Circular RNA hsa_circ_0014130 Inhibits Apoptosis in Non–Small Cell Lung Cancer by Sponging miR-136-5p and Upregulating BCL2

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ABSTRACT

Previous studies indicated that circular RNAs (circRNA) played vital roles in the development of non–small cell lung cancer (NSCLC). Although hsa_circ_0014130 might be a potential NSCLC biomarker, its function in NSCLC remains unknown. Thus, this study aimed to investigate the role of hsa_circ_0014130 in the progression of NSCLC. The levels of hsa_circ_0014130 in NSCLC tissues and adjacent normal tissues were determined by qRT-PCR. In addition, the expressions of Bcl-2 and cleaved caspase-3 in A549 cells were detected with Western blot analysis. Meanwhile, the dual luciferase reporter system assay was used to determine the interaction of hsa_circ_0014130 and miR-136-5p or Bcl-2 and miR-136-5p in NSCLC, respectively. The level of hsa_circ_0014130 was significantly upregulated in NSCLC tissues. Downregulation of hsa_circ_0014130 markedly inhibited the proliferation and invasion of A549 cells via inducing apoptosis. In addition, downregulation of hsa_circ_0014130 inhibited the tumorigenesis of subcutaneous A549 xenograft in mice in vivo. Meanwhile, mechanistic analysis indicated that downregulation of hsa_circ_0014130 decreased the expression of miR1365p–targeted gene Bcl-2 via acting as a competitive "sponge" of miR136-5p. In this study, we found that hsa_circ_0014130 was upregulated in NSCLC tissues. In addition, hsa_circ_0014130 functions as a tumor promoter in NSCLC to promote tumor growth through upregulating Bcl-2 partially via “sponging” miR136-5p.

Implications: In conclusion, hsa_circ_0014130 might function as a prognostic factor for patients with NSCLC and might be a therapeutic target for the treatment of NSCLC in future.

Introduction

Non–small-cell lung cancer (NSCLC) is the main cause of death in humans worldwide, which accounts for more than 80% of patients with lung cancer (1). Adenocarcinoma, squamous cell carcinoma, and large-cell lung cancer are the major histologic subtypes of NSCLC (2). At present, the overall 5-year survival rate of patients with NSCLC was only about 10% (3). Despite enormous advances in diagnostic technologies and treatment methods, the survival rate and prognosis of patients with NSCLC is generally considered poor (3, 4). One of the key causes of high morbidity and mortality rate was the low rate of early detection (5). NSCLC is generally considered poor (3, 4). One of the key causes of high morbidity and mortality rate was the low rate of early detection (5).

Circular RNAs (circRNA) are a class of noncoding RNA molecules, which was formed by exon back-splicing (6). CircRNAs extensively exist in mammalian cells, which have a closed loop structure without 5′ cap and 3′ tail (7). Previous studies indicated that circRNAs are closely associated with the development of human cancer, such as NSCLC (8, 9). Zhang and colleagues found that circAGFG1 promoted metastasis in NSCLC cells by sponging miR-203 (14). Xue and colleagues found that circAGFG1 promoted metastasis in NSCLC cells by sponging miR-203 (14). However, the role of hsa_circ_0014130 in NSCLC remains unclear and need further investigation.

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Materials and Methods

Patients and tissues samples

A total number of 30 paired NSCLC tissue samples and adjacent noncancerous tissue samples were obtained from patients with NSCLC in the First Affiliated Hospital, Harbin Medical University (Harbin, Heilongjiang, P.R. China), between September 2017 and April 2018. None of patients had received any preoperative radiotherapy and/or chemotherapy. This study was approved by the Institutional Ethical
Committee of the First Affiliated Hospital, Harbin Medical University (Harbin, Heilongjiang, P.R. China). Written informed consent was obtained from each patient.

**Cell culture**

Human NSCLC cell lines PC-9 and A549 were purchased from the Institute of Biochemistry and Cell Biology of the Chinese Academy of Sciences (Shanghai, China). Cells were cultured in DMEM (Thermo Fisher Scientific) supplied with 10% of FBS (Invitrogen), 100 U/mL penicillin, and 100 μg/mL streptomycin at 37°C in a humidified incubator (5% CO2).

