

Original Article

The long noncoding RNA TUG1 suppresses non-small-cell lung cancer through the TUG1/miR-31-5p/CDIP1 axis

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Abstract: Non-small-cell lung cancer (NSCLC) is estimated to make up 75-80% of all lung cancers and has high invasiveness and high mortality rates. Long noncoding RNA taurine upregulated 1 (TUG1) has been shown to be involved in NSCLC malignancies. In this research, the qRT-PCR assay results indicated that TUG1 is downregulated and the expression of miR-31-5p is increased in NSCLC tissues and cells. TUG1 overexpression leads to the suppression of cell viability, migration, and invasion but results in the promotion of cell apoptosis, as shown by CCK-8 and Transwell assays and flow cytometry analyses. Similarly, TUG1 upregulation also inhibits tumor growth *in vivo*. Starbase v.2.0, TargetScan, and dual-luciferase reporter assays indicated that TUG1 regulates the miR-31-5p expression levels directly, and meanwhile, miR-31-5p directly targets CDIP1. MiR-31-5p upregulation is able to antagonize the inhibiting effect on NSCLC progression induced by the TUG1 overexpression. Moreover, upregulated TUG1 inhibits CDIP1 expression by sponging miR-31-5p and further regulating the TNF- α pathway. In conclusion, TUG1 suppresses tumorigenesis through the miR-31-5p/CDIP1 axis via the TNF- α pathway, providing a theoretical basis for NSCLC clinical therapy.

Keywords: lncRNA TUG1, miR-31-5p, CDIP1, TNF- α pathway, NSCLC

Introduction

Lung cancer is an advanced cancer which greatly endangers people's lives [1], and 4/5 of all lung cancers are non-small-cell lung cancer (NSCLC). Moreover, in the absence of effective treatment, NSCLC patients have a low five-year survival rate [2]. Previous studies give evidence of the many factors and regulatory mechanisms involved in the occurrence and development of NSCLC [3, 4].

Long noncoding RNAs (lncRNAs) are a novel class of transcription genes without a protein-coding function [5]. Recently, accumulating evidence has indicated that lncRNAs play crucial roles in the progression and initiation of multiple tumors [6]. The long noncoding RNA taurine upregulated 1 (TUG1), which has 7.1 thousand

bases, is involved in the development of various malignancies, such as NSCLC [7], hepatocellular carcinoma [8], and oral squamous cell carcinoma [9]. In addition, TUG1 is overexpressed in urothelial carcinoma [10]. Unfavorable prognoses and disease statuses in osteosarcoma are closely related to the upregulation of TUG1 [11]. These previous studies proved that TUG1 plays a vital role in the carcinogenesis process, so we thoroughly investigated the role and its underlying molecular mechanism in NSCLC.

Over the past decades, a large number of studies uncovered the functions of microRNAs (miRNAs), which serve as carcinogens or tumor suppressor genes in the procession and initiation of NSCLC [12, 13]. Recently, multiple studies have reported that miRNA expression is

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involved in the progression of cancer [14, 15]. For example, miR-145 inhibits cell proliferation in NSCLC [16] and acts as a metastasis suppressor in lung cancer [17]. Moreover, miR-101 is involved in human breast carcinogenesis [18]. In colorectal cancer, miR-31-5p participates in the regulation of cell growth, migration, and invasion [19]. However, the role of miR-31-5p in tumorigenesis needs further investigation. Here, we aimed to investigate how and whether miR-31-5p plays a part in the progression of NSCLC.

The extrinsic and the intrinsic pathways are two separate apoptotic pathways. In response to stress conditions, such as the exposure to DNA damage, the intrinsic pathway is initiated, and the extrinsic pathway is initiated by activating the death receptors [20, 21]. Cell death-inducing p53-target protein 1 (CDIP1) is confirmed as a new p53 target gene, and it is a crucial downstream regulator of p53-dependent apoptosis, and p53-mediated apoptosis has been proved to be dependent on the intrinsic cell death pathway [22]. Moreover, the TNF- α family of cytokines was confirmed to be involved in the extrinsic death pathway by its binding to cognate receptors [23]. Lauren Brown and his colleagues reported that TNF- α participates in CDIP-dependent apoptosis [24]. Moreover, CDIP1 is positively correlated with tumorigenesis and tumor progression. CDIP1 can regulate the balance of organism metabolism [25]. However, the functional effects of CDIP1 on NSCLC progression remain unclear.

The present research discovered the underlying mechanisms of TUG1 and found that, in NSCLC tissues and cell lines, TUG1 has a lower expression level. The overexpression of TUG1 stimulates apoptosis, blocked cell viability, migration, and invasion in NSCLC cells. Additionally, we confirmed that miR-31-5p can regulate CDIP1 directly and can bind to TUG1. All our findings indicate that TUG1 regulates tumorigenesis through the miR-31-5p/CDIP1 axis via the TNF- α signal pathway in NSCLC.

Materials and methods

Acquisition of tissue samples and cell culture

Twenty-eight samples of NSCLC and paraneoplastic tissues were obtained from the First People's Hospital of Baiyin through surgical

resection. We stored all the samples at -80°C immediately. This research was approved by the Ethics Committee of the First People's Hospital of Baiyin. All the participants provided written informed consent prior to the surgery.

