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MiR-1275 promotes non-small cell lung cancer cell proliferation and metastasis by regulating LZTS3 expression

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Abstract. – OBJECTIVE: To detect the expressions of micro-ribonucleic acid 1275 (miR-1275) in non-small cell lung cancer (NSCLC) tissues and cells, analyze the correlations of the expression of miR-1275 with the clinicopathological features of NSCLC, and explore its biological function and potential molecular mechanism.

PATIENTS AND METHODS: Quantitative Real-time polymerase chain reaction (qRT-PCR) was used to detect the relative expression [illegible]els of miR-1275 in NSCLC tissues and ce[illegible] correlations of miR-1275 expression wi[illegible]clinicopathological features of NSCLC were s[illegible]tically analyzed. Clone formation assay, flo[illegible]tometry and transwell assay were used to de[illegible] the effects of interfering in miR-[illegible] expressi[illegible] on biological behaviors of NS[illegible] Bioinfor[illegible]matics was used to predict [illegible] dow[illegible]eam target genes of miR-1275, a[illegible]RT-PCR [illegible]nd Western blotting were utilized [illegible]verif[illegible] luciferase reporter g[illegible] ass[illegible] use[illegible] [illegible]idate the binding o[illegible]iR-1275 t[illegible]rget gene.

RESULTS: Th[illegible]ults of qR[illegible] showed that among 70 [illegible] tissues from [illegible]CLC patients, 52 cas[illegible] had [illegible]gulated miR-1275 expressions. MiR-1275 ex[illegible]ion was increased in NSCL[illegible]ells compared [illegible]that in 16 human bronc[illegible] epithelial (16HBE) [illegible]s. Interfering in miR[illegible]5 expr[illegible]sion could inhibit the prolifer[illegible]ati[illegible]asi[illegible]nd metastasis of NSCLC cells. Bioin[illegible] predic[illegible]n discovered that leu[illegible]cine zip[illegible]tative t[illegible]or suppressor 3 (LZTS3) [illegible] be a [illegible]e of miR-1275. Dual lucifer[illegible]as[illegible]porter a[illegible] confirmed that the two genes co[illegible] bind dire[illegible]y.

[illegible]USIONS: MiR-1275 is relatively high[illegible] in NSCLC. Highly expressed miR-[illegible]75 can promote the proliferation and metasta[illegible]f NSCLC through regulating the expression [illegible]S3.

Key Words:
NSCLC, miR-1275, Proliferation, Metastasis, LZTS3.

[illegible]troduction

Lung cancer is a [illegible]ant tumor with the highe[illegible]y rate among [illegible]ers[1]. Most patients are al[illegible]dy in the advanced sta[illegible] when diagnosed, and [illegible]e than 50% ha[illegible] had distant metastases. The in[illegible]ce rate of n[illegible]mall cell lung cancer (NSCLC) ac[illegible]nts for alm[illegible] 80-85% of lung cancer, and pat[illegible]al ty[illegible]of NSCLC mainly include squamous [illegible]oma (SCC) and adenocarcinoma [illegible]AD)[2]. Although current diagnosis and treatment of [illegible]C have been greatly improved, the 5-year sur[illegible]va[illegible]e of lung cancer patients is still below 18%[3], which is mainly caused by the lack of specific biomarkers for early diagnosis and detailed occurrence and development mechanisms of NSCLC. Therefore, to find new biological markers that can increase diagnostic rate, improve prognosis and serve as individualized treatment means in clinical practice, is urgently needed.

Micro-ribonucleic acids (miRNAs) are a class of small single-stranded non-coding RNAs with about 19-22 nucleotides in length, which are considered as important components of epigenetic regulation system. They mainly regulate the expression levels of genes after transcription by degrading target messenger RNA (mRNA) or inhibiting the translation of target gene[4,5]. MiRNAs are widely involved in various cellular processes, such as cell differentiation, proliferation, apoptosis, canceration and drug resistance[6,7]. Literature[8] reported that miR-339-5p inhibits lung cancer cell invasion and migration by regulating the epithelial-to-mesenchymal transition *via* BCL6 *in vitro*. Lin et al[9] found that miR-133b can reverse the sensitivity of NSCLC cells to cisplatin by regulating the expression of glutathione S-transferase pi-1 (GSTP1). However, the expression and role of miR-1275 in NSCLC have not been reported.

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Recent studies have shown that miR-1275 has up-regulated expressions in many tumors and plays a role similar as "oncogene" to promote the occurrence and development of tumors. MiR-1275 can promote the proliferation, invasion and metastasis of head and neck SCC cells by regulating the expressions of insulin-like growth factor 1 receptor (IGF-1R) and C-C chemokine receptor (CCR7)[10]. Besides, miR-1275 promotes the proliferation of hepatocellular carcinoma cells by binding to IGF2 mRNA[11]. In this work, miR-1275 was first found to be elevated in NSCLC tissues. Statistics also discovered that highly expressed miR-1275 was positively correlated with tumor size, tumor node metastasis (TNM) staging and lymph node metastasis in NSCLC patients, and it was confirmed by *in vitro* researches that highly expressed miR-1275 promoted the proliferation and metastasis of NSCLC cells.

