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Long non-coding RNA MIAT promotes non-small cell lung cancer progression by sponging miR-1246

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Abstract. – OBJECTIVE: Recently, long non-coding ribonucleic acids (lncRNAs) have attracted more attention for their roles in tumor progression. The aim of this study was to investigate the exact role of lncRNA MIAT in the progression of non-small cell lung cancer (NSCLC) and to explore the possible underlying mechanism.

PATIENTS AND METHODS: MIAT expression in NSCLC tissue samples was detected by quantitative Real Time-Polymerase Chain Reaction (qRT-PCR). The association between the sion of MIAT and the prognosis of NSC tients were explored. Furthermore, the d healing assay and the transwell assay were ducted in vitro. In addition, the luciferase as and the RNA immunoprecipitation assay (RI were used to elucidate the u mecha nism.

RESULTS: The MIAT exp ion in CLC tissues was significantly h r than corresponding normal t M MIAT expression was so the overall survival time of LC pa The migration and invasion ells were sig ntly promoted after MIA over-expres vitro. Meanwhile, th ion and cel nvasion were obviou remar inhibited after MIAT knock wn in vitro. formatics analysis pre d that microR 46 (miR-1246) was a novel target for MI . The expression R-124 s significantly down-regulated -regu d after the overexpression or dow n of M respectively. Further mecha says s d that miR-1246 was a t targ NSCLC.

CLUSI AT enhanced the NSCLC cell ration a nvasion via targeting miR-124 hich might be a potential biomarker in NS

Words:
non-coding RNA, Non-small cell lung cancer (NS MIAT, MiR-1246.

duction

ncer is one o most frequent cancer the world with high incidence and mortality. It is also th eading cause of tumor-related ths[1,2]. It is est ed that 234,030 new cases of cancer are d nosed globally in 2018[3]. Non-s ell lun ncer (NSCLC) accounts for abou ung cancer cases. A tremendous advance has been made in exploring the molecular tumorigenesis and therapeutic treatment of However, its 5-year survival rate is still wer an 15%[4]. Therefore, it is urgent to realize the underlying molecular mechanism of NSCLC and to find out new therapeutic targets for patients.

Long non-coding ribonucleic acids (lncRNAs) are a type of noncoding RNAs with more than 200 nucleotides in length. Numerous studies have shown that lncRNAs are a new frontier in the research of malignant diseases. For example, the LncRNA PVT1 is significantly up-regulated in gastric cancer, which contributes to the poor prognosis of patients[5]. By sponging to miR-124-3p, lncRNA OGFRP1 participates in the proliferation of NSCLC of cells[6]. In addition, activated by ZEB1, the lncRNA HCCL5 accelerates cell viability, cell migration, epithelial-mesenchymal transition (EMT) and the malignancy of hepatocellular carcinoma[4].

As another subgroup of non-coding RNAs, microRNAs (miRNAs) are small RNAs with about 19–22 nucleotides in length. MiRNAs are involved in the repression or degradation of target RNA transcripts. It has been reported that a single miRNA modulates a diverse of protein-coding or noncoding RNAs in human cells. For example, miR-1269a acts as an onco-miRNA in NSCLC *via* down-regulating SOX6[7]. Through

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targeting PDCD4 in human breast cancer, miRNA-183-5p inhibits cell apoptosis, which may offer a potential therapeutic target for breast cancer[8].

Previous researches have suggested that lncRNA MIAT plays an important role in tumor biology and development. However, the exact function of MIAT in NSCLC has not been fully elucidated. Our work found that the MIAT expression was significantly up-regulated in NSCLC tissues. MIAT promoted the NSCLC cell migration and invasion *in vitro*. Moreover, further experiments explored the underlying mechanism of MIAT function in NSCLC development.

Patients and Methods

Cell Lines and Clinical Samples

60 NSCLC patients who received surgery at the Fujian Cancer Hospital and the Fujian Medical University Cancer Hospital were enrolled in this study. Before the operation, written informed consent was obtained. No radiotherapy or chemotherapy was performed for any patient before the operation. Tissues were collected from [illegible] gery and were stored immediately at –80 [illegible] for subsequent use. All tissues were confirmed [illegible] experienced pathologist. This investigation [illegible] approved by the Ethics Committee of Fujian Cancer Hospital and the Fujian [illegible] niversity Cancer Hospital required.