**Quantitative real-time PCR**

TRIzol reagent (Thermo Fisher Scientific) was used to extract total RNA from the tissue samples and cells according to the standard protocol. The complementary DNA (cDNA) was carried out using the PrimeScript RT Master Mix (TaKaRa). After that, qPCR was performed to detect the relative expression of circRNA and miRNA using SYBR Green premix Ex Taq (TaKaRa) on the Applied Biosystems 7500 Real Time PCR System (Applied Biosystems). The sequences of the primers were: hsa_circ_0014130_forward: 5'-AGAAGTTGGGACCATCTGTGGG-3'; reverse: 5'-AAAGTCCAGAGGTGTCCTGCTTG-3'. GAPDH Forward: 5'-TCAAGAGGTGGTGAAGCAGG-3'; reverse: 5'-TCAAGGTTGGAGGATGG-3'. The level of hsa_circ_0014130 was normalized to the internal control GAPDH using the 2-ΔΔCt method.

**Lentivirus production and cell transfection**

The lentivirus vector (Thermo Fisher Scientific) was used to express total RNA from the tissue samples and cells according to the standard protocol. The complementary DNA (cDNA) was carried out using the PrimeScript RT Master Mix (TaKaRa). After that, qPCR was performed to detect the relative expression of circRNA and miRNA using SYBR Green premix Ex Taq (TaKaRa) on the Applied Biosystems 7500 Real Time PCR System (Applied Biosystems). The sequences of the primers were: hsa_circ_0014130_forward: 5'-AGAAGTTGGGACCATCTGTGGG-3'; reverse: 5'-AAAGTCCAGAGGTGTCCTGCTTG-3'. GAPDH Forward: 5'-TCAAGAGGTGGTGAAGCAGG-3'; reverse: 5'-TCAAGGTTGGAGGATGG-3'. The level of hsa_circ_0014130 was normalized to the internal control GAPDH using the 2-ΔΔCt method.

**Transwell invasion assay**

The A549 cells (5 × 10^4 cells suspended in 100 μL serum-free media) were seeded into the top chambers that were covered with Matrigel (BD Biosciences). In addition, DMEM with 10% FBS (600 μL) was added into the bottom compartments as a chemotaxattractant. Twenty-four hours later, the cells attached to the top compartments were wiped using cotton swabs. After that, cells on the bottom surface of the inserts were fixed with 4% paraformaldehyde, and then stained with 0.2% crystal violet. After washing with PBS, cells were photographed using a laser confocal microscope (Olympus Corp.). Five independent fields of each membrane were counted.

**Luciferase reporter assay**

Oligonucleotides containing the wild-type (WT) or mutant (MT) miR-136-5p-binding sites of the 3' UTR of the Bcl-2 mRNA or hsa_circ_0014130 cDNA fragment were ligated into the pmirGLO luciferase reporter vector (Promega), respectively. For hsa_circ_0014130 reporter assay, hsa_circ_0014130 reporter construct (WT or MT) was cotransfected with miR-136-5p mimics and NC, respectively, using Lipofectamine 2000 (Invitrogen). For Bcl-2 reporter assay, Bcl-2 reporter construct (WT or MT) was cotransfected with miR-136-5p mimics and NC, respectively, using Lipofectamine 2000 (Invitrogen). Forty-eight hours later, the luciferase activities were measured using a Dual-Luciferase Reporter Assay System (Promega) with Renilla luciferase activity as endogenous control.

**FISH analysis**

FISH analysis was performed as described previously (15, 16). Alexa Fluor 555-labeled hsa_circ_0014130 oligonucleotide probes (Alexa Fluor 555-labeled miR-136-3p), oligonucleotide probes were synthesized by GenePharma. Empty pcDNA3.1 vector was used as negative control (NC). The hsa_circ_0014130-shRNA1 and hsa_circ_0014130-shRNA2 plasmids were transfected into 293T cells, respectively. Seventy-two hours later, the supernatant was collected. PC-9 or A549 cells were then infected with NC or hsa_circ_0014130-shRNAs supernatant for 72 hours, respectively. qRT-PCR was used to detect the level of hsa_circ_0014130 in PC-9 and A549 cells.

miR-136-5p mimics, miR-136-5p inhibitor, and negative control (NC) oligos were purchased from Thermo Fisher Scientific. A549 cells were transfected with miR-136-5p mimics or miR-136-5p inhibitor using Lipofectamine 2000 (Thermo Fisher Scientific) following the manufacturer's protocol for 72 hours.