Patients and Methods

Tissues

A total of 70 pairs of NSCLC tissues and corresponding adjacent tissues (5 cm away from t[illegible] tissues) were derived from specimens su[illegible] resected in our hospital from June 2012 [illegible] December 2015. All tissues were confirmed b[illegible] pathologists, and all patients received no t[illegible]ment before surgery. After spe[illegible] were o[illegible]tained by clinical operation, t[illegible] we[illegible]olated o[illegible] ice for material collection [illegible]hin 0.5 [illegible] h. This study was approved by t[illegible]hics C[illegible]mittee of the First Affiliated H[illegible]pital [illegible] College, and patien[illegible]gned in[illegible]d consent.

Cell Culture

Normal 16 h[illegible]man b[illegible]ial epithelial (16HBE) cells and [illegible]CLC cell lin[illegible]49, SPCA-1, PC-9, H292, [illegible]H460 were obtain[illegible]om Shanghai Institu[illegible] Biochemistry and Cell Biology, Chinese Ac[illegible] of S[illegible]nces (Shanghai, China), cultured in Ros[illegible]k Memo[illegible] Institute (RPMI)-1640 [illegible]dium [illegible]lbecc[illegible] modified Eagle medium ([illegible]EM) ([illegible], South Logan, UT, USA) co[illegible]ning 10[illegible]al bovine serum (FBS) (HyCl[illegible] South Logan, UT, USA), and incubated at [illegible] of 7.2-7.4, a humidity of 95%, and [illegible]O_2 volume fraction of 5%.

[illegible]titative Real-Time Polymerase Chain Reaction (qRT-PCR)

Total RNA was extracted from cells using TRIzol (Invitrogen Corporation, Carlsbad, CA, USA) assay, and then complementary deoxyribonucleic acid (cDNA) was synthesized based on the instructions of reverse transcription kits (Invitrogen Corporation, Carlsbad, CA, [illegible]). Then, amplification was performed a[illegible] qRT-PCR instructions (Invitrogen [illegible]rporation, Carlsbad, CA, USA), and amplifi[illegible]n curve and solubility curve were confirmed a[illegible]mpletion of the reaction. Above proced[illegible]es we[illegible]ated 3 times for each experiment[illegible]ample, and [illegible]erage cycle threshold (Ct) [illegible]ue was taken. [illegible] miR-1275 and leucin[illegible]er put[illegible]e tumor s[illegible]pressor 3 (LZTS3) mR[illegible]sion lev[illegible] were calculated using [illegible]met[illegible] Primers [illegible]olved: miR-1275 F [illegible]GTGCAGG[illegible]CC[illegible]GGT-, R 5'-GCCGC[illegible]TATCGACT[illegible]3', U6 F 5'-CTCG[illegible]T"C[illegible]AGCACA-3', R 5'-AACGCT TCACGAAT[illegible]GT-3' and interference seq[illegible] si-miR-127[illegible]-UCAACAUCAGUC[illegible]A UAAGC-3'. Prime[illegible] and interference se[illegible]nces were designed and synthesized by Ak[illegible]ics (Shangh[illegible] China).

Ce[illegible]ne D[illegible]ction

Aft[illegible]ere transfected with small interference (si)-miR-1275 and control sequence for [illegible]lls from experimental group and control [illegible]re inoculated into a 6-well plate at 1000/well and cultured in the 5% CO_2 incubator at 37°C for 14 d. When clone formation was macroscopic, culture was terminated. Then, cells were fixed with methanol for 15 min, stained for 20 min and photographed, and the number of macroscopic colonies was counted.

Flow Cytometry

NSCLC cells were seeded in the 6-well plate, transiently transfected with si-miR-1275 and si-normal control (si-NC) and then cultured for 48 h. After that, cells were digested with ethylene diamine tetraacetic acid (EDTA)-free pancreatin, collected, re-suspended with precooled 75% ethanol and placed in a refrigerator at -20°C for fixation overnight. Lastly, the intracellular DNA content was detected by flow cytometry propidium iodide (PI) staining.

Cell Wound Healing Assay

After 48 h of transfection, cells were taken from each group and seeded in the 6-well plate. When 80% cells were fused, 10 μL pipette were used to draw a horizontal stroke (in Chinese characters) on the bottom of the culture plate. Then, phosphate-buffered saline (PBS) was added to

elute suspended cells. After that, cells were photographed at 0 and 36 h after culture, respectively, according to the experimental design.

Transwell Assay

Cells were treated and collected as described above, and cell density was adjusted to 2.5×10^5/mL. 200 µL above cell suspension were added in the upper chamber of a transwell chamber (50 mg/L BD matrigel diluted at 1:7 were added in the transwell chamber), and 700 µL RPMI-1640 medium or DMEM containing 10% fetal bovine serum (FBS) were added in the lower chamber at the same time. The transwell chamber was incubated for 24 or 48 h, followed by formaldehyde fixation, crystal violet staining, observation and counting.