SPCA1, H1299, PC-9, [illegible]8 and [illegible] normal human bronchial epithe[illegible]ell ([illegible] obtained from the S[illegible]ghai [illegible] Cell Bank (Shanghai, China). [illegible]ells we[illegible]red in Dulbecco's Modified [illegible]e's Medium ([illegible]M; Gibco, Rockville, M[illegible]) consisting [illegible] of fetal bovine serum [illegible]S; G[illegible] Rockville, MD, USA) and penicil[illegible]n. Besides, th[illegible] were maintained in an inc[illegible]r with 5% of C[illegible]7°C.

Cell [illegible]nsfect[illegible]

[illegible]synth[illegible]ed, th[illegible]ntiviral virus targeting M[illegible] cloned[illegible]o pLenti-EF1a-EGFP-F2A-Puro[illegible]r (B[illegible]tiaInc, San Diego, CA, [illegible]293T[illegible]e used to package MIAT lent[illegible]ses (MI[illegible] and empty vector (control), whi[illegible]ere then transfected into SPCA1 NSCLC ce[illegible], MIAT expression in transfect[illegible]ells was conducted using quantitative Real [illegible]e-Polymerase Chain Reaction (qRT-PCR).

[illegible] Pharma provided us lentivirus expressing [illegible]t-hairpin RNA (shRNA) against MIAT (MIAT/shRNA). MIAT/shRNA was cloned into pGPH1/Neo vector (GenePharma, [illegible] China), which was then transfect[illegible]to H[illegible] cells.

RNA Extraction and qRT-PC[illegible]

The Total RNA in tiss[illegible] and c[illegible]s ex[illegible]tracted by TRIzol reag[illegible] (Invitrogen[illegible] bad, CA, USA). Subse[illegible]tly, th[illegible]xtracted [illegible] RNA was reverse-tr[illegible]ribed t[illegible]mplementary deoxyribose nucleic [illegible]cD[illegible] throus[illegible]e reverse Transcript[illegible] Ki[illegible]ka Bio[illegible]hology Co., Ltd., Dal[illegible] China). [illegible]pri[illegible] used in this study w[illegible]as follows: [illegible]imers forward: [illegible]GTTCACAA[illegible]ACACTG-3′, reverse: [illegible]-TC[illegible]TTTGGCATTCTAGG-3′; β-actin primers for[illegible] 5′-GATGGAAATC-GT[illegible]GCT-3′ and [illegible]se: 5′-TGGCACT-T[illegible]TGGAAATGC-3′. The thermal cycle was [illegible]ollows: 30 s at [illegible]5°C, 5 s for 40 cycles at 95°C, [illegible] 35 s at 60°C.

W[illegible]d Heal[illegible] Assay

C[illegible]t transferred into 6-well plates (Corning, [illegible]orning, NY, USA) and cultured in [illegible]MEM medium overnight. Once scratched with [illegible]e, the cells were cultured in serum-free [illegible]ME[illegible] Wound closure was viewed at different time points.

Transwell Assay

5×10^4 cells in 200 µL serum-free DMEM were transformed to the upper chamber of an 8 µm pore size insert (Millipore, Billerica, MA, USA) coated with or without 50 µg Matrigel (BD Biosciences, San Jose, CA, USA). Meanwhile, the lower chamber was added with DMEM and FBS. 48 h later, after wiped by cotton swab, the top surface of chambers was immersed for 10 min with precooling methanol. Then they were stained with crystal violet for 30 min. Three fields were randomly selected for each sample, and the number of migrating cells was counted.

Luciferase Reporter Gene Assay

For the luciferase reporter gene assay, the 3′-UTR of MIAT was cloned into pGL3 vector (Promega, Madison, WI, USA), namely wild-type (WT) 3′-UTR. The quick-change site-directed mutagenesis kit (Stratagene, Cedar Creek, USA) was used for site-directed mutagenesis of miR-1246 binding site in MIAT 3′-UTR, namely mutant (MUT) 3′-UTR. Subsequently, the cells were

transfected with WT-3′-UTR or MUT-3′-UTR and miR-ctrl or miR-1246 for 48 h. Finally, the luciferase activity was detected by the dual luciferase reporter assay system (Promega, Madison, WI, USA).

