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Original Article

CircFOXK2 induces non-small cell lung cancer tumorigenesis through the miR-328-5p/PKP3 axis

Tongwei Xiang[1*], Liping Chen[2], Huaying Wang[1], Tao Yu[1], Tang Li[1], Jipeng Li[2], Wanjun Yu[1]

[1] *Department of Respiratory and Critical Care Medicine, Yinzhou People's Hospital, The Affiliated People's Hospital of Ningbo University, Ningbo, China*

[2] *Department of Central Laboratory, Yinzhou People's Hospital, The Affiliated People's Hospital of Ningbo University, Ningbo, China*

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Abstract

Circular RNAs (circRNAs) are non-coding RNAs (ncRNAs) implicated in the onset and advancement of various human cancers. Among these, circFOXK2 has been linked to non-small cell lung cancer (NSCLC); however, its precise functions and underlying molecular mechanisms are not fully understood. This study shows the first experimental findings that circFOXK2 promotes NSCLC tumor progression by modulating the miR-328-5p/PKP3 signaling pathway. Levels of circFOXK2, miR-328-5p, and PKP3 were evaluated by qRT-PCR. Cellular (NSCLSC) proliferation was examined via CCK-8 assays, migratory capacity via wound healing, and invasive potential via Transwell assays. Potential binding interactions between miR-328-5p and circFOXK2 were first assessed using bioinformatic analysis and verified using a dual-luciferase reporter assay (DLRGAs). Regulatory relationships among circFOXK2, miR-328-5p, and PKP3 were further investigated through qRT-PCR analysis. Elevated expression of circFOXK2 and reduced levels of miR-328-5p were observed in NSCLC cell lines and tissues. Functionally, circFOXK2 enhanced cellular propagation, dissemination, and invasion in vitro. Mechanistic evaluation revealed that circFOXK2 upregulates PKP3 by acting as an miR-328-5p sponge. The findings demonstrate that circFOXK2 contributes to NSCLC tumorigenesis via modulation of the miR-328-5p/PKP3 pathway, identifying this signaling axis as a potential therapeutic target in NSCLC.

Keywords: CircFOXK2, miRNA-328-5p, NSCLC, PKP3.

1. Introduction

Globally, lung cancer (LC) persists as a predominant cause of cancer-related mortality [1,2]. Among them, NSCLC comprises approximately 80% of all LC diagnoses [3] and is distinguished by its markedly poor prognosis. This epidemiological and clinical burden underscores the critical necessity for the advancement of innovative and efficacious therapeutic modalities for NSCLC management [4].

Circular RNAs are a recently characterized subclass of ncRNAs distinguished by their covalently closed loop configuration [5]. This unique conformation provides resistance to exonuclease-mediated degradation, giving circRNAs increased stability compared to linear RNAs. As a result, circRNAs have gained significant attention as promising, stable biomarkers for various cancers [6-8]. Growing research has shown that circRNAs play crucial roles in cancer progression and cellular regulation [9]. One of the main mechanisms through which circRNAs exert post-transcriptional regulatory control involves acting as molecular sponges for miRNAs [10]. By sequestering microRNAs, circRNAs prevent them from binding to target mRNAs, thus modulating gene expression. Besides this, circRNAs can interact directly with proteins, influence transcriptional processes, regulate translation, and participate in epigenetic modulation [11]. Recent studies have implicated circRNAs in the tumorigenesis of various malignancies [12-15]. For instance, circATP8A1, contained within exosomes secreted by gastric cancer (GC) cells, promotes M2 macrophage polarization through the circATP8A1/miR-1-3p/STAT6 axis, thus contributing to tumor advancement [16]. Similarly, circNOX4 drives NSCLC development by sponging miR-329-5p, resulting in fibroblast activation protein upregulation and increased IL-6 expression [17]. *CircFOXK2*, a specific member of the circRNA family, has been associated with oncogenic processes. Previous investigations have shown that *circFOXK2* accelerates pancreatic cancer progression by sponging miR-942, although the downstream regulatory events remain incompletely elucidated [18]. Moreover, *circFOXK2* has been reported to promote breast cancer growth *via* the IGF2BP3/miR-370 signaling axis [19]. Despite these observations, the biological significance and molecular mechanisms of *circFOXK2* in NSCLC have not

* Corresponding author.
E-mail address: 603358673@qq.com (T. Xiang).
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been comprehensively investigated.

This study shows that *circFOXK2* promotes NSCLC tumorigenesis by modulating the miR-328-5p/*PKP3* signaling axis *in vitro*, providing new insights into the molecular pathology of NSCLC and identifying possible targets for therapeutic intervention.

2. Materials and methods

2.1. Collection of tissue specimens

Tumor tissue specimens, along with respective adjacent healthy tissues, were obtained from 35 individuals diagnosed with NSCLC at the Affiliated People's Hospital of Ningbo University after surgical resection. Following collection, samples were preserved in liquid nitrogen to maintain RNA integrity. Adjacent tissues represented those located within 2 cm of the tumor margin, whereas normal control tissues were collected from sites > 5 cm away from the primary lesion [20]. Before surgery, patients did not receive any treatment, i.e., radiotherapy and chemotherapy. Consent form (written) was collected from each participant, and the Clinical Research Ethics Committee of the respective University approved the experimental procedure.