**Western blot analysis**

Total proteins were isolated from A549 cells using RIPA buffer (Thermo Fisher Scientific) and then quantified using BCA method (Beyotime Institute of Biotechnology). Appropriate amounts of proteins were separated by 10% SDS-PAGE, and then transferred onto polyvinylidene difluoride (PVDF) membrane (Thermo Fisher Scientific). After that, the membrane was blocked in 5% skim milk at room temperature. Then, the membrane was incubated in primary antibodies at 4°C overnight, including anti-Bcl-2 (1:1,000, Abcam), anti-cleaved caspase 3 (1:1,000, Abcam), and anti-β-actin (1:1,000, Abcam). Later on, the membranes were incubated with secondary antibodies (1:5,000, Abcam) at the room temperature for 1 hour and then visualized using an ECL Chemiluminescent Substrate Reagent Kit (Thermo Fisher Scientific). β-Actin acted as the internal control.

**Animal study**

Four- to 6-week-old BALB/c nude mice were purchased from the Shanghai SLAC Animal Center (Shanghai, China) and animals were maintained following the guidelines for use and care of laboratory animals. All animal experiments were approved by the Institutional Ethical Committee of the First Affiliated Hospital, Harbin Medical University (Harbin, Heilongjiang, P.R. China). Animals were randomized into three groups: blank, NC, and...
hsa_circ_0014130-shRNA1 group. A total of $1 \times 10^7$ A549 cells infected with hsa_circ_0014130-shRNA1 were injected subcutaneously into the left flank of nude mice (3 per group). Tumor volume was monitored every week with a caliper and analyzed using the formula $V = (\text{length} \times \text{width}^2)/2$. All nude mice were sacrificed after 4 weeks and the entire tumors were dissected out and weighed.

**Statistical analysis**

All data were repeated in triplicate. Data are presented as mean ± SD. All statistical analyses were performed using GraphPad Prism software (version 7.0). One-way ANOVA and Tukey tests were carried out for multiple group comparisons. A $P < 0.05$ was considered as a statistically significant.

**Results**

**Hsa_circ_0014130 was upregulated in NSCLC tissues**

To explore whether expression of hsa_circ_0014130 is dysregulated in NSCLC, qRT-PCR was applied. As shown in Fig. 1A, the level of hsa_circ_0014130 in NSCLC tissues was markedly higher than that in the corresponding adjacent nontumor tissues. In addition, to assess whether hsa_circ_0014130 expression can discriminate between NSCLC tissues and adjacent normal tissues, ROC analysis was used. The area under the ROC curve (AUC) of 0.7486 indicated that the expression of hsa_circ_0014130 could discriminate between NSCLC tissues and adjacent normal tissues (Fig. 1B). As shown in Table 1, hsa_circ_0014130 expression correlated with clinicopathologic parameters, including tumor size, lymphatic metastasis, distant metastasis, and TNM stage. These data indicated that the level of hsa_circ_0014130 was upregulated in NSCLC tissues, and was associated with a poor prognosis.

**Downregulation of hsa_circ_0014130 inhibited the proliferation of NSCLC cells**

To investigate the biological function of hsa_circ_0014130 in NSCLC, we used two shRNAs (hsa_circ_0014130-shRNA1 and hsa_circ_0014130-shRNA2) to downregulate hsa_circ_0014130 in two NSCLC cells, PC-9 and A549. qRT-PCR results indicated that hsa_circ_0014130-shRNA1 downregulated the level of hsa_circ_0014130 more significantly than hsa_circ_0014130-shRNA2 in PC-9 and A549 cells (Fig. 2A and B). CCK-8 assay indicated that downregulation of hsa_circ_0014130 significantly inhibited the proliferation of NSCLC cells compared with NC treatment (Fig. 2C and D). Hsa_circ_0014130-shRNA1 inhibited about 45% growth in PC-9 cells and about 52% growth in A549 cells. Therefore, A549 cells were utilized in the following experiments. These results suggested that downregulation of hsa_circ_0014130 could inhibit the proliferation of NSCLC cells.

**Downregulation of hsa_circ_0014130 suppressed the invasion of A549 cells via inducing apoptosis**

To investigate the role of hsa_circ_0014130 on the apoptosis of A549 cells, flow cytometry assay was used. As shown in Fig. 3A and B, downregulation of hsa_circ_0014130 obviously induced the apoptosis of A549 cells.