RNA Immunoprecipitation Assay (RIP)

Magna RIP RNA-Binding Protein Immunoprecipitation Kit (Millipore, Billerica, MA, USA) was used for RIP assay. Co-precipitated RNAs were detected by qRT-PCR.

Statistical Analysis

Statistical Product and Service Solutions (SPSS) 20.0 (IBM SPSS Statistics for Windows, Armonk, NY, USA) was used for all statistical analysis. Data were presented as mean ± standard deviation (SD). Chi-square test, Student *t*-test and Kaplan-Meier method were selected when appropriate. $p<0.05$ was considered statistically significant.

Results

MIAT Expression in NSCLC Tissues and Cells

Firstly, qRT-PCR was conducted to de MIAT expression in 60 NSCLC tissues and NSCLC cell lines. As a resu was significantly up-regulated in N C tis samples (Figure 1A). Meanwhile, t IAT e sion in NSCLC cells was signifi high the normal human b chi l cell line (16HBE) (Figure 1B

High Expression of MIAT Was Correlated with Poor Overall Su of NSCLC Patients

The survival of patients after s ry was analyzed through the Kaplan-Meie od. According to the median expression of M NSCLC patients were divided into group ding high-MIAT group and lo IAT group. of Kaplan-Meier analy howed hat the h MIAT level indicate orse s al of NSCLC patients (Figure 1C).

Overexpres of MI m the Migration Invasion f ells

SPCA1 lls were chose or the overexpression IAT. fection efficiency was confirmed by qRT-PCR (2A). Results of wound heal y revealed tha MIAT was overexp d, the migration ability of NSCLC cells was ificantly enha ed (Figure 2B). Furthermore, nswell assay a ound that after MIAT overexion *in vitro*, number of migrated cells and i cells in ed remarkably (Figure 2C, 2D).

Knockdown of MIAT Inhibited the Migration and Invasion NSCLC Cells

NSCLC cells were selected for the knockown MIAT. Transfection efficiency was confirmed by qRT-PCR as well (Figure 3A). Wound healing assay demonstrated that after MIAT was knocked down, the migration ability of NSCLC cells was significantly inhibited (Figure 3B). Similarly, transwell assay indicated that after MIAT was knocked down in the NSCLC cells, the number of migrated and invaded cells decreased significantly (Figure 3C, 3D).

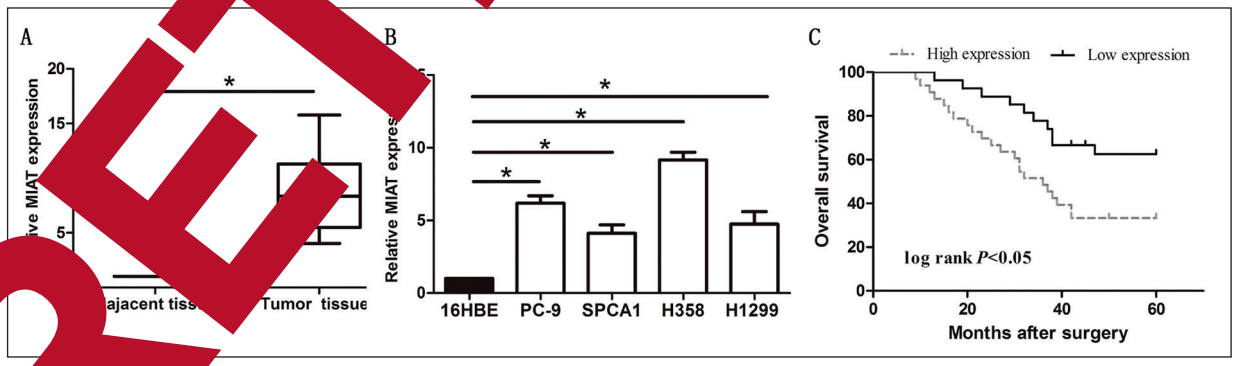


Figure 1. Up-regulated expression level of MIAT in NSCLC tissues and cell lines. ***A,*** MIAT expression was significantly higher in NSCLC tissues compared with adjacent tissues. ***B,*** The expression level of MIAT relative to β-actin was determined in human NSCLC cell lines and normal human bronchial epithelial cell (16HBE) by qRT-PCR. ***C,*** The higher expression of MIAT was associated with the worse overall survival of NSCLC patients. Data were presented as mean ± standard error of the mean. *$p<0.05$.