From the American Tissue Culture Collection (Manassas, VA, USA), we purchased four NSCLC cell lines (A549, H1650, H1299, and H1975). The human bronchial epithelial cells (HBE) we used were obtained from the BeNa culture collection (Beijing China). A549, H1650, and HBE cells were proliferated in 10% fetal bovine serum (FBS) (Gibco) complemented with Dulbecco's modified eagle medium (DMEM) (Gibco, Carlsbad, CA, USA) and antibiotics (100 U/mL penicillin and 100 $\mu\text{g}/\text{mL}$ streptomycin) (Hyclone, Logan, UT, USA), while H1299 and H1975 cells were incubated in Roswell Park Memorial Institute-1640 (RPMI-1640) (Thermo Fisher Scientific) complemented with 10% FBS and antibiotics. We cultivated the cells in a 37°C carbon dioxide incubator with 5% CO_2 .

Transient transfection

Genepharma (Shanghai, China) provided the products we needed, such as small interfering RNA (siRNA) targeting TUG1 (si-TUG1) and its corresponding control (si-NC), and the overexpression of TUG1 (pcDNA-TUG1) vectors. The miR-31-5p mimics, the miR-31-5p inhibitors, and their matched controls were provided by RIBOBIO (Guangzhou, China). 5×10^4 cells/well of NSCLC cells were inoculated in six-well plates and cultivated overnight before the transfection. Then, the siRNA or over-expression vectors were transfected into A549 and H1650 using LipofectamineTM2000 (Thermo Fisher Scientific, Rockford, IL, USA). After the cells were transfected for 24 h, we collected the cells for further experiments.

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

The total RNA was made from the tumors and cells and extracted using Trizol (Thermo Fisher Scientific). An All-in-OneTM miRNA First-Strand cDNA Synthesis Kit (GeneCopoeia, Rockville, MD, USA) was used to process the RNA inverse transcription and the PCR was implemented with iQTM SYBR[®] Green Supermix (Bio-Rad, Hercules, CA), using GAPDH as the internal control. With the purpose of calculating the

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relative expressions of these genes, the $2^{-\Delta\Delta Ct}$ method was used after normalization to GAPDH. Special primers were synthesized in Genepharma (Shanghai, China) as below: TUG1 (Forward, 5'-GACAGAGGCGACAGGAACGACG-3'; Reverse, 5'-CACCATGCAACATCGAACCG-3'), CDIP1 (Forward, 5'-TCAAACCTCATGGGTTCTCC-3'; Reverse, 5'-GTGTCATCCAACGTGGTCAG-3') miR-31-5p (Forward, 5'-TCGATACGGTCTAGAACGGA-3'; Reverse, 5'-GTCGTATCCAGTGGTGTGCTG-3') GAPDH (Forward, 5'-ATTCCATGGCACCGTCAAGGCTGA-3'; Reverse, 5'-TTCTCCATGGTGGTGAAGACGCCA-3').

Cell viability

We used cell counting kit-8 (CCK-8) kits (Sigma, Santa Clara, CA) to determine the cell viability. After the transfection, the cells were incubated for 48 h. Then, eWST-8 reagent (Sigma) was added following the manufacturer's instructions and incubated for 2 h. Subsequently, we used a multiscan spectrum (Bio-Rad) to read the plate at 450 nm.

Flow cytometry analysis of the apoptosis

We used an FITC Annexin V Apoptosis Detection Kit I (BD Biosciences, San Jose, CA, USA) in conjunction with propidium iodide (PI) to measure the cell apoptosis. We stained the resuspended cells with FITC Annexin V and Propidium iodide (PI) according to the protocol. Then, a flow cytometer (BD Biosciences) was used to measure the apoptotic cells. Three replicating holes were needed in the assay.

Western blot analysis

A RIPA lysis buffer was applied to extract the total proteins derived from the tissues or cells. We used a BCA Protein Assay Kit (Beyotime, Shanghai, China) to identify the protein concentrations, and then the protein was denatured in boiling water for 5-10 min. In order to separate the different molecular weight proteins, we used SDS-PAGE gels to separate the quantitative proteins, and diverted them onto polyvinylidene difluoride membranes (PVDF) (Millipore, Billerica, MA, USA). 5% (w/v) albumin from bovine serum (BSA) (Solarbio, Beijing, China) was used to block the nonspecific antigenic determinants in the membranes for 2 h at room temperature. Then we blotted the membranes with the indicated primary anti-

bodies such as CDIP1 (Thermo Fisher Scientific, PA5-20697, 1:2000), TNF- α (Cell Signaling Technologies, 3707, 1:1000) and GAPDH (Abcam, Cambridge, MA, USA, ab9485, 1:2500) overnight at 4°C and incubated them with a second antibody (Abcam, ab6721, 1:2000) for 40 min at room temperature. After washing with TBST four times, 5 min/time, the signals were measured using a commercial enhanced chemiluminescence chromogenic substrate (Millipore) and quantified using Image Lab software (Bio-Rad, Hercules, CA, USA).

Transwell migration and invasion assays

The cell migration of the A549 and H1650 cells was measured using Transwell chambers (8 μ m pore; Corning, Inc. Corning, NY, USA). 1×10^6 cells were seeded in the upper chamber not enveloped with Matrigel (BD Biosciences). Then, the medium was placed into the low chamber and cultured for 24 h. Subsequently, we stained the migrating cells with crystal violet and counted them using an inverted microscope. The upper chamber was covered with Matrigel for the invasion assay.