Dual Luciferase Reporter Gene

Wild-type and mutant LZTS3-3'-untranslated region (3'UTR) reporter gene plasmids were constructed. Then, reporter gene plasmids, Renilla luciferase-thymidine kinase promoter (pRL-TK) plasmids, miR-1275 mimics and their negative control plasmids were transfected into HEK293T cells. After 48 h, assay was carried out acco[illegible] to instructions of dual luciferase detection [illegible] time, Shanghai, China), and the ratio of fire[illegible]fluorescence intensity to Renilla fluorescence intensity was used to reflect the relative fluorescence intensity of different treatment groups.

Western Blotting

Total protein was extracted from [illegible]s in experimental group and control group, [illegible] protein concentration was measured *via* bic[illegible]inic acid (BCA) assay (Beyotime, Sh[illegible]hai, C[illegible]). Samples in the same amount [illegible]re taken f[illegible]ach group and subjected t[illegible]dium dodecyl s[illegible] polyacrylamide gel e[illegible]phore[illegible] (SDS-PAG[illegible]). Then, protein wa[illegible] tra[illegible] onto a [illegible]olyvinylidene difluori[illegible] (PVDF[illegible]brane ([illegible]ipore, Billerica, MA[illegible]SA). After [illegible] the membrane was blocke[illegible] skimmed mi[illegible]ubated with LZTS3 an[illegible]body a[illegible]lyceraldehyde-3-phosphate dehydrogenase (GA[illegible] antibody at 4°C overnigh[illegible] washed with [illegible] buffered saline and T[illegible]en-20 (TBST-20) for [illegible]ree times (10 min/t[illegible]e). Next, the membrane was added with sec[illegible]ary antibod[illegible] [illegible]cubated at room temperature fo[illegible]h, followed [illegible] washing with TBST for three tim[illegible] min/ti[illegible]). Lastly, enhanced chemiluminescen[illegible] solution (Thermo Fisher Scientif[illegible], Waltham, MA, USA) was added, followed by [illegible] development and fixing.

Table I. Correlation between miR-12[illegible]on and cl[illegible]athological characteristics of NSCLC patients (n = 70).

Characteristics	m[illegible]275 L[illegible]no. [illegible]	miR-1275 High no. case	x^2-test *p*-value
Age (years)			
> 65	[illegible]	30	0.594
≤ 65	[illegible]	22	
Gender			
Male	8	28	0.588
Femal[illegible]	10	24	
Histol[illegible]al subtype			
S[illegible]mous cell carcinoma	12	26	0.278
[illegible]carcin[illegible]	6	26	
TN[illegible]			
Ia + I[illegible]	11	14	0.005*
[illegible]a + IIb	5	17	
[illegible]	2	21	
Tu[illegible] size			
[illegible] cm	14	21	0.013*
[illegible]	4	31	
[illegible]ymph [illegible]metastasis			
Negative	12	19	0.032*
[illegible]sitive	6	33	
S[illegible]ng history			
Smokers	14	31	0.254
Never Smokers	4	21	

*$p < 0.05$.

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Statistics Analysis

Statistical product and service solutions (SPSS) 17.0 software (SPSS Inc., Chicago, IL, USA) were used for analysis. Data were expressed as mean ± standard deviation ($\bar{x}$±s). Comparison between groups was done using One-way ANOVA test followed by Least Significant Difference (LSD). Correlation between two ordinal variables was detected via Spearman correlation analysis. Pearson's test was employed for comparison between two classified variables. p<0.05 suggested that the difference was statistically significant.