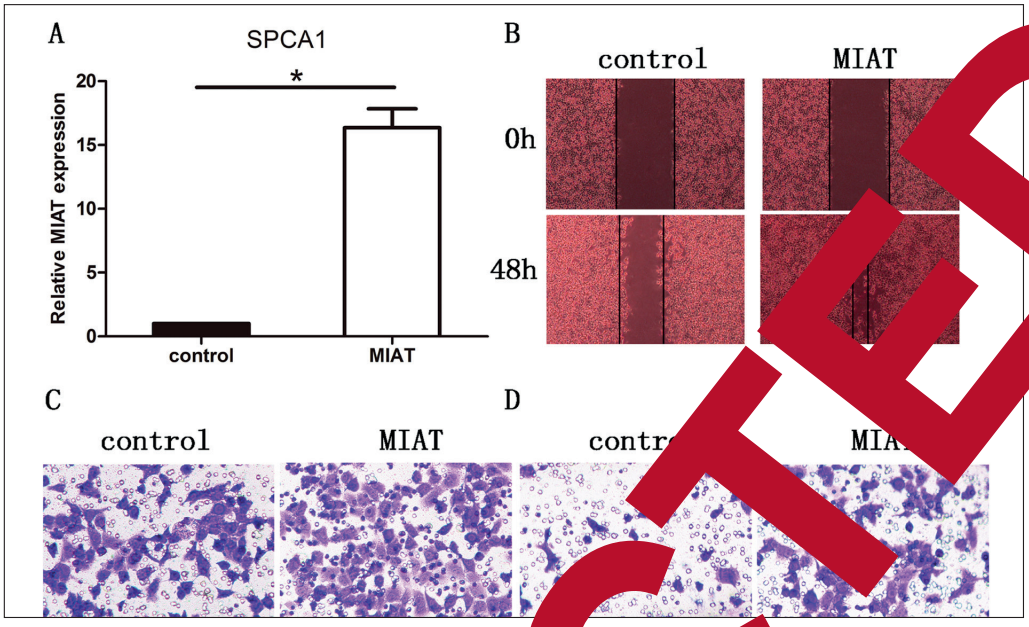
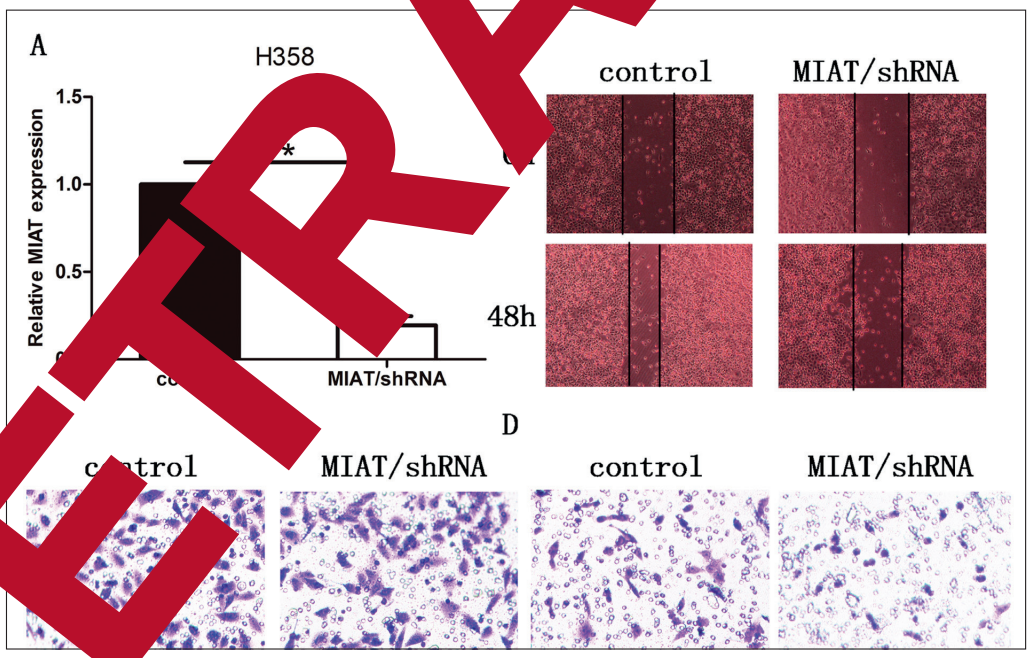