Dual-luciferase reporter assay

The partial fragments of the TUG1 containing miR-31-5p were calculated using Starbase v.2.0, and the prediction of binding sites between CDIP1 and miR-31-5p was done using TargetScan (http://www.targetscan.org/vert_72/). Subsequently, the wild-type (wt) sequences of TUG1 or CDIP1 and the mutant type (mut) sequences of TUG1 or CDIP1, which target the miR-31-5p binding sites were mutated, and then they were designed and synthesized respectively. Then these genetic fragments were recombined to the pmirGLO vectors (Promega, Madison, WI, USA) and then inserted into the luciferase genes downstream, and then we constructed the wt-TUG1, mut-TUG1, wt-CDIP1, or mut-CDIP1 vectors. After that, the luciferase activity was measured using a dual-luciferase assay kit (Promega) using THERMO Varioskan Flash (Thermo Fisher Scientific).

Animal experiments

BALB/c male nude mice were used to measure the tumorigenesis in the present study. The animal experiments were licensed by the Animal

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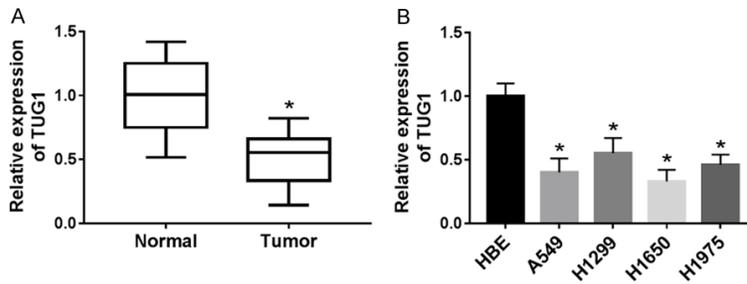


Figure 1. Low expressions of TUG1 in NSCLC tissues and cell lines. The expressions of TUG1 in the NSCLC tissues (A) and cell lines (B) were measured using qRT-PCR. * $P < 0.05$.

Care and Use Committee of the First People's Hospital of Baiyin. pcDNA-TUG1 and pcDNA-NC were stably transfected into the A549 cells respectively, and then we injected the steady transfer cells into the left flank of the nude mice, and then the mice were divided into three groups: the control group ($n=10$), the pcDNA-NC ($n=10$) group, and the pcDNA-TUG1 group ($n=10$). Subsequently, the tumors' lengths and widths were determined every 4 days, and we calculated the tumor volumes as follow: $\text{volume} = (\text{length} \times \text{width})^2 / 2$. All the mice were euthanized after 28 days, and the tumor weights were determined, and the tumor tissues were collected.

Statistical analysis

All the experimental values are presented as the mean \pm standard deviation (mean \pm SD) of the experiments, which were done in triplicate. We used SPSS Graduate Pack, version 19.0 (IBM Corp., Armonk, NY, USA) to analyze the data. Statistically significant differences were evaluated using Student's *t*-tests for the paired comparisons. The multiple-group comparisons were performed using one-way analyses of variance with Tukey's post hoc tests. The correlational analyses between the different genes were conducted using Spearman correlation analyses. $P < 0.05$ indicated a significant difference.

Results

The down-regulation of TUG1 in the NSCLC tissues and cell lines

In order to explore the function of TUG1 in NSCLC, the TUG1 expression levels were measured in the NSCLC tissues and in the paracancerous tissues, as well as in the NSCLC and

HBE cells. TUG1 was significantly downregulated in the NSCLC tissues, compared to the normal tissues (**Figure 1A**). Moreover, a decrease in the TUG1 expressions also occurred in the NSCLC cell lines (A549, H1299, H1650, and H1975) compared with the HBE cells (**Figure 1B**).

TUG1 overexpression promoted apoptosis and suppressed cell proliferation, migration, and invasion in the NSCLC cells

To further explore the function of TUG1 in NSCLC, functional assays were performed. pcDNA-NC or pcDNA-TUG1 were transfected into the A549 and H1650 cells, respectively. The TUG1 overexpression significantly increased the expression of TUG1 in both the A549 and H1650 cells (**Figure 2A**). TUG1 overexpression notably suppressed the cell viability of the A549 and H1650 cells (**Figure 2B**). Flow cytometry was used to determine the apoptotic rate of the NSCLC cells, and the data demonstrated that the TUG1 upregulation increased cell apoptosis (**Figure 2C**). Moreover, the cell migration (**Figure 2D**) and invasion (**Figure 2E**) were prominently decreased by the pcDNA-TUG1 in the NSCLC cells.

TUG1 overexpression suppressed tumor growth in vivo

Abnormal versions of TUG1 occur in NSCLC tissues and cells, indicating that TUG1 is involved in the development of NSCLC. Thus, we constructed pcDNA-TUG1 and transfected it into A549 cells to establish a cell line. This stable A549 cell line was injected into the nude mice. The results proved that the tumor volume (**Figure 3A**) and weight (**Figure 3B**) were apparently suppressed by the TUG1 upregulation. Also, the TUG1 levels were also increased in the tumor tissues isolated from the nude mice (**Figure 3C**). These results indicate that TUG1 plays a critical role in the progression of NSCLC.