**Table 1. The relationship between hsa_circ_0014130 and clinicopathologic parameters of patients with NSCLC.**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Number</th>
<th>Relative expression</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤50</td>
<td>12</td>
<td>1.112 ± 0.566</td>
<td>0.541</td>
</tr>
<tr>
<td>&gt;50</td>
<td>18</td>
<td>1.268 ± 0.677</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td>0.468</td>
</tr>
<tr>
<td>Male</td>
<td>19</td>
<td>1.313 ± 0.668</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>11</td>
<td>1.211 ± 0.612</td>
<td></td>
</tr>
<tr>
<td>Tumor size (cm)</td>
<td></td>
<td></td>
<td>0.042</td>
</tr>
<tr>
<td>≤5</td>
<td>17</td>
<td>1.078 ± 0.467</td>
<td></td>
</tr>
<tr>
<td>&gt;5</td>
<td>13</td>
<td>1.561 ± 0.756</td>
<td></td>
</tr>
<tr>
<td>Lymphatic metastasis</td>
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<td>0.048</td>
</tr>
<tr>
<td>N0</td>
<td>12</td>
<td>0.971 ± 0.445</td>
<td></td>
</tr>
<tr>
<td>N1–N3</td>
<td>18</td>
<td>1.631 ± 0.611</td>
<td></td>
</tr>
<tr>
<td>Distant metastasis</td>
<td></td>
<td></td>
<td>0.033</td>
</tr>
<tr>
<td>M0</td>
<td>13</td>
<td>0.846 ± 0.515</td>
<td></td>
</tr>
<tr>
<td>M1</td>
<td>17</td>
<td>1.795 ± 0.721</td>
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<tr>
<td>TNM stage</td>
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<td></td>
<td>0.027</td>
</tr>
<tr>
<td>I–II</td>
<td>10</td>
<td>0.772 ± 0.651</td>
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</tr>
<tr>
<td>III–IV</td>
<td>20</td>
<td>1.861 ± 0.339</td>
<td></td>
</tr>
</tbody>
</table>

*P < 0.05 (Student t test).
ability of A549 cells decreased notably after the cells were infected with hsa_circ_0014130-shRNA1 or hsa_circ_0014130-shRNA2 plasmids (Fig. 3C and D). A549 cells infected with hsa_circ_0014130-shRNA1 exhibited higher decrease in cell viability and invasion, compared with that of in hsa_circ_0014130-shRNA2 group. Therefore, hsa_circ_0014130-shRNA1 cells were utilized in the following experiments. These data illustrated that downregulation of hsa_circ_0014130 could suppress the invasion of A549 cells via inducing apoptosis.

Hsa_circ_0014130 functions as a ceRNA of miR-136-5p in NSCLC

Evidence has been shown that circRNAs contain multiple binding sites for miRNAs, which could act as miRNA sponge (17, 18). Online bioinformatics tool circular RNA interactome (https://circinteractome.nia.nih.gov) was used to determine the potential targets of hsa_circ_0014130. Thirty-two potential miRNA targets of hsa_circ_0014130 were identified. The data indicated that four miRNAs, miR-136-5p, miR-127-5p, miR-197, and miR-142-5p were closely associated with hsa_circ_0014130. Meanwhile, miR-136-5p, miR-127-5p, miR-197, and miR-142-5p have been found to play important roles in the progression of human cancers (4, 19–21). These data indicated that miR-136-5p was a binding target of hsa_circ_0014130 (Fig. 4A; Supplementary Fig. S1A–S1C). In addition, dual luciferase reporter assay was applied to validate the potential targets of hsa_circ_0014130. The data indicated that miR-136-5p mimics significantly inhibited the luciferase activity of psiCHECK-2-hsa_circ_0014130-WT, but it did not affect the luciferase activity of psiCHECK-2-hsa_circ_0014130-MT (Fig. 4B). However, limited relationships between hsa_circ_0014130 and miRNAs (miR-127-5p, miR-197, and miR-142-5p) were assessed using the dual luciferase reporter assay (Supplementary Fig. S1A–S1C). These data indicated that miR-136-5p was a binding target of hsa_circ_0014130. In addition, online bioinformatics tool TargetScan indicated that Bcl-2 might be a potential target of miR-136-5p (Fig. 4C). Dual luciferase reporter assay illustrated that miR-136-5p mimics significantly suppressed the luciferase activity of psiCHECK-2-Bcl-2-WT (Fig. 4D). These data indicated that Bcl-2 was a binding target of miR-136-5p. Meanwhile, the FISH assay indicated that hsa_circ_0014130 and miR-136-5p were partially colocalized in the cytoplasm (Fig. 4E), suggesting the direct interaction of hsa_circ_0014130 with miR-136-5p. These data indicated that hsa_circ_0014130 functions as a ceRNA of miR-136-5p in NSCLC.