Figure 2. Overexpression of MIAT promoted the migration and [illegible]sion of SPCA1 [illegible]LC cells. ***A,*** The MIAT expression in SPCA1 NSCLC cells transduced with MIAT lentiviruses (MI[illegible]and empty vect[illegible]ontrol) was detected by qRT-PCR. β-actin was used as an internal control. ***B,*** Wound healing ass[illegible]wed that the [illegible]expression of MIAT significantly increased the migration of SPCA1 NSCLC cells (magnification: 10×). [illegible]swell[illegible]showed that the number of migrated cells increased significantly *via* overexpression of MIAT in SPCA1 [illegible]well assay showed that the number of invaded cells increased significantly *via* overexpress[illegible]f MIAT in SPCA1 cells (magnification: 40×). The results represented the average of three independent experiments (me[illegible]ror of the mean). *$p<0.05$, as compared with control cells.



Figu[illegible] Knockdown of MIAT inhibited the migration and invasion of H358 NSCLC cells. ***A,*** The MIAT expression in H3[illegible]ransduced with MIAT shRNA (MIAT/shRNA) and empty vector (control) was detected by qRT-PCR. β[illegible]was used as an internal control. ***B,*** Wound healing assay showed that the knockdown of MIAT significantly inhibited [illegible]migration of H358 NSCLC cells (magnification: 10×). ***C,*** Transwell assay showed that the number of migrated cells [illegible]antly decreased *via* knockdown of MIAT in H358 cells. ***D,*** Transwell assay showed that the number of invaded cells sig[illegible]ly decreased *via* knockdown of MIAT in H358 cells (magnification: 40×). The results represented the average of three [illegible]pendent experiments (mean ± standard error of the mean). *$p<0.05$, as compared with control cells.