2.2. Cell culture conditions

Human NSCLC cell lines (H661, H460, A549, and SPC-A1) and the normal bronchial BEAS-2B cell line were procured from the Institute of Biochemistry and Cell Biology, Chinese Academy of Sciences (Shanghai, China). Cells were maintained in DMEM (C3118-0500; VivaCell Biosciences, China) enriched with 10% heat-inactivated fetal bovine serum (16140071; Gibco, USA), 100 U/mL penicillin, and 100 µg/mL streptomycin (PB180120; Procell, China) under appropriate culture conditions (5% CO_2, 37 °C). Media were replaced at three-day intervals. Sub-culturing was carried out using 0.25% trypsin-EDTA (Gibco, 25200056) [21].

2.3. Cell transfection protocol

For *circFOXK2* overexpression, the full-length cDNA sequence was cloned between flanking inverted repeat sequences within a circular RNA expression vector to facilitate back-splicing [22]. Specific siRNAs targeting the back-splice junction region of *circFOXK2* were designed for selective gene silencing. All genetic constructs, including the overexpression plasmid and siRNAs, were purchased from GenePharma (Shanghai, China). Moreover, modulation of miR-328-5p levels was examined using transfection of cells with synthetic miR-328-5p mimics, inhibitors (anti-miR-328-5p), and respective negative controls (NC and anti-NC), all supplied by GenePharma. SPC-A1 cells (3×10^5/mL) were inoculated in 6-well plates and cultivated for 24 h. Lipofectamine® 2000 (Invitrogen, USA; 11668019) was used as the transfection reagent as directed, with dilution of 3 µL in 50 µL of FBS-free DMEM and standing at 25 °C for 5 min, before mixing with 50 nM of the respective nucleic acid constructs for 20 min before being added to cells for 4-6 h. Transfection efficiencies were assessed *via* qRT-PCR. The siRNA sequences targeting *circFOXK2* are provided in Table 1.

2.4. qRT-PCR analysis

Total RNA was extracted using TRIzol (Invitrogen; 15596026CN). For circRNA and mRNA detection, the RNA (1 µg) was reverse-transcribed to cDNA using TransScript First-Strand cDNA Synthesis SuperMix (AT301-02; TransGen Biotech), with TransScript miRNA First-Strand cDNA Synthesis SuperMix (TransGen Biotech) used for miRNAs. Next, qRT-PCR was undertaken using PerfectStart Green qPCR SuperMix (AQ602-01; TransGen Biotech) on an ABI 7500 Real-Time PCR System (Applied Biosystems, USA). Relative expression of *circFOXK2*, miR-328-5p, and *PKP3* was assessed using the $2^{-\Delta\Delta CT}$ method [23]. Primer sequences were designed using the NCBI website and verified with BLAST; sequences are given in Table 2.

2.5. Cell proliferation assessment

Proliferation was assessed using CCK-8 assays (FC101-01; TransGen Biotech, China) as directed. SPC-A1 cells (2×10^3/well) were inoculated in 96-well plates and cultivated for 24 h, which was designated as day 0. Next, CCK-8 solution (10 µL) was introduced to individual wells for an additional 2 h. Absorbance (OD_{450}) was observed using a cMax Plus microplate reader (USA) on days 1, 2, and 3 [24].

2.6. Wound healing migration assays

Migratory capacity was investigated using wound-healing assays. SPC-A1 cells were grown in 6-well plates until 90% confluent. A sterile pipette tip (200 µL) was applied for scratching the monolayer (time point 0 h), producing a cell-free gap. Cells were then kept in FBS-free medium for 48 h. Closure of the gap was monitored under light microscopy at 24 and 48 h, and migration distances were quantified using ImageJ. Triplicate experiments were

Table 1. siRNA sequences targeting circFOXK2.

siRNA	*circFOXK2* targeting sequence (5′-3′)
si-circFOXK2	5′-GAAGGUGCACAUUCAGGUUTT-3′

Table 2. Primer sequences used for qRT-PCR analysis.

Genes	Forward primers (5′-3′)	Reverse primers (5′-3′)
circFOXK2	TAATGGCTGACAACTCACA	GCTTCTCTCTCTTCTCGCT
circFOXK2-328MUT	CACCTCATCAGCCCTCTGCGGAGG GCCACGGGAACCATCAGCGC	GCGCTGATGGTTCCCGTGGCCCTCC GCAGAGGGCTGATGAGGTG
GAPDH	TCAGTGGTGGACCTGACCTG	TGCTGTAGCCAAATTCGTTG
miR-328-5p	CCCTGAGCCCCTCCTGCCCCC	
U6	CTCGCTTCGGCAGCACA	AACGCTTCACGAATTTGCGT
PKP3	ACGTGCATGGGTTCAACAG	CTGCTGAGGGCAGGTCAAT

undertaken [25].

2.7. Transwell invasion assays

The invasive capacity of cells was assessed using 8 µm-pore Transwell inserts (BD Biosciences, USA) following coating with Matrigel (Corning, USA). Cells (5 × 104) in serum-free media were inoculated into the top compartment, while the bottom compartment contained media with 10% FBS. After 36 h, migrated cells were fixed and stained with methanol and crystal violet (Thermo Scientific, USA; R40073), respectively, and quantified microscopically [26].