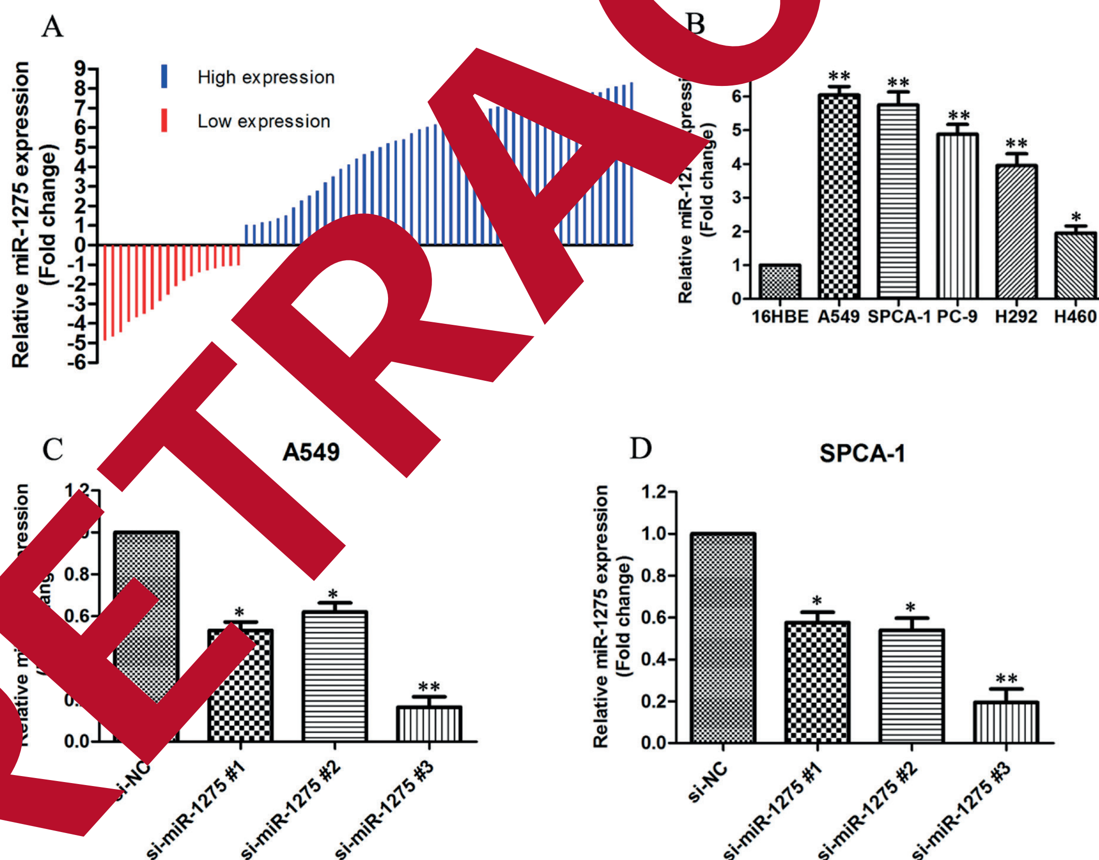
Results

MiR-1275 was Highly Expressed in NSCLC Tissues and Cells

QRT-PCR showed that among 70 cases of NSCLC tissues, 52 cases had up-regulated miR-1275 expressions compared with those in adjacent tissues (Figure 1A). Statistical analysis indicated that highly expressed miR-1275 was positively correlated with tumor size, [illegible] staging, and lymph node metastasis [illegible] with NSCLC (Table I). To further i[illegible]stigate the biological function of miR-1275, [illegible]T-PCR was applied to detect its relative expre[illegible] levels in NSCLC cells and 16HBE, an[illegible] the res[illegible]owed that miR-1275 expressio[illegible] NSCLC [illegible]was increased (Figure 1B). [illegible]xt, miR-1275 in[illegible]ence sequence was [illegible]ned, [illegible]thesized a[illegible]d transfected into N[illegible]SCL[illegible] [illegible]nd the e[illegible]ficiency of the interf[illegible]ce wa[illegible]mined [illegible] 48 h (Figure 1C-D[illegible]

Effect o[illegible] [illegible]iR-1[illegible] on the Proliferation of NSCLC Cells

E[illegible]ental and [illegible]l sequences were tr[illegible]fected into NSCLC [illegible]ells. The results of



Fig[illegible]e 1. MiR-1275 is highly expressed in NSCLC. ***A,*** Relative expression levels of miR-1275 in 70 cases of NSCLC tissues are measured by qRT-PCR assay, in which increased expression is found in 52 cases of tissues, with U6 as an internal reference. ***B,*** Relative expression levels of miR-1275 in NSCLC cells and 16HBE are measured by qRT-PCR assay. ***C-D,*** Transfection efficiency is detected after NSCLC cells are transfected with si-miR-1275 and miR-NC for 48 h (**p<0.01, *p<0.05).