Hsa_circ_0014130’s oncogenic roles are partially via sponging miR-136-5p and then activating Bcl-2

Having verified hsa_circ_0014130 was a target of miR-136-5p, the mechanism of miR-136-5p in hsa_circ_0014130-shRNA1–induced apoptosis on A549 cells was still unclear. As shown in Fig. 5A and Supplementary Fig. S2A, the level of miR-136-5p was markedly increased in A549 and PC-9 cells following transfection with...
miR-136-5p mimics, respectively, whereas the level of miR-136-5p was significantly decreased following transfection with miR-136-5p inhibitor. In addition, the level of Bcl-2 was decreased, and the expression of cleaved caspase-3 was increased in A549 and PC-9 cells following infection with hsa_circ_0014130, which were obviously reversed in the presence of miR-136-5p inhibitor (Fig. 5B–D; Supplementary Fig. S2B–S2D). These data indicated that hsa_circ_0014130 acts as an oncogene via hsa_circ_0014130/miR-136-5p/Bcl-2 axis.

Downregulation of hsa_circ_0014130 inhibited the tumorigenesis of A549 subcutaneous xenograft in vivo

We established a NSCLC xenograft model in mice to further explore the role of hsa_circ_0014130 on tumor growth in vivo. As shown in Fig. 6A–C, downregulation of hsa_circ_0014130 significantly inhibited xenograft tumor volume and tumor weight compared with NC group. In addition, we tested the expressions of Bcl-2 and cleaved caspase-3 in tumor tissues in vivo. The results indicated that silencing of hsa_circ_0014130 markedly downregulated the protein level of Bcl-2, and upregulated the protein level of cleaved caspase-3 in tumor tissues (Fig. 6D–F). These data illustrated that downregulation of hsa_circ_0014130 could inhibit the tumorigenesis of A549 subcutaneous xenograft in vivo.

Discussion

Predictive and identification biomarkers are urgently needed for patients with NSCLC. Previous studies indicated that some circRNAs are associated with the development of NSCLC, which participated in multiple biological processes, such as cell proliferation, apoptosis, and metastasis (6, 22, 23). Zhang and colleagues found that hsa_circ_0014130 was aberrantly expressed in NSCLC tissues and might be a new circular RNA biomarker in NSCLC (10). In this study, we confirmed that hsa_circ_0014130 was upregulated in NSCLC tissues. Meanwhile, hsa_circ_0014130 expression correlated with...
clinicopathologic parameters, including tumor volume and distant metastasis, indicating that hsa_circ_0014130 is associated with a poor prognosis (10). However, the function of hsa_circ_0014130 in the occurrence and progression of NSCLC remain unclear.

It has been shown that aberrantly expressed miRNAs are associated with the progression and prognosis of human cancers (24). CircRNAs could bind to miRNAs and regulate miRNAs function as miRNA sponges (25). Meanwhile, circRNA–miRNA–mRNA axis might play an important role in cancer-related pathways (25). Huang and colleagues found that circRNA_001946 could promote EMT and metastasis of NSCLC cells via a circAGFG1/miR-203/ZNF281 axis (14). On the basis of this feature of circRNAs, we aimed to explore the underlying mechanism of hsa_circ_0014130 on the progression of NSCLC, regulating miRNA sponges. In this study, online bioinformatics analysis and dual luciferase reporter assay indicated that hsa_circ_0014130 might act as ceRNAs to regulate miR-136-5p.

In addition, Bcl-2 act as a proapoptotic protein, which plays an important role in promoting cellular survival (26). Bioinformatics analysis and dual luciferase reporter assay confirmed that miR-136-5p targeted Bcl-2 mRNA at its 3'-UTR, and Bcl-2 might be a potential target of miR-136-5p.

Next, the role of hsa_circ_0014130 in proliferation of NSCLC cells was explored. Downregulation of hsa_circ_0014130 significantly inhibited the proliferation and invasion of A549 cells via inducing apoptosis. In addition, hsa_circ_0014130-shRNA1 treatment significantly decreased the expression of Bcl-2 in A549 cells. However, when A549 cells were treated with hsa_circ_0014130-shRNA1 plus miR-136-5p inhibitor, the unfavorable role of hsa_circ_0014130 on protein expression of Bcl-2 was increased by miR-136-5p overexpression. Our results indicated that miR-136-5p is sponged by hsa_circ_0014130 and targets Bcl-2. Chi and colleagues indicated that circRNA circPIP5K1A (hsa_circ_0014130) promoted the proliferation of NSCLC cells via sponging miR-600 and then promoting HIF-1α (27). In addition, overexpression of