2.8. Colony formation assays

The clonogenic ability of NSCLC cells was examined through colony formation analysis. In brief, 500 cells were inoculated in the wells of a 6-well plate and grown for 14 days, with medium replenishment after 3-4 days. Colonies were fixed in formaldehyde for 20 min, stained with 0.5% crystal violet for 20 min, rinsed with PBS (thrice), and counted manually [27].

2.9. Dual-luciferase reporter gene assays

Potential binding between miR-328-5p and the *circFOXK2* 3′ untranslated region was predicted using the Arraystar miRNA target prediction platform, the CircInteractome database, and StarBase. These predictions were verified experimentally using DLRGAs. Wild-type (*circFOXK2*-WT) constructs with the predicted miR-328-5p binding site were cloned into the Renilla pGL3 vector (Promega, USA; E1751), whereas mutant (*circFOXK2*-MUT) constructs were generated through site-directed mutagenesis of the binding site. SPC-A1 cells were co-transfected with either WT or mutant vectors and miR-328-5p mimics or negative control oligonucleotides (miR-NC). Luciferase activities were assessed after 48 h using a DLRGA System (E1910; Promega, USA) [28].

2.10. Statistical analysis

Triplicate experiments were conducted. Data are depicted as means ± standard deviation (SD). Correlation between miR-328-5p, *circFOXK2*, and *PKP3* levels was evaluated *via* Pearson's correlation coefficient. Two groups were compared using t-tests, while variances among multiple groups (> 2 groups) were evaluated by one-way analysis of variance (ANOVA) followed by Tukey's post hoc test. A p-value < 0.05 was deemed statistically significant [29].

3. Results

3.1. Upregulation of *circFOXK2* in NSCLC cells and tissues

For gene expression profiling, qRT-PCR indicated markedly higher levels of *circFOXK2* in tumor relative to normal BEAS-2B cells, with the highest levels seen in SPC-A1 cells (Figure 1A). Similarly, *CircFOXK2* levels were also markedly raised in tumor tissue samples relative to the respective adjacent non-cancerous tissue (Figure 1B). Overall, these findings indicate that *circFOXK2* levels were elevated in both NSCLC cells and tissues.

3.2. *circFOXK2* regulated NSCLC cell penetration, propagation, and migration in *vitro*

SPC-A1 cells, which showed the highest endogenous *circFOXK2* expression, were selected for functional assays. Transfection efficiency for *circFOXK2* silencing (si-*circFOXK2*) and overexpression (pEX-3-*circFOXK2*) was verified *via* qRT-PCR (Figure 2A). CCK-8 assays showed that *circFOXK2* knockdown markedly inhibited propagation and colony formation relative to the controls, while overexpressing *circFOXK2* substantially increased these parameters (Figure 2B). Transwell assays indicated that suppression of *circFOXK2* expression reduced the invasive ability of SPC-A1 cells, while its overexpression enhanced invasion (Figure 2C and 2D). Wound healing assays further revealed a reduction in migration potential after *circFOXK2* silencing and an increase with *circFOXK2* overexpression (Figure 2E and 2F).

3.3. Direct Binding of *circFOXK2* to miR-328-5p

Bioinformatic predictions using Arraystar's target prediction software, CircInteractome, and StarBase databases identified miR-328-5p and miR-942 as potential *circFOXK2*-binding microRNAs. Previous evidence has shown that *circFOXK2* promotes the proliferation and dissemination of pancreatic tumors by binding to RNA-binding proteins and functioning as a sponge for miR-942[18], thus supporting the use of miR-942 as a positive control. DLRGAs showed that overexpression of miR-328-5p substantially diminished luciferase activities in the wild-type *circFOXK2* reporter (*circFOXK2*-WT) (Figure 3A).

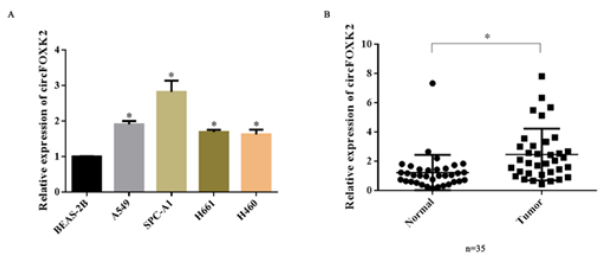

Fig. 1. Upregulation of *circFOXK2* levels in cells and tumors. (A) Expression of *circFOXK2* in tumor and BEAS-2B cells. (B) Expression of *circFOXK2* in tumor and non-tumorous tissues (n = 35). *p < 0.05.