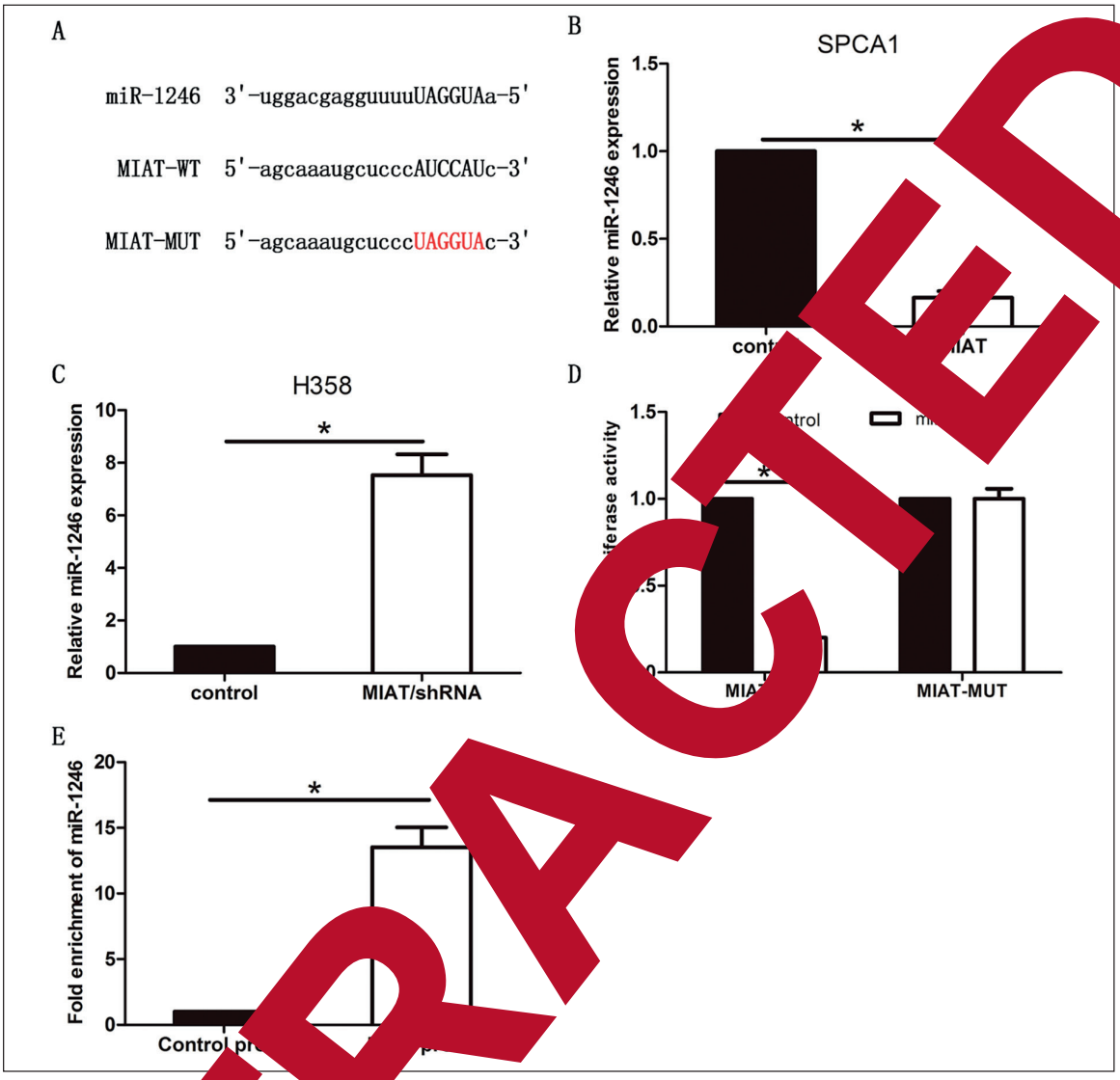


Figure 4. Reciprocal ssion betw AT and miR-1246. ***A,*** The binding sites of miR-1246 on MIAT. ***B,*** The MiR-1246 expression decr significantly in entivirus group compared with control group. ***C,*** The MiR-1246 expression increased significa IAT/shRNA gr ompared with control group. ***D,*** The co-transfection of miR-1246 and MIAT-WT stron ecr iferase activity. Co-transfection of miR-control and MIAT-WT did not change luciferase activity. Meanwh , co-tran of miR-1246 and MIAT-MUT did not change luciferase activity either. ***E,*** RIP assay results demo ted that miR-1 ld be remarkably enriched in MIAT group compared with control group. The results represente verage of three inde nt experiments. Data were presented as mean ± standard error of the mean. *p<0.05.

The n Be en MiR-1246 and MIAT in C

base http://starbase.sysu.edu.cn/mi RNA.php as used to predict miRNAs that ch contained complementary base with M 6 is a tumor suppressor which suppress cancer cell proliferation. Therefore, focused on miR-1246 among these miRNAs w ere interacted with MIAT (Figure 4A). Inde the qRT-PCR assay showed that the expression of miR-1246 in MIAT lentivirus cells was significantly lower than that of the control cells (Figure 4B). Meanwhile, the expression of miR-1246 in MIAT/shRNA cells was significantly higher than that of the control cells (Figure 4C). Furthermore, the luciferase reporter gene assay revealed that co-transfection of MIAT-WT and miR-1246 significantly decreased the luciferase activity. However, no significant changes were observed in luciferase activity after the

co-transfection of MIAT-MUT and miR-1246 (Figure 4D). Subsequent RIP assay demonstrated that miR-1246 could be remarkably enriched in MIAT group(,)compared with control group. This suggested that MIAT might work as a miR-1246 sponge (Figure 4E). In summary, these data demonstrated that miR-1246 was a direct target of MIAT.