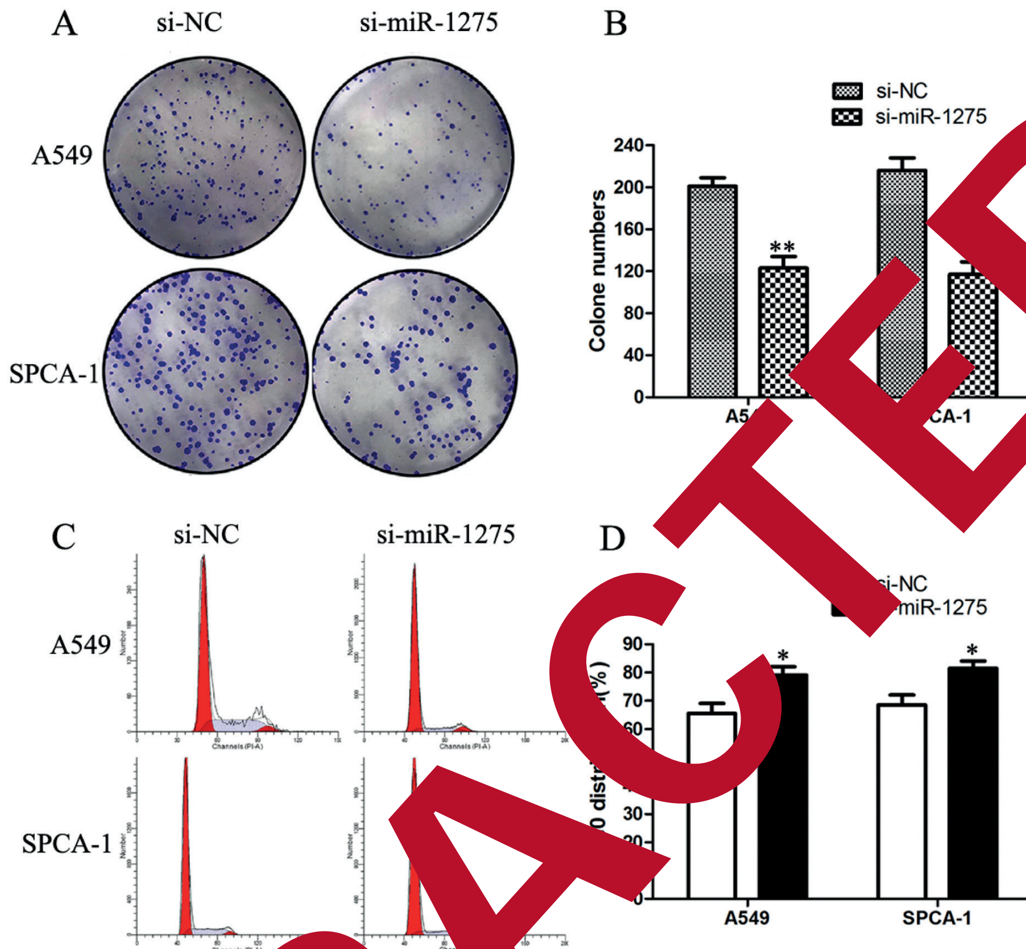


Figure 2. Effect of miR-1275 o[illegible] prolife[illegible] of NSCL[illegible]ls. ***A-B,*** Proliferation ability of NSCLC cells is detected via clone formation assay after in[illegible]ing in ex[illegible]sions of mi[illegible]1275 in A549 and SPCA-1 cells, and the results show that the proliferation ability of NSCLC [illegible] inhi[illegible] C[illegible]ll cycle progression of NSCLC cells is detected by flow cytometry after NSCLC cells are tra[illegible]cted [illegible]iR-NC for 48 h; it is found that NSCLC cell cycle is arrested in G1/0 phase. (***p*<0.01, **p*<0[illegible]

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clon[illegible]rmation assay showed that interference in [illegible]275 [illegible]ression in NSCLC cells inhibited cel[illegible]ation (F[illegible]re 2A-B). Flow cytom[illegible] reve[illegible]hat si[illegible]R-1275 arrested NSCLC [illegible]ycle in [illegible]se (Figure 2C-D).

Im[illegible]ct of miR-1275 on NSCLC Metastasis

[illegible]te the role of miR-1275 in the me[illegible]stasis of NSCLC cells, cells were treated as [illegible]ribed above. According to wound healing as[illegible]t was found that interfering in miR-1275 expression inhibited cell migration ability (Figure 3A-B). Transwell assay showed that interfering in miR-1275 expression inhibited the invasion and migration abilities of NSCLC cells in comparison with control group (Figure 3C and D).

MiR-1275 Regulated LZTS3 Expression

To investigate the potential molecular mechanisms of miR-1275 in exerting biological functions in NSCLC cells, bioinformatics (http://www.mirdb.org/) was utilized to predict the downstream target genes of miR-1275 (Figure 4A), and qRT-PCR and Western blotting were carried out to verify that the expression of LZTS3 was regulated by miR-1275 (Figure 4B- C). Then, dual luciferase reporter gene assay was applied, and the results indicated that