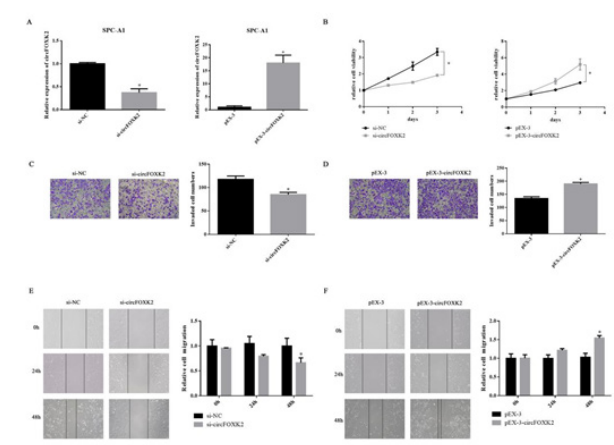

Fig. 2. Functional role of *circFOXK2* in regulating tumor growth, invasion, and migration. (A) *circFOXK2* expression in SPC-A1 cells transfected with si-NC, si-*circFOXK2*, pEX-3, or pEX-3-*circFOXK2*. (B) Cell proliferation determined by CCK-8 assay. (C, D) Invasive ability assessed by Transwell assays. (E, F) Migration capacity assessed by wound healing assays. *p < 0.05.

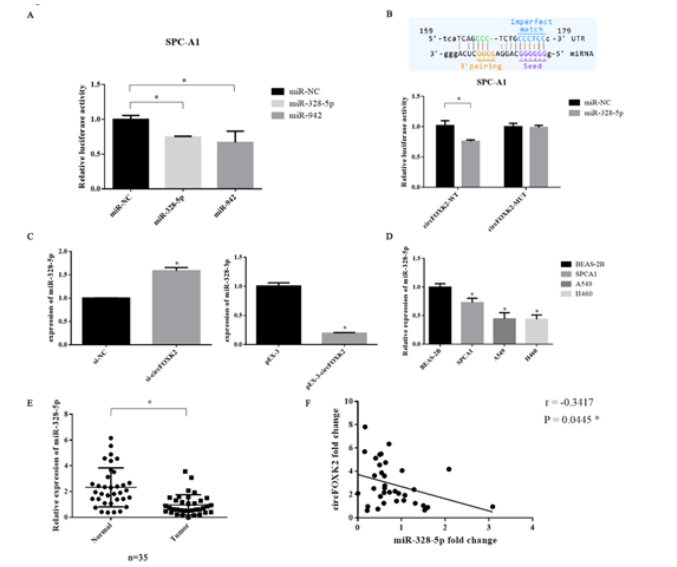

Fig. 3. Direct binding between *circFOXK2* and miR-328-5p. (A) Prediction of candidate miRNAs interacting with *circFOXK2*, validated *via* DLRGA. (B) Schematic of the predicted miR-328-5p binding site and corresponding mutation within *circFOXK2*. (C) miR-328-5p levels in SPC-A1 cells after *circFOXK2* knockdown or overexpression, shown by qRT-PCR. (D) miR-328-5p levels in BEAS-2B, A549, and H460 cells. (E) miR-328-5p levels in NSCLC tissues and adjacent non-cancerous tissues (n = 35). (F) Pearson's correlations between *circFOXK2* and miR-328-5p in tumor tissue samples (n = 35). **p* < 0.05.

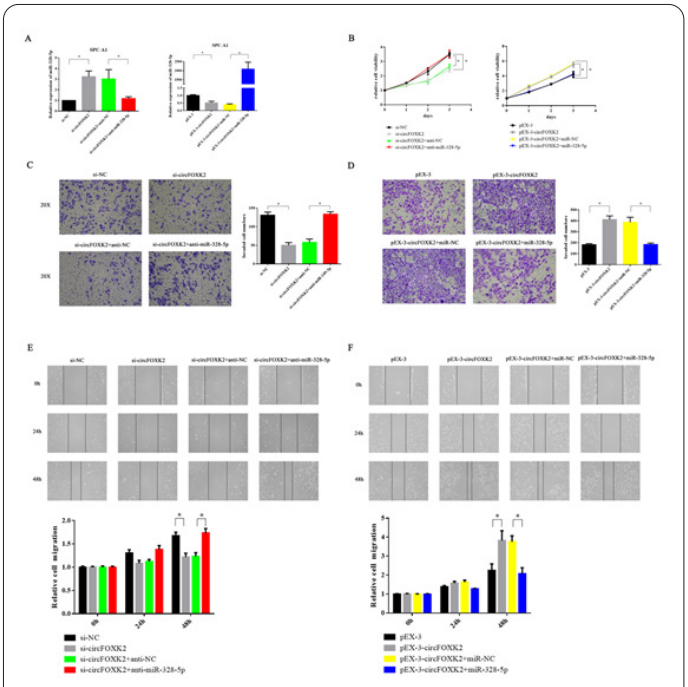

Fig. 4. Modulation by miR-328-5p of *circFOXK2*-mediated regulation of NSCLC proliferation, invasion, and migration. (A) Transfection conditions for si-*circFOXK2* + anti-NC, si-NC, si-*circFOXK2*, pEX-3, pEX-3-*circFOXK2*, si-*circFOXK2* + anti-miR-328-5p, pEX-3-*circFOXK2* + miR-328-5p, and pEX-3-*circFOXK2* + miR-NC. (B) Cell proliferation was examined by CCK-8 assays. (C, D) Cell invasion was noted *via* Transwell assays. (E, F) Wound healing assays assessed cell migration. **p* < 0.05.