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**Figure 4.**

Hsa_circ_0014130 functions as a ceRNA of miR-136-5p in NSCLC. **A**, Sequence alignment of miR-136-5p with the putative binding sites within the WT or MT regions of hsa_circ_0014130. **B**, The luciferase activity in A549 cells following cotransfecting with hsa_circ_0014130-WT/MT 3'-UTR plasmid and miR-136-5p mimics were detected using dual luciferase reporter assay. **C**, Sequence alignment of miR-136-5p with the putative binding sites within the WT or MT regions of Bcl-2. **D**, The luciferase activity in A549 cells following cotransfecting with Bcl-2-WT/MT 3'-UTR plasmid and miR-136-5p mimics were detected using dual luciferase reporter assay. **E**, The cellular localization of hsa_circ_0014130 and miR-136-5p in A549 cells was analyzed by FISH assay. *P < 0.01, compared with the NC group.*
circRNA circPIP5K1A could promote the metastasis of NSCLC cells via upregulation HIF-1α (27). Our data demonstrated that hsa_circ_0014130's oncogenic functions are partially via sponging miR-136-5p, and then activating Bcl-2. Bcl-2 is located at the outer mitochondrial membrane, which could restrain the release of cytochrome C and inhibit the activation of the caspase, and then exert its antiapoptotic function (28). Therefore, via downregulation of Bcl2, knockdown of hsa_circ_0014130 could inhibit cell apoptosis and suppress tumorigenesis in NSCLC. The conclusions are consistent, while hsa_circ_0014130 has another mechanism of action against human NSCLC.

This study had some limitations. It has been shown that oncogenic drivers are important to cancer development and maintenance (29). Some of the known oncogenic drivers have been identified, including ROS1, RET, EGFR, ALK, and KRAS, which have been found to play potential prognostic or predictive roles in the development of NSCLC (29). However, in this study, we have not come to conclusion that the relationship between hsa_circ_0014130 and the oncogenic drivers in NSCLC. Therefore, in the future, it will be important to clarify whether hsa_circ_0014130 could facilitate the progression of NSCLC via regulating the oncogenic drivers.

Figure 5. Hsa_circ_0014130's oncogenic roles are partially via sponging miR-136-5p, and then activating Bcl-2 in A549 cells. A, The level of miR-136-5p in A549 cells transfected with the miR-136-5p mimics or inhibitor was detected by qRT-PCR. B, A549 cells were infected with hsa_circ_0014130-shRNA1 and cotransfected with hsa_circ_0014130-shRNA1 and miR-136-5p inhibitor. Expression levels of Bcl-2 and cleaved caspase-3 in A549 cells were detected with Western blotting. C and D, The relative expression of Bcl-2 and cleaved caspase-3 in A549 cells were quantified via normalization to β-actin. **, P < 0.01, compared with the NC group; ##, P < 0.01, compared with the shRNA1 group.
Conclusion
In this study, our data revealed that highly expressed hsa_circ_0014130 is an oncogenic circRNA that facilitates the progression of NSCLC via miR-136-5p/Bcl-2 axis. In addition, hsa_circ_0014130 might function as a prognostic factor in NSCLC. Therefore, hsa_circ_0014130 might be a potential biomarker and therapeutic target for the treatment of NSCLC.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Authors’ Contributions
Conception and design: Y. Geng, Y. Bao, W. Zhang, L. Deng, H. Zheng
Development of methodology: Y. Bao, L. Deng, D. Su
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): Y. Bao, L. Deng, D. Su, H. Zheng
Writing, review, and/or revision of the manuscript: Y. Geng, W. Zhang, L. Deng
Study supervision: Y. Geng, W. Zhang

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Received October 7, 2019; revised December 16, 2019; accepted February 12, 2020; published first February 14, 2020.

References


Correction: Circular RNA hsa_circ_0014130 Inhibits Apoptosis in Non–Small Cell Lung Cancer by Sponging miR-136-5p and Upregulating BCL2

In the original version of this article (1), the author order is incorrect for the final four authors. This error has been corrected in the latest online HTML and PDF versions of the article. The authors regret this error.

**Reference**


Published online July 1, 2020.
Mol Cancer Res 2020;18:1110
doi: 10.1158/1541-7786.MCR-20-0499
©2020 American Association for Cancer Research.
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