MIR-31-5p is negatively regulated by TUG1 in NSCLC

The binding sites between miR-31-5p and TUG1 were predicted by Starbase v.2.0 (**Figure**

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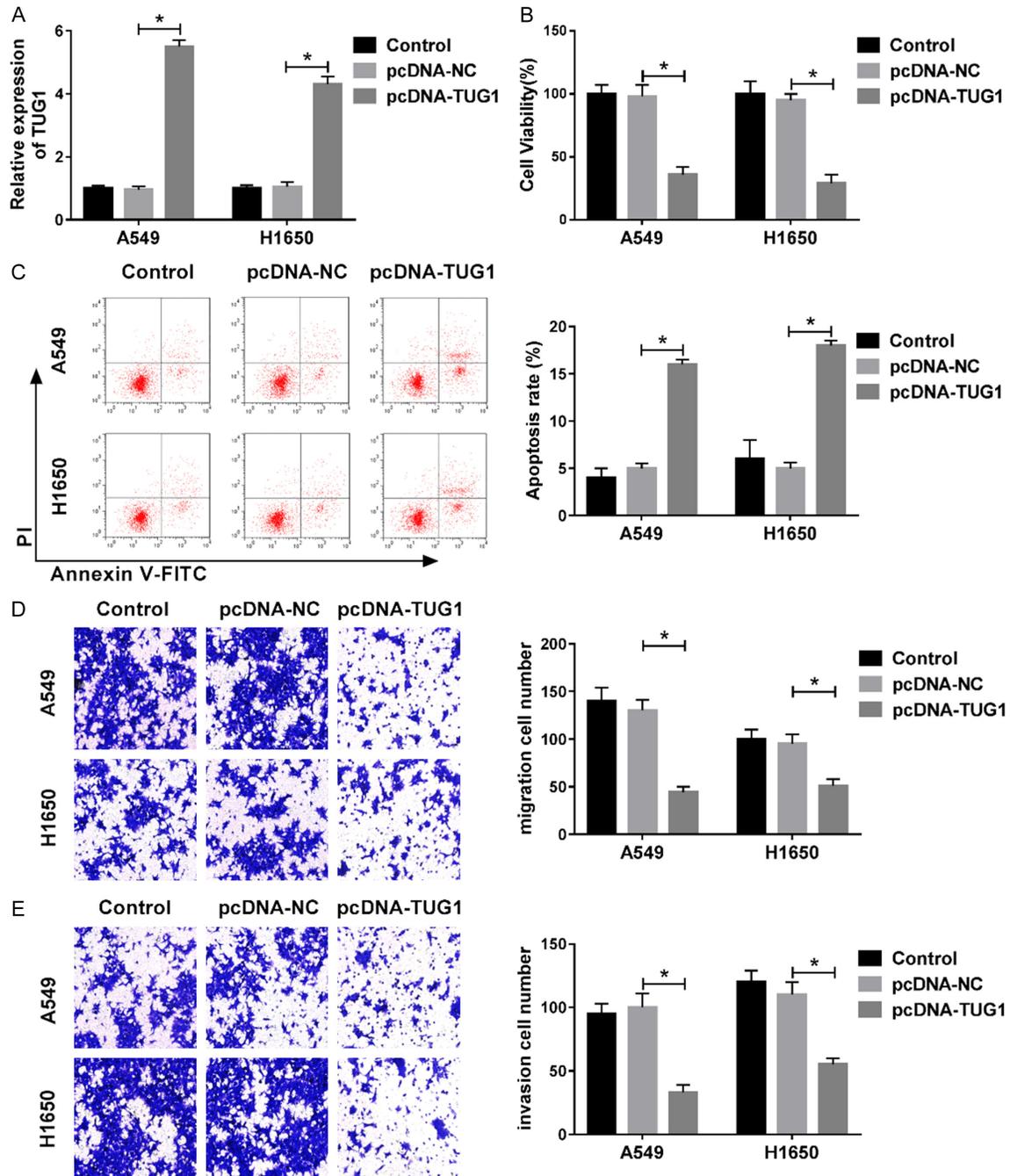


Figure 2. The overexpression of TUG1 promotes apoptosis and suppresses proliferation, migration, and invasion in NSCLC cells. (A-E) A549 and H1650 cells were transfected with pcDNA-NC or pcDNA-TUG1. (A) The measurement of TUG1 with qRT-PCR. The cell viability (B), apoptosis (C), migration (D), and invasion (E) were measured using CCK-8, flow cytometry, and Transwell assays, respectively. * $P < 0.05$.

5A). Research findings indicate that the miR-31-5p expression levels were remarkably boosted in the NSCLC tissues (Figure 4A) and cells (Figure 4B). Then, we performed a dual-luciferase reporter assay to verify the previous results. These results demonstrated that com-

pared with the control, the luciferase activity was dramatically repressed in the HSCLC cells co-transfected with the wt-TUG1 and miR-31-5p mimics, but the luciferase activity of cells with mut TUG1 and miR-31-5p co-transfection was not affected (Figure 5B and 5C), meaning

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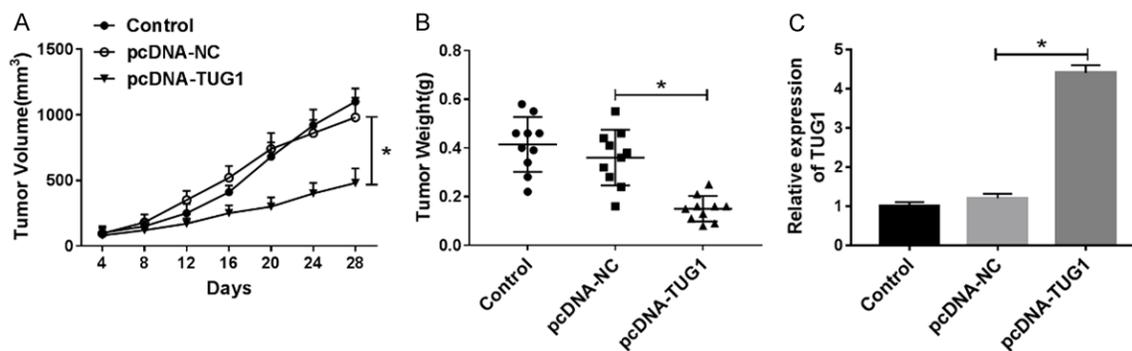