Site-directed mutagenesis of the predicted binding region was carried out using mutation primers, and results indicated that overexpression of miR-328-5p markedly lowered luciferase activity in *circFOXK2*-WT but did not affect the mutant reporter (*circFOXK2*-MUT) (Figure 3B). To verify the binding pattern between *circFOXK2* and miR-328-5p transcripts, *circFOXK2* was either silenced or overexpressed, followed by qRT-PCR assessment of miR-328-5p levels. Knockdown of *circFOXK2* substantially increased miR-328-5p levels, while overexpression of *circFOXK2* led to reduced miR-328-5p levels (Figure 3C). In NSCLC cells, miR-328-5p expression was downregulated and showed a negative correlation with *circFOXK2* levels (Figure 3D). Analysis of clinical NSCLC samples indicated markedly lower miR-328-5p levels in tumor tissues relative to the respective non-tumorous tissues (Figure 3E). Pearson's correlations further confirmed a remarkable negative association between the levels of *circFOXK2* and miR-328-5p in tumor specimens (Figure 3F).

3.4. Regulation of NSCLC advancement *in vitro* by *circFOXK2 via* miR-328-5p interaction

To investigate whether miR-328-5p mediates *circFOXK2*-driven NSCLC progression, rescue experiments were performed in SPC-A1 cells. Transfection efficiency for miR-328-5p inhibition (anti-miR-328-5p) and overexpression was confirmed (Figure 4A). CCK-8 assays revealed that *circFOXK2* silencing reduced proliferation, an effect partially reversed by miR-328-5p inhibition. However, the enhanced proliferation induced by *circFOXK2* overexpression was substantially reduced when miR-328-5p was overexpressed (Figure 4B). Transwell assays revealed that knocking down *circFOXK2* substantially decreased invasive ability, and this effect was alleviated by miR-328-5p inhibition (Figure 4C). In comparison, *circFOXK2* overexpression enhanced invasion, which was counteracted by miR-328-5p overexpression (Figure 4D). Wound healing assays revealed that *circFOXK2* knockdown substantially reduced migratory capacity, and miR-328-5p inhibition partially restored migration (Figure 4E). In comparison, overexpression of *circFOXK2* promoted migration, an effect that was suppressed by miR-328-5p overexpression (Figure 4F). These findings indicate that *circFOXK2* promotes tumor cell proliferation, penetration, and migration through miR-328-5p targeting.

3.5. *circFOXK2* upregulates *PKP3* by sponging miR-328-5p

A previous report showed that miR-328-5p directly targets *PKP3* in NSCLC [30]. Moreover, qRT-PCR analysis revealed that silencing *circFOXK2* reduced *PKP3* expression in SPC-A1 cells, whereas overexpression of *circFOXK2* increased *PKP3* levels (Figure 5A). *PKP3* was substantially increased in NSCLC cells and tumor tissues relative to controls (Figure 5B, 5C). Correlation analysis depicted a considerable favorable association between *circFOXK2* and *PKP3* expression in clinical specimens (Figure 5D).

4. Discussion

Many studies have shown a strong association between circular RNAs and the initiation, advancement, and dissemination of multiple malignancies, including lung cancer [31-33]. Due to their covalently closed-loop structure, circular RNAs show enhanced stability compared to linear transcripts, making them attractive candidates for use as diagnostic and prognostic biomarkers [34]. Uncontrolled expression of *circFOXK2* has been documented in various

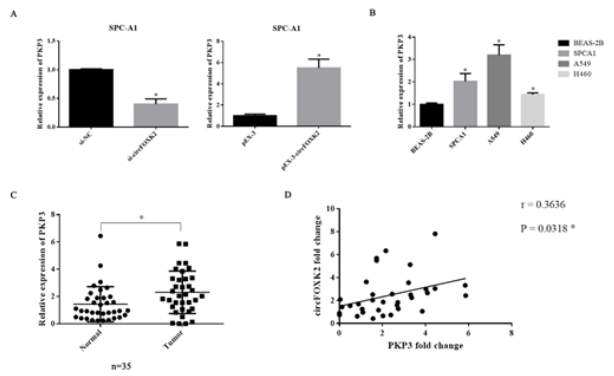

Fig. 5. *PKP3* is targeted directly by miR-328-5p. (A) Relative *PKP3* mRNA levels in SPC-A1 cells transfected with si-NC, si-*circFOXK2*, pEX-3, or pEX-3-*circFOXK2*, measured by qRT-PCR. (B, C) qRT-PCR analysis of *PKP3* mRNA levels in NSCLC cells and tissues (n = 35). (D) Correlation analysis of *circFOXK2* and *PKP3* expression in tumor tissues (n = 35). *$p < 0.05$.

tumor types and is closely linked to cancer pathogenesis [35,36]; however, its functional relevance in NSCLC has remained unclear.