Discussion

An increasing number of researches have explored the important regulatory roles of ncRNAs in the mammalian genes. It has been reported that the ncRNA dysfunction is involved in epigenetic alterations, which contributes to tumorigenesis and metastasis. Therefore, numerous studies based on tumor-related ncRNAs may provide novel ideas for the diagnosis and treatment of malignancies. It has already been reported that ncRNAs contribute to the malignancy of tumor cells, especially for NSCLC. By targeting CD73/NT5E, the overexpression of miR-30a-5p inhibits the proliferation of NSCLC6 cells. In addition, miR-106b-5p facilitates cell proliferation and suppresses cell apoptosis in NSCLC through targeting regulation of BTG3 expression[9].

Located on chromosome 22q12, MIAT (myocardial infarction associated transcript) was originally identified to be involved in myocardial infarction (MI), contributing to the risk of MI[10]. Recent researchers have found that MIAT is involved in numerous diseases, including malignant tumors. For example, MIAT serves as an oncogene in pancreatic cancer, promoting cell proliferation and metastasis, which can be reversed by miR-155-5p. By sponging miR-155-5p, MIAT enhances the progression of breast cancer *via* serving as a competing of DUSP7[12]. By modulating miR-141/DDX5 signaling pathway, MIAT facilitates the growth and metastasis of gastric cancer[13]. In addition, MIAT enhances colorectal cancer growth and metastasis by regulating miR-132/Nectin-1 pathway[14]. We showed that MIAT was significantly up-regulated in NSCLC tissues and cells. Besides, there was significant correlation between patients' prognosis and MIAT expression level. Furthermore, MIAT overexpression in NSCLC cells, cell migration and invasion abilities were significantly promoted. However, after MIAT was knocked down in NSCLC cells, cell migration and invasion abilities were significantly inhibited. The above results indicated that MIAT promoted tumorigenesis of NSCLC and act as an oncogene.

Recently, the reciprocal influence between lncRNAs and miRNAs has emerged. Similar sequences targeted by miRNAs are found, meanwhile, miRNAs can be sequestered from mRNA. LncRNAs have been reported to participate in the tumor progression as competing endogenous RNAs. For example, lncRNA CRNDE facilitates the progression of colorectal carcinoma through binding to miR-[illegible]. Through inhibiting miR-200[illegible]429, lncRNA HEIH promotes the proliferation and metastasis of melanoma[16]. Numerous lncRNAs are reported to be abnormally expressed and need for tumorigenesis. Some reports have suggested that miR-1246 functions as either tumor suppressor or an oncogene. MiR-1[illegible] is low-expressed in cervical cancer, which is negatively related to the development of cervical cancer and HPV infection status[17]. Through targeting CCNG2, exosomal miR-1246 facilitates the proliferation and invasion of breast cancer. This may induce drug resistance in breast cancer[18]. In addition, miR-1246 promotes chemoresistance and cancer stemness in oral carcinomas targeting CCNG2[19]. Through the conversion of the expression of miR-1290, miR-1246 functions as a tumor-initiator and promotes the progression of NSCLC[20]. Moreover, miR-1246 enhances the migration of NSCLC cells through targeting cytoplasmic polyadenylation element-binding protein 4[21].

In the present study, the miR-1246 expression was significantly down-regulated after the overexpression of MIAT. However, miR-1246 expression was obviously upregulated after knockdown of MIAT. The luciferase reporter gene assay confirmed that miR-1246 could directly bind to MIAT. Moreover, miR-1246 was significantly enriched by MIAT RIP assay. The results above suggested that MIAT might promote tumorigenesis of NSCLC *via* targeting miR-1246.

Conclusions

We observed that MIAT was remarkably up-regulated in NSCLC, and was negatively correlated with poor prognosis of patients. Besides, MIAT could enhance NSCLC metastasis through targeting miR-1246. Our findings suggested that MIAT might contribute to therapy for NSCLC as a candidate target.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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