Figure 3. The overexpression of TUG1 suppresses tumor growth in NSCLC. (A-C) The injection of cells transfected with pcDNA-NC or pcDNA-TUG1 was involved in tumorigenesis. The tumor volumes (mm³) (A) and tumor weights (g) (B) were measured. The TUG1 levels were determined using qRT-PCR (C) after the tumorigenesis. n=10, *P<0.05.

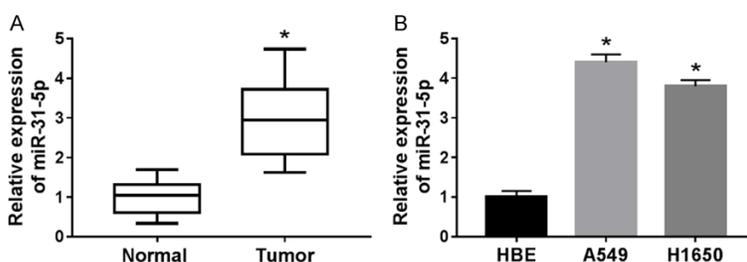


Figure 4. High expressions of miR-31-5p in the NSCLC tissues and cell lines. Measurement of miR-31-5p in the NSCLC tissues (A) and cell lines (B) using qRT-PCR. *P<0.05.

that the TUG1 function in NSCLC targeted miR-31-5p. Moreover, the upregulation of TUG1 attenuated the miR-31-5p expression level in NSCLC (Figure 5D), but the knockdown of TUG1 enhanced the miR-31-5p expression (Figure 5E). In addition, the miR-31-5p was significantly inversely correlated with TUG1 (Figure 5F).

The miR-31-5p mimic recovered the effect of TUG1 overexpression on cell viability, apoptosis, migration, and invasion

The overexpression of miR-31-5p eliminated the suppressive effect of the TUG1-induced expression increase of miR-31-5p (Figure 6A). A flow cytometry analysis demonstrated that miR-31-5p regained the promotion effect of the TUG1 overexpression on cell apoptosis (Figure 6C). Meanwhile, the attenuated cell viability (Figure 6B), migration (Figure 6D) and invasion (Figure 6E) induced by TUG1 upregulation were evidently enhanced by the miR-31-5p mimic. Therefore, the miR-31-5p mimic restored the effects of the TUG1 upregulation on cell viability, apoptosis, migration, and invasion.

CDIP1 is a target gene of miR-31-5p

Bioinformatics revealed the binding sites among miR-31-5p and CDIP1 3'UTR through the Targetscan online website (Figure 7A), enabling us to make further explorations of the effect of miR-31-5p in NSCLC. A dual-luciferase reporter assay revealed that, in the NSCLC cells co-transfected with wt-CDIP1 and miR-31-

5p mimic group, the luciferase activity was significantly increased, but there was no significant change in the mut-CDIP1 group (Figure 7B, 7C). The CDIP1 expression level, which was measured using western blot, was suppressed by the miR-31-5p mimic (Figure 7D) but was increased by the miR-31-5p inhibitor (Figure 7E).

TUG1 regulates the TNF- α pathway by affecting the CDIP1 expression

As shown in Figure 8A, 8B, TUG1 overexpression raises the CDIP1 protein level significantly, which was abolished by the miR-31-5p upregulation, suggesting that TUG1 regulates CDIP1 by sponging miR-31-5p. However, the downstream molecular mechanism is unclear. Thus, we investigated the regulatory effect of TUG1 on the TNF- α pathway. Our data showed that the TNF- α levels were enhanced by the upregulation of TUG1 (Figure 8A), while the miR-31-5p mimic restored the TUG1-induced higher expression of TNF- α (Figure 8B). The results indicated that TUG1 regulates the TNF- α

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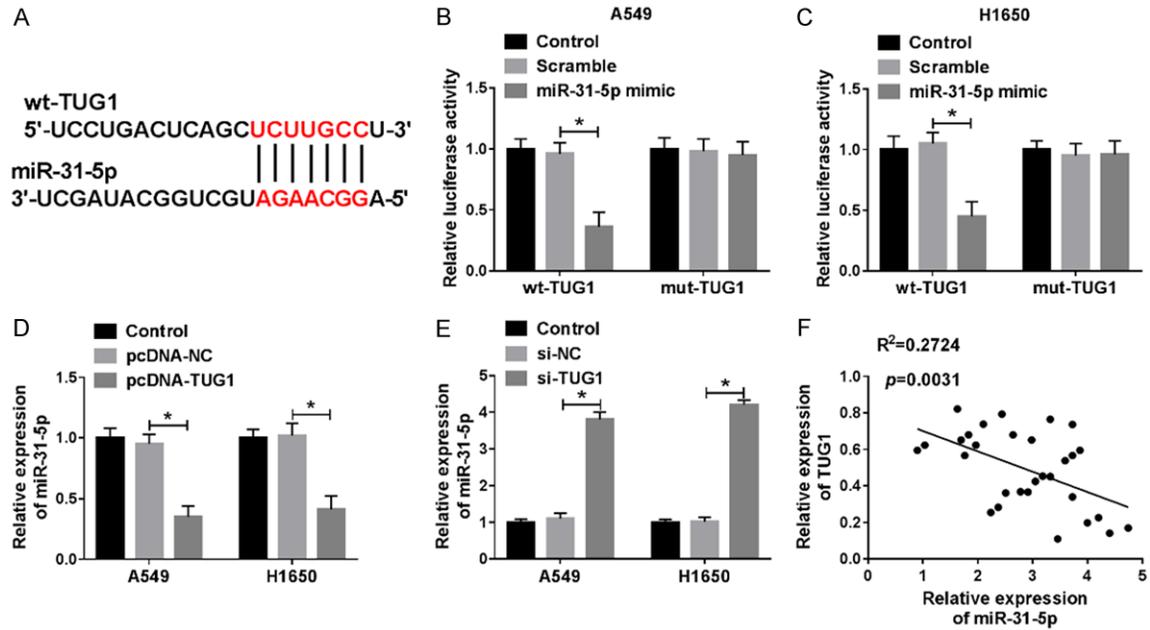


