Cancer Res 2013; 73(3): 1180-1189.*
10. *Hu H, Wu J, Yu X, Zhou J, Yu H, Ma L. Long non-coding RNA MALAT1 enhances the apoptosis of cardiomyocytes through autophagy inhibition by regulating TSC2-mTOR signaling. Biol Res 2019; 52(1): 58.*
11. *Wang L, Zhang Y, Xin X. Long non-coding RNA MALAT1 aggravates human retinoblastoma by sponging miR-20b-5p to upregulate STAT3. Pathol Res Pract 2020; 216(6): 152977.*
12. *Gao YX, Gao HX, Xu XY, Ding FK. Effects of lncRNA MALAT1 and lncRNA NKILA on proliferation, invasion and apoptosis of retinoblastoma. Eur Rev Med Pharmacol Sci 2020; 24(16): 8296-8307.*
13. *Huang J, Yang Y, Fang F, Liu K. MALAT1 modulates the autophagy of retinoblastoma cell through miR-124-mediated stx17 regulation. J Cell Biochem 2018; 119(5): 3853-3863.*
14. *Ma P, Li Y, Zhang W, Fang F, Sun J, Liu M, Li K, Dong L. Long Non-coding RNA MALAT1 inhibits neuron apoptosis and Neuroinflammation while stimulates Neurite outgrowth and its correlation With MiR-125b Mediates PTGS2, CDK5 and FOXQ1 in Alzheimer's Disease. Curr Alzheimer Res 2019; 16(7): 596-612.*
15. *Lu L, Luo F, Liu Y, Liu X, Shi L, Lu X, Liu Q. Posttranscriptional silencing of the lncRNA MALAT1 by miR-217 inhibits the epithelial-mesenchymal transition via enhancer of zeste homolog 2 in the malignant transformation of HBE cells induced by cigarette smoke extract. Toxicol Appl Pharmacol 2015; 289(2): 276-285.*
16. *Yong H, Wu G, Chen J, Liu X, Bai Y, Tang N, Liu L, Wei J. lncRNA MALAT1 accelerates skeletal muscle cell apoptosis and inflammatory response in sepsis by decreasing BRCA1 Expression by recruiting EZH2. Mol Ther Nucleic Acids 2020; 19: 97-108.*
17. *Amodio N, Raimondi L, Juli G, Stamato MA, Caracciolo D, Tagliaferri P, Tassone P. MALAT1: a druggable long non-coding RNA for targeted anti-cancer approaches. J Hematol Oncol 2018; 11(1): 63.*
18. *Yang X, Yang J, Lei P, Wen T. LncRNA MALAT1 shuttled by bone marrow-derived mesenchymal stem cells-secreted exosomes alleviates osteoporosis through mediating microRNA-34c/SATB2 axis. Aging (Albany NY) 2019; 11(20): 8777-8791.*
19. *Oner MG, Rokavec M, Kaller M, Bouznad N, Horst D, Kirchner T, Hermeking H. Combined Inactivation of*

TP53 and MIR34A promotes colorectal cancer development and progression in mice via increasing levels of IL6R and PAI1. Gastroenterology 2018; 155(6): 1868-1882.

20. *Wang LL, Huang WW, Huang J, Huang RF, Li NN, Hong Y, Chen ML, Wu F, Liu J. Protective effect of hsa-miR-570-3p targeting CD274 on triple negative breast cancer by blocking PI3K/AKT/mTOR signaling pathway. Kaohsiung J Med Sci 2020; 36(8): 581-591.*
21. *Liu H, Deng H, Zhao Y, Li C, Liang Y. LncRNA XIST/miR-34a axis modulates the cell proliferation and tumor growth of thyroid cancer through MET-PI3K-AKT signaling. J Exp Clin Cancer Res 2018; 37(1): 279.*
22. *Song L, Chen TY, Zhao XJ, Xu Q, Jiao RQ, Li JM, Kong LD. Pterostilbene prevents hepatocyte epithelial-mesenchymal transition in fructose-induced liver fibrosis through suppressing miR-34a/Sirt1/p53 and TGF-beta1/Smads signalling. Br J Pharmacol 2019; 176(11): 1619-1634.*
23. *Zhang X, Hamblin MH, Yin KJ. The long noncoding RNA Malat1: Its physiological and pathophysiological functions. RNA Biol 2017; 14(12): 1705-1714.*
24. *Lin Y, Liu S, Su L, Su Q, Lin J, Huang X, Wang C. miR-570 inhibits proliferation, angiogenesis, and immune escape of hepatocellular carcinoma. Cancer Biother Radiopharm 2018; 33(6): 252-257.*
25. *Wang W, Li F, Mao Y, Zhou H, Sun J, Li R, Liu C, Chen W, Hua D, Zhang X. A miR-570 binding site polymorphism in the B7-H1 gene is associated with the risk of gastric adenocarcinoma. Hum Genet 2013; 132(6): 641-648.*