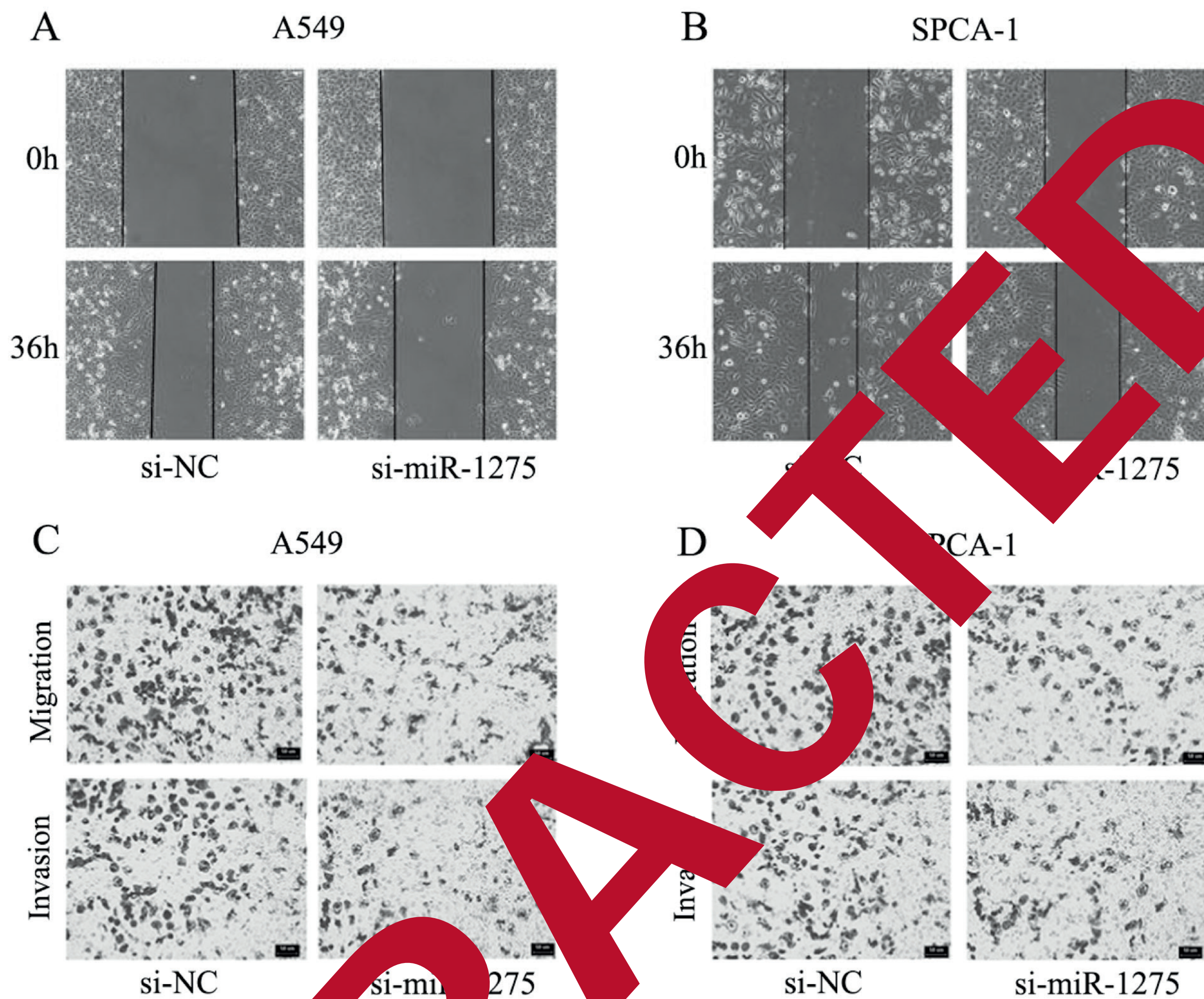

Figure 3. Impact of miR-127[illegible]CLC[illegible]. ***A-B,*** Metastasis ability of NSCLC cells is detected *via* wound healing assay, and it is fo[illegible] that [illegible]ce in [illegible]ression of miR-1275 can inhibit cell migration ability (×200). ***C-D,*** Proliferation and metas[illegible]s abilities a[illegible]ted via transwell assay, and it is found that interference in miR-1275 expression can inhibit cell migr[illegible]nd invasion a[illegible](Bar=50 um).

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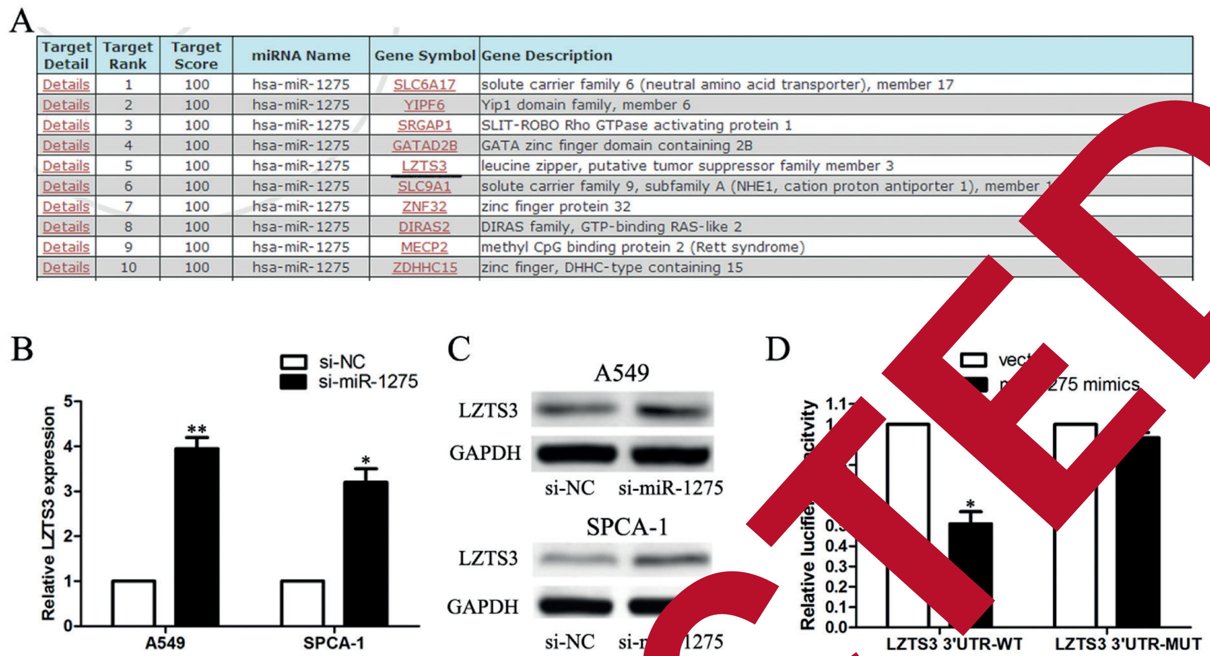
miR[illegible]5 was able to bind directly to LZTS3 mR[illegible] (Figu[illegible]4D).