Figure 5. MiR-31-5p was a direct target of TUG1. (A) The putative binding sites between TUG1 and miR-31-5p. (B and C) The luciferase activity in the A549 and H1650 cells co-transfected with luciferase reporter plasmids (wt-TUG1 or mut-TUG1) and miR-31-5p or the corresponding control. The effects of TUG1 overexpression (D) or knockdown (E) on the expression of miR-31-5p. (F) An analysis of the correlation between TUG1 and miR-31-5p. * $P < 0.05$.

signal pathway by mediating the miR-31-5p/CDIP1 axis.

Discussion

Recently, plenty of evidence has appeared revealing the underlying mechanisms of lncRNA in tumor development and initiation [26, 27]. Multiple lncRNAs have been shown to be involved in various cancers, including NSCLC [28-31]. A growing number of studies have proved that TUG1 is closely related to tumorigenesis [32, 33]. Li *et al.* showed that TUG1 expression is increased in tongue squamous cell carcinoma tissues compared with normal tissue samples [34]. Lin *et al.* revealed that TUG1 is down-regulated in NSCLC tumor tissues [30]. The research results from Zhang *et al.* demonstrated that TUG1 inhibits the NSCLC carcinogenesis process [32]. We observed that the expression of TUG1 was consistently and significantly downregulated in NSCLC. Also, upregulated TUG1 suppresses cell growth and metastasis but facilitates cell apoptosis. However, further research needs to be performed to confirm the underlying role of TUG1 in the progression of NSCLC.

More and more studies have proved that miRNA participates in the progression of carcino-

mas [35-37], including NSCLC [38]. For example, miR-221 was reported to function as an oncogene in NSCLC [39]. MiR-31 is involved in the oncogenic effects of KRAS on lung carcinogenesis [40]. Moreover, miR-31-5p has been shown to participate in the mediation of the cell cycle in human cancer [41]. Additionally, miR-31-5p is strongly related to the progression of wild-type RAS metastatic colorectal cancer [42]. Unfortunately, the mode of action and the role miR-31-5p plays in NSCLC remain elusive. In our study, the data revealed that miR-31-5p expression is up-regulated in NSCLC tissues and cells.

A growing number of studies are revealing the molecular mechanisms that take place between miRNA and TUG1. Chen *et al.* reported that TUG1 promotes neuronal apoptosis through miRNA-9 [43]. TUG1 functions as a negative regulating factor to enhance cell proliferation and metastasis in gallbladder carcinoma [44]. Additionally, TUG1 has been shown to induce osteosarcoma cell metastasis through its targeting of miR-143-5p [45]. Moreover, Zhou *et al.* showed that TUG1 mediates cancer progression by sponging miRNA [46]. In this study, we focused on the relationship between TUG1 and miR-31-5p in NSCLC. The Targets-can online network was used to predict the