Circular RNAs exert diverse regulatory roles in gene expression, with one of the most prominent mechanisms being the sequestration of microRNAs, thus preventing their interaction with target mRNAs [37]. For instance, circFOXK2 targeted miR-485-5p, which could bind to PD-L1 [38]. This study provides evidence that *circFOXK2* is significantly elevated in NSCLC cells and tissues and that it enhances cellular proliferation, migration, and invasion *in vitro*. MicroRNA-328-5p was detected as a functional target of *circFOXK2*. It has been found that miR-328-5p is dysregulated in multiple cancers and functions essentially in tumor suppression. For example, in breast cancer, miR-328-5p levels are decreased, leading to increased tumor growth, chemoresistance, and cell cycle disruption [39]. In this study, *circFOXK2* was shown to serve as a ceRNA for miR-328-5p, reducing its tumor-suppressive effects. Functional rescue experiments indicated that altering miR-328-5p levels could partially counteract the oncogenic effects of *circFOXK2* on NSCLC cells. Further investigation of downstream targets revealed that *PKP3* is directly controlled by miR-328-5p, in line with previous reports [30]. *PKP3* has been related to promoting malignant features in NSCLC, including increased proliferation, motility, and metastatic potential [30,40,41]. These findings suggest that *circFOXK2* indirectly increases *PKP3* expression by sponging miR-328-5p, thus promoting NSCLC progression.

This investigation appears to be the first to describe the *circFOXK2*/miR-328-5p/*PKP3* regulatory axis in NSCLC. These observations not only expand the understanding of circular RNA–microRNA–mRNA interactions in tumor biology but also identify this pathway as a potential molecular target for future therapeutic development. However, a limitation of the current study is the absence of exploration of downstream pathways such as MAPK, PI3K/AKT, NF-κB, and JAK-STAT. Which will be necessary in future studies to validate the clinical application of these findings.

Compared to previous NSCLC studies [42], this research broadens the understanding of the ceRNA network involving circRNAs and miRNAs. These findings provide an effective preclinical basis for developing new therapeutic strategies targeting NSCLC.

This study demonstrates that *circFOXK2* exerts oncogenic effects in NSCLC cancer by functioning as a molecular sponge for miR-328-5p, thus upregulating *PKP3* expression. This *circFOXK2*/miR-328-5p/*PKP3* axis promotes tumor cell growth, invasion, and dissemination *in vitro*. These findings provide a preclinical foundation for considering this regulatory pathway as a potential target in the emergence of novel therapeutic options for NSCLC.

Conflicts of interest

All authors have completed the ICMJE uniform disclosure form. The authors have no conflicts of interest to declare.

Consent for publications

The author read and approved the final manuscript for publication.

Ethics approval and consent to participate

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This investigation was authorized by the Clinical Research Ethics Committee of Ningbo University and was carried out according to the guidelines of the Declaration of Helsinki.

Availability of data and material

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Authors' contributions

Tongwei Xiang hypothesized and designed the project. Tongwei Xiang, Liping Chen, Tao Yu, and Jipeng Li performed the experiments and analyzed the data. Tongwei Xiang wrote the manuscript. Liping Chen, Tang Li and Huaying Wang provided advice and critical comments. Wanjun Yu is responsible for research supervision and funding acquisition. All the authors read and approved the final manuscript.

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References

1. Siegel RL, Giaquinto AN, Jemal A (2024) Cancer statistics, 2024. CA Cancer J Clin 74: 12–49 doi: 10.3322/caac.21820
2. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, Jemal A (2024) Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers

in 185 countries. CA Cancer J Clin 74: 229–263 doi: 10.3322/caac.21834
3. Wolf AMD, Oeffinger KC, Shih TY, Walter LC, Church TR, Fontham ETH, Elkin EB, Etzioni RD, Guerra CE, Perkins RB, Kondo KK, Kratzer TB, Manassaram-Baptiste D, Dahut WL, Smith RA (2024) Screening for lung cancer: 2023 guideline update from the American Cancer Society. CA Cancer J Clin 74: 50–81 doi: 10.3322/caac.21811
4. LoPiccolo J, Gusev A, Christiani DC, Jänne PA (2024) Lung cancer in patients who have never smoked - an emerging disease. Nat Rev Clin Oncol 21: 121–146 doi: 10.1038/s41571-023-00844-0
5. Azizzad Ranji E, Kahrizi D, Khanahmadi M, Rashidi Monfared S (2025) CircRNAs: Biogenesis, identification and expression analysis. Cell Mol Biomed Rep 5: 63–79 doi: 10.55705/cmbr.2025.460043.1248
6. Zhang L, Gao H, Li X, Yu F, Li P (2024) The important regulatory roles of circRNA-encoded proteins or peptides in cancer pathogenesis (Review). Int J Oncol 64: 19 doi: 10.3892/ijo.2023.5607
7. Conn VM, Chinnaiyan AM, Conn SJ (2024) Circular RNA in cancer. Nat Rev Cancer 24: 597–613 doi: 10.1038/s41568-024-00721-7
8. Zhang J, Luo Z, Zheng Y, Duan M, Qiu Z, Huang C (2024) CircRNA as an Achilles heel of cancer: characterization, biomarker and therapeutic modalities. J Transl Med 22: 752 doi: 10.1186/s12967-024-05562-4
9. Butz H, Patócs A, Igaz P (2024) Circulating non-coding RNA biomarkers of endocrine tumours. Nat Rev Endocrinol 20: 600–614 doi: 10.1038/s41574-024-01005-8
10. Zhang W, Xu C, Yang Z, Zhou J, Peng W, Zhang X, Li H, Qu S, Tao K (2024) Circular RNAs in tumor immunity and immunotherapy. Mol Cancer 23: 171 doi: 10.1186/s12943-024-02082-z
11. Heidari-Ezzati S, Moeinian P, Ahmadian-Nejad B, Maghbbouli F, Abbasi S, Zahedi M, Afkhami H, Shadab A, Sajedi N (2024) The role of long non-coding RNAs and circular RNAs in cervical cancer: modulating miRNA function. Front Cell Dev Biol 12: 1308730 doi: 10.3389/fcell.2024.1308730
12. Dlamini Z, Ladomery MR, Kahraman A (2024) Editorial: The RNA revolution and cancer. Front Endocrinol (Lausanne) 15: 1422599 doi: 10.3389/fendo.2024.1422599
13. Margvelani G, Maquera KAA, Welden JR, Rodgers DW, Stamm S (2025) Translation of circular RNAs. Nucleic Acids Res 53: gkae1167 doi: 10.1093/nar/gkae1167
14. Razipour M, Jamali Z, Khorsand M, Zargar M, Maghsudlu M, Ghadami E, Shakoori A (2025) Circular RNAs in laryngeal cancer. Clin Chim Acta 564: 119916 doi: 10.1016/j.cca.2024.119916
15. Qiu M, Chen Y, Zeng C (2024) Biological functions of circRNA in regulating the hallmarks of gastrointestinal cancer (Review). Int J Oncol 64: 49 doi: 10.3892/ijo.2024.5637
16. Deng C, Huo M, Chu H, Zhuang X, Deng G, Li W, Wei H, Zeng L, He Y, Liu H, Li J, Zhang C, Chen H (2024) Exosome circATP8A1 induces macrophage M2 polarization by regulating the miR-1-3p/STAT6 axis to promote gastric cancer progression. Mol Cancer 23: 49 doi: 10.1186/s12943-024-01966-4
17. Zhao Y, Jia Y, Wang J, Chen X, Han J, Zhen S, Yin S, Lv W, Yu F, Wang J, Xu F, Zhao X, Liu L (2024) circNOX4 activates an inflammatory fibroblast niche to promote tumor growth and metastasis in NSCLC via FAP/IL-6 axis. Mol Cancer 23: 47 doi: 10.1186/s12943-024-01957-5
18. Wong CH, Lou UK, Li Y, Chan SL, Tong JH, To KF, Chen Y (2020) CircFOXK2 Promotes Growth and Metastasis of Pancreatic Ductal Adenocarcinoma by Complexing with RNA-Binding Proteins and Sponging MiR-942. Cancer Res 80: 2138–2149 doi: 10.1158/0008-5472
19. Zhang W, Liu H, Jiang J, Yang Y, Wang W, Jia Z (2021) CircRNA circFOXK2 facilitates oncogenesis in breast cancer via IGF2BP3/miR-370 axis. Aging (Albany NY) 13: 18978–18992 doi: 10.18632/aging.203347
20. Wang H, Si S, Jiang M, Chen L, Huang K, Yu W (2021) Leukemia inhibitory factor is involved in the pathogenesis of NSCLC through activation of the STAT3 signaling pathway. Oncol Lett 22: 663 doi: 10.3892/ol.2021.12924
21. Jiang M, Bai H, Fang S, Zhou C, Shen W, Gong Z (2024) CircLIFRSA/miR-1305/PTEN axis attenuates malignant cellular processes in non-small cell lung cancer by regulating AKT phosphorylation. Mol Cancer 23: 208 doi: 10.1186/s12943-024-02120-w
22. Zhang Y, Song X, Feng Y, Qian Y, Chen B, Zhang T, Wang H, Chen Y, Yu X, Ding H, Li R, Ge P, Xu L, Dong G, Jiang F (2025) The circRNA cEMSY Induces Immunogenic Cell Death and Boosts Immunotherapy Efficacy in Lung Adenocarcinoma. Cancer Res 85: 497–514 doi: 10.1158/0008-5472
23. Du X, Luo W, Li H, Gu Q, Huang P, Wang C, Li N, Liu F, Xia C (2025) Hsa_circ_0125356 promotes gemcitabine resistance by modulating WNT canonical and non-canonical pathways via miR-582-5p/FGF9 axis in non-small cell lung cancer. Mol Cancer 24: 59 doi: 10.1186/s12943-025-02259-0
24. Wang Y, Yang T, Li Q, Zheng Z, Liao L, Cen J, Chen W, Luo J, Xu Y, Zhou M, Zhang J (2025) circASAP1 induces renal clear cell carcinoma ferroptosis by binding to HNRNPC and thereby regulating GPX4. Mol Cancer 24: 1 doi: 10.1186/s12943-024-02122-8
25. Huang M, Sun J, Jiang Q, Zhao X, Huang H, Lei M, Jiang S, Yuan F, Liu Z (2025) CircKIAA0182-YBX1 Axis: A Key Driver of Lung Cancer Progression and Chemoresistance. Cancer Lett 612: 217494 doi: 10.1016/j.canlet.2025.217494
26. Chen S, Cai D, Zhao Q, Wu J, Zhou X, Xu H, Li X, Zhang R, Peng W, Li G, Nan A (2025) NSUN2-mediated m5C modification of circFAM190B promotes lung cancer progression by inhibiting cellular autophagy. Int J Biol Macromol 306: 141528 doi: 10.1016/j.ijbiomac.2025.141528
27. Xia L, Li G, Zhou Q, Feng YU, Ma H (2025) CircRNA circ_0015278 induces ferroptosis in lung adenocarcinoma through the miR-1228/P53 axis. Oncol Res 33: 465–475 doi: 10.32604/or.2024.050835
28. Sun X, Feng P, Chen H, Ji Z, Zhuang L, Zhu T, Ji G, Wang J (2025) Hsa_circ_0048764 facilitates the progression of non-small cell lung cancer by targeting miR-1178-3p/HMGA1 axis. Cell Signal 125: 111484 doi: 10.1016/j.cellsig.2024.111484
29. Jiang M, Bai H, Fang S, Zhou C, Shen W, Gong Z (2024) CircLIFRSA/miR-1305/PTEN axis attenuates malignant cellular processes in non-small cell lung cancer by regulating AKT phosphorylation. Mol Cancer 23: 208 doi: 10.1186/s12943-024-02120-w
30. Liu Z, Wang T, She Y, Wu K, Gu S, Li L, Dong C, Chen C, Zhou Y (2021) N6-methyladenosine-modified circIGF2BP3 inhibits CD8+ T-cell responses to facilitate tumor immune evasion by promoting the deubiquitination of PD-L1 in non-small cell lung cancer. Mol Cancer 20: 105 doi: 10.1186/s12943-021-01398-4
31. Li H, Wu F, Han Y, Guo Z, Chen T, Ma Z (2025) CircRNA regulates lung cancer metastasis. Gene 935: 149060 doi: 10.1016/j.gene.2024.149060
32. Zhao P, Zhu Z, Zheng X, Song Y, Chen C, Xu G, Ke X (2025) Effects of circulating RNAs on tumor metabolism in lung cancer (Review). Oncol Lett 29: 204 doi: 10.3892/ol.2025.14950
33. Liu W, Niu J, Huo Y, Zhang L, Han L, Zhang N, Yang M (2025) Role of circular RNAs in cancer therapy resistance. Mol Cancer 24: 55 doi: 10.1186/s12943-025-02254-5
34. John A, Almulla N, Elboughdiri N, Gacem A, Yadav KK, Abass AM, Alam MW, Wani AW, Bashir SM, Rab SO, Kumar A, Wani AK (2025) Non-coding RNAs in Cancer: Mechanistic insights and therapeutic implications. Pathol Res Pract 266: 155745 doi:

10.1016/j.prp.2024.155745

35. Chen W, Zhao W, Wu X, Fang T, Chen Z, Chen Z, Su W, Zhao X, Hu Y, Xu Y, Fang S, Zhou C (2025) circFOXK2 Stabilizes STMN1 mRNA via PABPC1 to Promote the Progression of NSCLC. Cancer Med 14: e70729 doi: 10.1002/cam4.70729
36. Xiang T, Chen L, Wang H, Yu T, Li T, Li J, Yu W (2024) The Circular RNA circFOXK2 Enhances the Tumorigenesis of Non-Small Cell Lung Cancer Through the miR-149-3p/IL-6 Axis. Biochem Genet 62: 95–111 doi: 10.1007/s10528-023-10394-w
37. Zheng H, Liu X, Peng J, Zhou Y, Cheng H, Xue Z, Wu C (2023) Circular RNA PARG adjusts miR-140-3p to influence progression in sepsis. Cell Mol Biol (Noisy-le-grand) 69: 105–111 doi: 10.14715/cmb/2023.69.5.17
38. Zhang N, Fan J, Deng Z (2022) CircFOXK2 enhances tumorigenesis and immune evasion in non-small cell lung cancer by miR-485-5p/PD-L1 axis. Anticancer Drugs 33: 437–447 doi: 10.1097/CAD.0000000000001287
39. Luo T, Yan Y, He Q, Ma X, Wang W (2018) miR-328-5p inhibits MDA-MB-231 breast cancer cell proliferation by targeting RAGE. Oncol Rep 39: 2906–2914 doi: 10.3892/or.2018.6353
40. Liu B, Feng Y, Xie N, Yang Y, Yang D (2024) FERMT1 promotes cell migration and invasion in non-small cell lung cancer via regulating PKP3-mediated activation of p38 MAPK signaling. BMC Cancer 24: 58 doi: 10.1186/s12885-023-11812-3
41. Hu Y, Liu X, Yuan Z, He J, Ma R, Wang Y, Yi G (2025) Induction of necroptosis in lung adenocarcinoma by miR-10b-5p through modulation of the PKP3/RIPK3/MLKL cascade. Oncol Rep 53: 56 doi: 10.3892/or.2025.8889
42. Wang J, Zhao X, Wang Y, Ren F, Sun D, Yan Y, Kong X, Bu J, Liu M, Xu S (2020) circRNA-002178 act as a ceRNA to promote PDL1/PD1 expression in lung adenocarcinoma. Cell Death Dis 11: 32 doi: 10.1038/s41419-020-2230-9