[illegible]cussion

[illegible]re and more miRNAs have been reported [illegible]d to play important roles in cell [illegible]oliferation, apoptosis, angiogenesis, epithe[illegible]mesenchymal transition (EMT) and tumor st[illegible]ell maintenance by directly or indirectly regulating the expressions of genes, thus promoting/inhibiting the occurrence and development of NSCLC[12].

Researches[13,14] have confirmed that miRNA-let-7, the first miRNA discovered in human, can regulate the growth and proliferation of tumor cells by inhibiting the expressions of oncogenes such as rat sarcoma (RAS), myelocytomatosis (Myc) and cyclin-dependent kinase 6 (CDK6). In NSCLC cell and animal experiments, it is also proved that let-7 is a typical tumor suppressor[15]. In addition, miR-338-3p has been proved to have a down-regulated expression in highly metastatic NSCLC cells, and it can inhibit the migration and invasion of NSCLC cells *via* the targeted regulation of sex-determining region Y (SRY)-related HMG-box 4 (SOX4)



Target Detail	Target Rank	Target Score	miRNA Name	Gene Symbol	Gene Description
Details	1	100	hsa-miR-1275	SLC6A17	solute carrier family 6 (neutral amino acid transporter), member 17
Details	2	100	hsa-miR-1275	YIPF6	Yip1 domain family, member 6
Details	3	100	hsa-miR-1275	SRGAP1	SLIT-ROBO Rho GTPase activating protein 1
Details	4	100	hsa-miR-1275	GATAD2B	GATA zinc finger domain containing 2B
Details	5	100	hsa-miR-1275	LZTS3	leucine zipper, putative tumor suppressor family member 3
Details	6	100	hsa-miR-1275	SLC9A1	solute carrier family 9, subfamily A (NHE1, cation proton antiporter 1), member 1
Details	7	100	hsa-miR-1275	ZNF32	zinc finger protein 32
Details	8	100	hsa-miR-1275	DIRAS2	DIRAS family, GTP-binding RAS-like 2
Details	9	100	hsa-miR-1275	MECP2	methyl CpG binding protein 2 (Rett syndrome)
Details	10	100	hsa-miR-1275	ZDHHC15	zinc finger, DHHC-type containing 15

Figure 4. MiR-1275 regulates the expression of LZTS3. ***A,*** Bioin[illegible]atics show tha[illegible]R-1275 can bind to LZTS3 mRNA. ***B,*** LZTS3 mRNA expression changes after interfering in miR-1275 [illegible]ssion are de[illegible]ed via qRT-PCR. ***C,*** LZTS3 protein expression changes after interfering in miR-1275 expression are detect[illegible] Wester[illegible]otting. ***D,*** Direct binding of miR-1275 to LATS3 mRNA is proved through dual luciferase r[illegible] gene. (**p<0.[illegible]5).

expression[16]. MiR-34a and miR-[illegible], members of the miR-34 family, are [illegible]nd transcribed by p53 upon DNA damage, [illegible]us regulating cell cycle arrest [illegible]poptos[illegible] tumor cells. MiR-34a has a [illegible]wn-[illegible]n in lung cancer and [illegible]hibits ce[illegible]liferation as a tumor suppres[illegible]ene in a p[illegible]ependent manner[17]. Shi [illegible] [illegible]rmed that [illegible]34a can inhibit the colony-form[illegible]ability of NSCLC cells, implyi[illegible]hat it has the [illegible]tion of anti-tumor stem c[illegible] Moreover, in this [illegible]k, it was found via *in vitro* experiments for the first time that inter[illegible]e in [illegible]-1275 could inhibit the proliferation [illegible]astasis of NSCLC cells.