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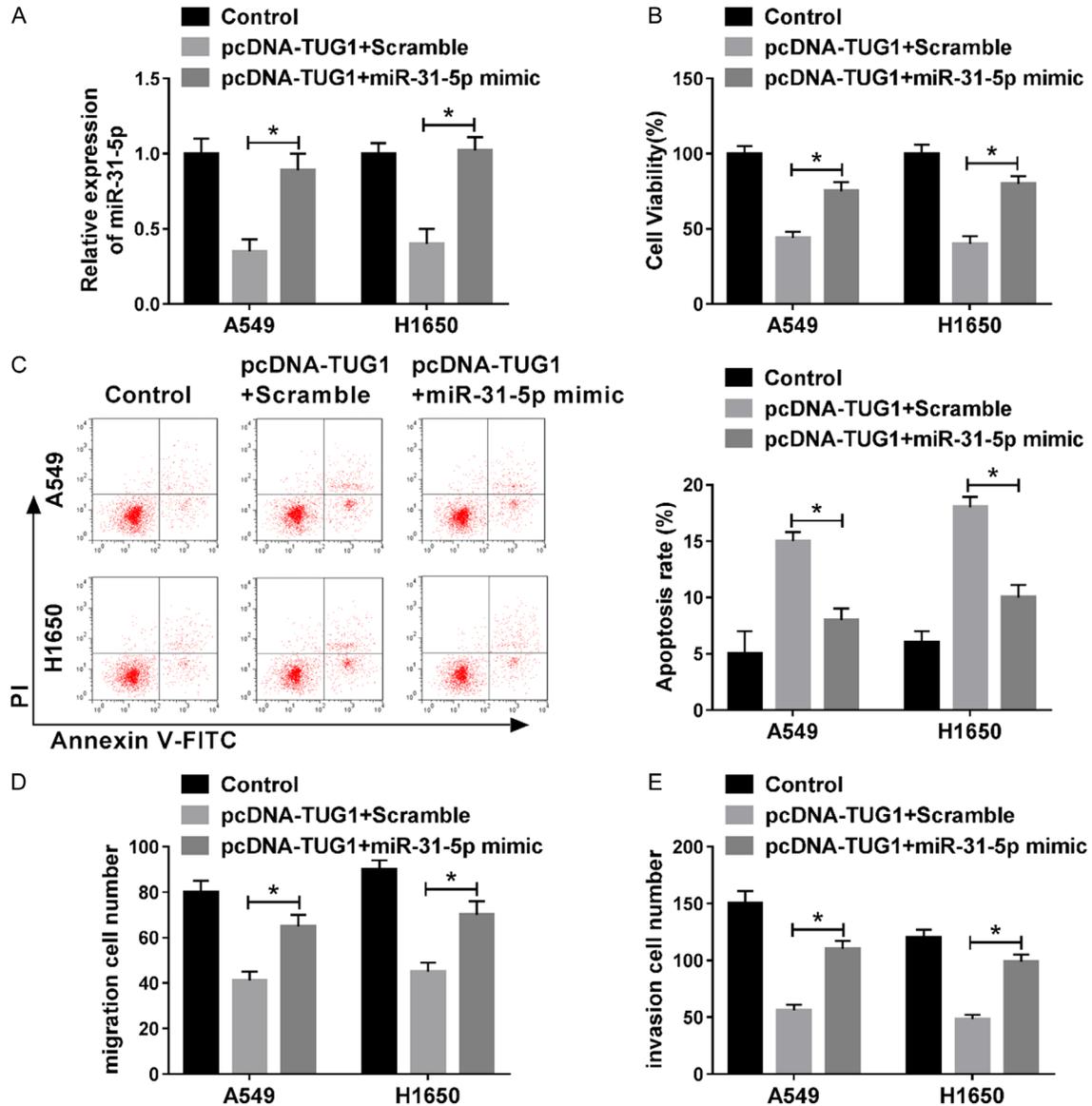


Figure 6. The miR-31-5p mimic recovered the effects of TUG1 overexpression on cell viability, apoptosis, migration, and invasion. (A-E) A549 and H1650 cells were transfected with a control, pcDNA-TUG1+scramble, and the pcDNA-TUG1+miR-31-5p mimic. The miR-31-5p level was measured using qRT-PCR (A). The cell viability (B), apoptosis (C), migration (D), and invasion (E) were measured using CCK-8, flow cytometry and Transwell assays, respectively. * $P < 0.05$.

binding sites. Our results demonstrated that miR-143-5p is a target of TUG1, and TUG1 regulates the development of NSCLC by sponging miR-143-5p.

CDIP, a target gene of p53, plays a considerable role in tumorigenesis. Additionally, CDIP has been shown to be correlated with TNF α -induced apoptosis in cancer cells [47]. We assumed that miR-31-5p mediates tumorigenesis through CDIP1 via the TNF α signal pathway. The possibility of miR-31-5p binding to

CDIP1 was predicted by the online network. The CDIP1 and TNF α levels are regulated by TUG1 and the miR-31-5p mimic in the A549 and H1650 cells. CDIP1 turned out to be a direct target of miR-31-5p. Additionally, TUG1 can regulate CDIP1 expression by targeting miR-31-5p to mediate the TNF α pathway, suggesting that CDIP has a regulatory role in NSCLC.

Generally, the development of NSCLC is a complicated process. Meanwhile, our research pro-

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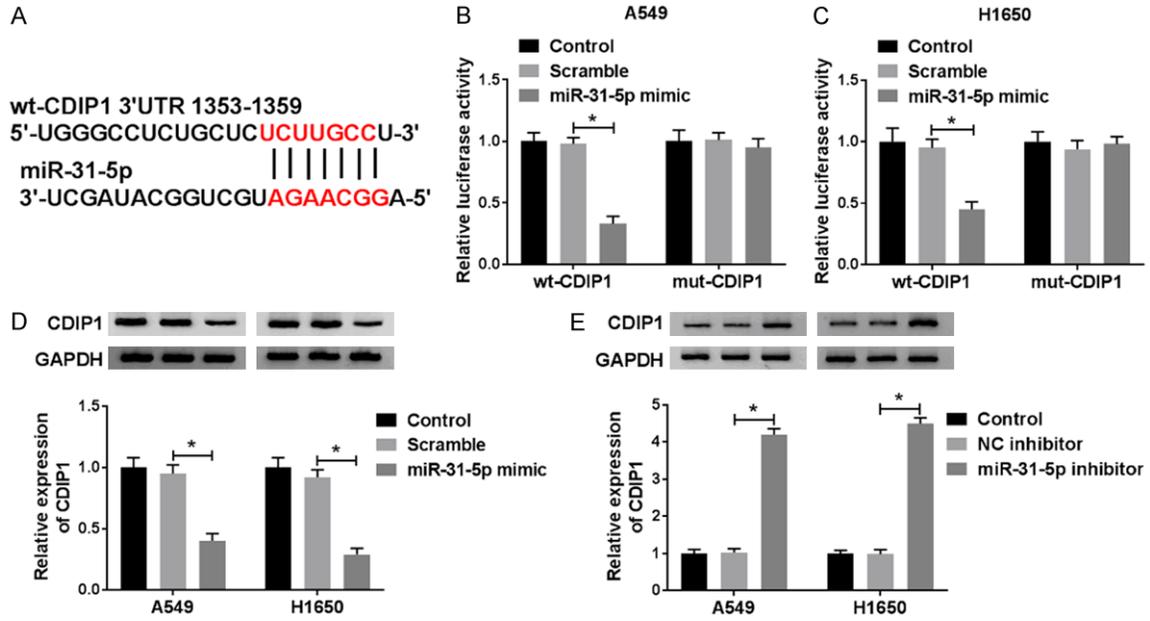