[illegible]iterat[illegible][20] rep[illegible]d that the regulation mechanisms o[illegible]s in NSCLC include genomi[illegible] abnormali[illegible], epigenetic changes, miRNA se[illegible]nce single nucleotide polymorphisms, and i[illegible] between miRNA and competing [illegible]dogenous RNA (ceRNA) and protein. Among [illegible] ceRNAs contain multiple miRNA binding si[illegible] which act by competitively binding miRNA to mRNA. In this study, potential downstream target genes of miR-1275 were first predicted using bioinformatics and verified via qRT-PCR and other experiments. Finally, it was found through dual luciferase reporter gene assay that miR-1275 could directly bind to LZTS3 mRNA.

Conclusions

We showed that miR-1275 expression is increased in NSCLC. Highly expressed miR-1275 may play a similar role as "oncogene" and promotes the proliferation and metastasis of NSCLC cells through the targeted regulation of LZTS3 expression. In addition, targeted treatment of miR-1275/LZTS3 may provide an important basis for the reversal of the formation of NSCLC malignant phenotype in clinic.

Conflict of Interest

The Authors declare that they have no conflict of interest.

Fund

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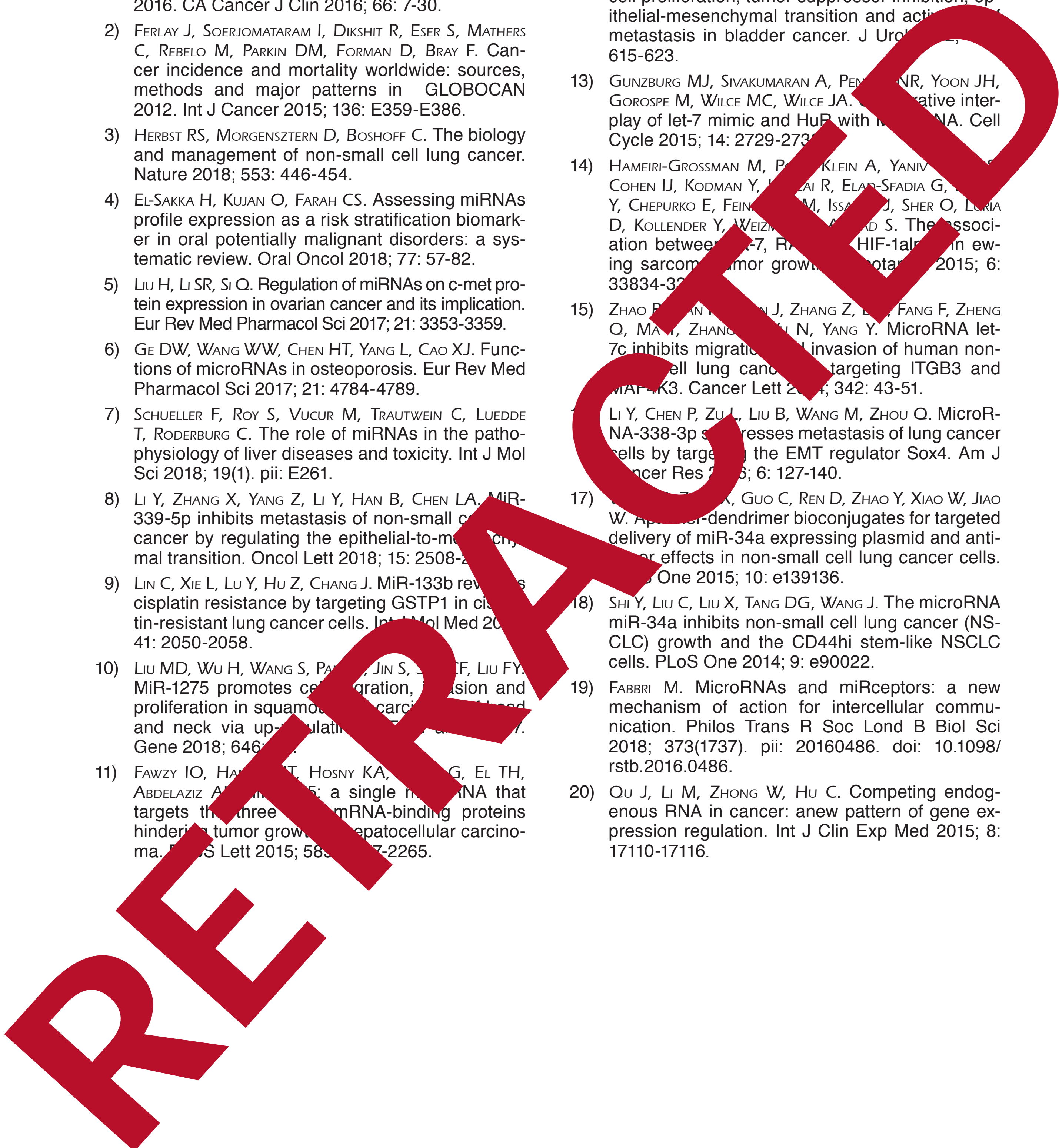

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