Figure 7. CDIP1 is a target gene of miR-31-5p. A. The predicted binding sites between CDIP1 and miR-31-5p. B and C. The luciferase activity was determined in the A549 and H1650 cells co-transfected with luciferase reporter plasmids (wt-CDIP1 or mut-CDIP1) and miR-31-5p or the corresponding control. D and E. Determination of the CDIP1 protein expressions in the NSCLC cells transfected with the miR-31-5p mimic or the miR-31-5p inhibitor. * $P < 0.05$.

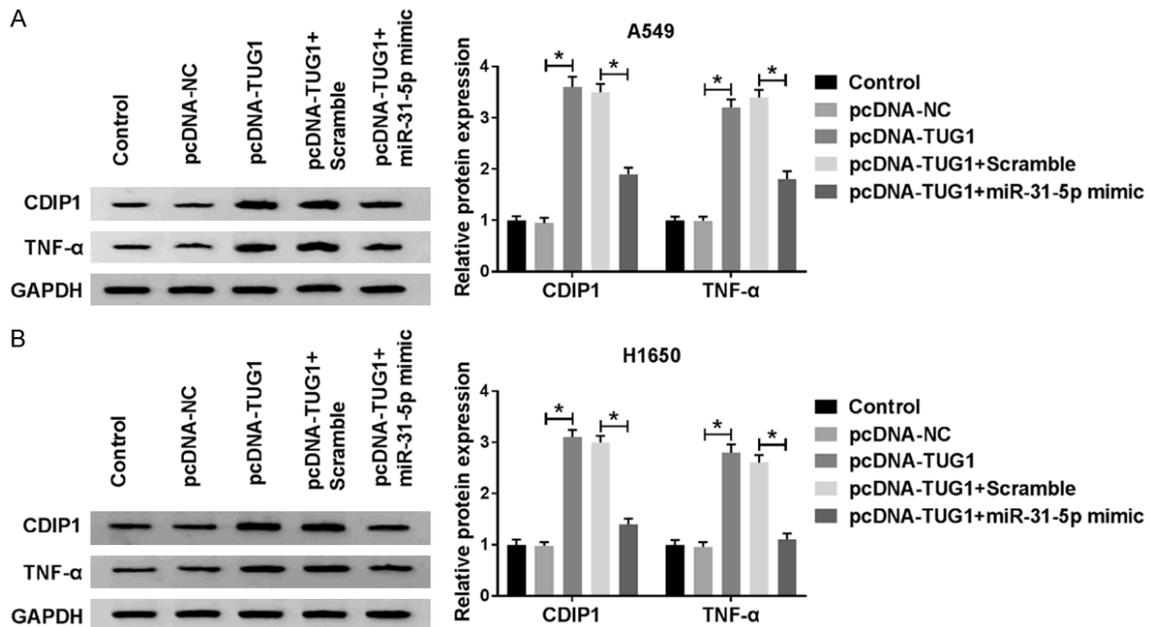


Figure 8. TUG1 regulates the TNF- α pathway by affecting the CDIP1 expression. A549 (A) and H1650 (B) were transfected with a control, pcDNA-NC, pcDNA-TUG1, pcDNA-TUG1+scramble, or pcDNA-TUG1+miR-31-5p, and we determined the CDIP1 and TNF- α expressions using western blot. * $P < 0.05$.

ved that TUG1 acts as an oncogene; otherwise, it is downregulated in NSCLC tissues and regulates the tumorigenesis of NSCLC through the

TUG1/miR-31-5p/CDIP1 axis via the TNF- α signal pathway. However, the molecular mechanisms need further study. Hence, further clini-

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cal or pre-clinical assays should be investigated using patient samples or animal models in future.

Conclusion

TUG1 is aberrantly brought down in NSCLC tissues and cells. The increased expression of TUG1 induces apoptosis and blocks cell proliferation, migration, and invasion. Additionally, TUG1 can bind to miR-31-5p, thus regulating the CDIP1 expression. The overexpression of miR-31-5p abolishes the effects of TUG1 up-regulation on the cell proliferation, apoptosis, migration, and invasion in NSCLC cells. Furthermore, the overexpression of TUG1 promotes the TNF- α pathway by affecting the expression of CDIP1. Moreover, our data demonstrate that upregulating TUG1 promotes apoptosis and suppresses cell proliferation, migration and invasion through the TUG1/miR-31-5p/CDIP1 axis via the TNF- α pathway in NSCLC cells, providing a theoretical basis for the treatment of NSCLC.

Acknowledgements

The present study was approved by the ethical review committee of the First People's Hospital of Baiyin.

Disclosure of conflict of interest

None.

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