INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer all over the world and has a high degree of malignancy. Although tremendous efforts have been made in the treatment and prevention of CRC, the 5-year survival rate remains low. Therefore, screening molecular targets related to CRC is critical for the therapy and prognosis of CRC.

For the past few years, more and more scholars focus on the molecular regulation principle of cancer to find potential...
molecular targets for cancer treatment. Circular RNA (circRNA) is a special RNA molecular with stable structure, and its role in the development of a variety of diseases has been explored, such as CRC. Studies have shown that hsa_circ_0005963 promoted drug resistance and glycolysis in CRC through sponging miR-122. Besides, circPACRGL had been found to be up-regulated in CRC, and it could accelerate CRC cell migration, invasion, and proliferation via miR-142-3p/miR-506-3p-TGF-β1 axis. Hsa_circ_0045932 was up-regulated in human umbilical venous endothelial cell injury and inflammatory and could target miR-20a-5p to inhibit inflammatory response and cell apoptosis. However, the function and mechanism of hsa_circ_0045932 in CRC progression have not been reported.

MiR-873-5p plays pivotal role in human diseases, including papillary thyroid cancer and non-alcoholic fatty liver disease. MiR-873-5p was lessened in lung cancer, and its suppression promoted lung cancer cell carcinoma stem cell-like traits. More importantly, miR-873-5p had been found to inhibit CRC cell metastasis. However, the connection between hsa_circ_0045932 and miR-873-5p remains unclear.

Hexokinase 2 (HK2) is a rate-limiting enzyme in glucose metabolism. Studies have shown that HK2 overexpression can accelerate glycolysis. High expression of HK2 in hepatocellular carcinoma cells has biological and prognostic meaning. Chen et al. exhibited that long non-coding RNA PVT1 regulated aerobic glucose metabolism, metastasis, and proliferation in gallbladder cancer cells by positively regulating the expression of HK2. miR-513a-5p might inhibit glycolysis in CRC cells by negatively regulating HK2. However, the function of HK2 and its mechanism in CRC are not fully clarified, and the relationships among hsa_circ_0045932, miR-873-5p, and HK2 have not been reported.

Our study aims to explore the role and mechanism of hsa_circ_0045932 in CRC progression. Through analyzing, we confirmed the interactions among hsa_circ_0045932, miR-873-5p, and HK2. The proposed hsa_circ_0045932/miR-873-5p/HK2 axis provides a new direction for the treatment of CRC.

### MATERIALS AND METHODS

#### 2.1 | Clinical tissue samples

Our study was approved by the Ethics Committee of the Number Two Hospital of Shanxi Medical University. In this study, CRC tissues (n = 80) and normal adjacent tissues (n = 80) were gathered from 80 CRC patients in the Number Two Hospital of Shanxi Medical University. All enrolled CRC patients signed written informed consents. According to the median relative expression value of hsa_circ_0045932 in tumor tissue, patients were divided into high hsa_circ_0045932 expression group (n = 40) and low hsa_circ_0045932 expression group (n = 40).

### Table 1 Sequences used for RT-qPCR

| Name       | Primers sequences for PCR (5′-3′)                  |
|------------|---------------------------------------------------|
| hsa_circ_0045932 | Forward CGACACTTCCGCTTTGGGA Reverse TTCTGCATGACACACAGCAT       |
| HK2        | Forward GTGAACTTGGAGAGGCTCCAC Reverse CTCAACTGGTGTCGGTGGCA       |
| miR-873-5p | Forward GCGGAGGCCAGAACCTTGTA Reverse CTCAACTGGTGTCGGTGGCA       |
| β-actin    | Forward CTTCCATCTGGCCTGGCCTGT Reverse GCTGTCACCTTCCACCGTTCCC       |
| U6         | Forward CTCGCTTCCGACGACACTATACT Reverse ACGCTTCAGAATTTTCGTC       |

#### 2.2 | Cell lines and cell culture

CRC cell lines (HCT116, LoVo, SW480, and SW620) and the normal colonic epithelial cell line (HCoEpiC) were purchased from Hunan Fenghui Biological Technology Co., Ltd. All cells were cultured in RPMI-1640 medium (Sigma-Aldrich) containing 10% FBS (TIANHANG) and 1% penicillin–streptomycin solution (Invitrogen) in standard conditions (37°C, 5% CO₂).

#### 2.3 | RNA extraction and RT-qPCR

TriQuick Reagent (Solarbio) was utilized for extracting total RNA, and RNA concentration was tested. The extracted RNA was reverse-transcribed into cDNA using cDNA Synthesis Kit (Invitrogen), and then, qRT-PCR was performed using SYBR Green (TIANGEN) on PCR system (Thermo Fisher Scientific). The levels of genes were evaluated with 2−ΔΔCT method and normalized to U6 (for miRNA) or β-actin (for mRNA/circRNA). Primer sequences were listed in Table 1.

#### 2.4 | Cell transfection

The shRNA targeting hsa_circ_0045932 (sh-hsa_circ_0045932), miR-873-5p inhibitor and mimic (anti-miR-873-5p and miR-873-5p), HK2 overexpression plasmid (pCDNA-HK2), and their corresponding controls were all obtained from Hunan Fenghui Biological Technology Co., Ltd. They were transfected into cells according to the instructions of Lipofectamine 3000 reagent (Invitrogen) when cells reached 60% confluences.

#### 2.5 | Cell proliferation analysis

The cell viability was tested via the guidance of MTT Assay Kit (Abcam). In short, cells were seeded into 96-well plates. Each well
was added with MTT (20μl) and incubated for 4 h. Then, cells were treated with dimethyl sulfoxide solution (DMSO; 150μl; Beyotime Biotechnology), and then, the absorbance at 490nm was detected using a microplate reader (Molecular Devices).

EdU experiment was operated according to the instructions of EdU apollo 567 in vitro kit (Solarbio). In short, cells were seeded into a 96-well plate. After transfection for 48 h, cells were incubated with EdU solution (50μM), fixed with paraformaldehyde (4%), permeated by Triton-X-100 (0.5%), stained with Apollo reaction, and then stained with DAPI. The EdU positive cells were counted and captured with fluorescence microscope (Olympus).

2.6 | Transwell assay

The transwell chambers pre-coated without or with matrigel were used to test cell migratory and invasive abilities, respectively. 2 × 10⁶ cells with serum-free were added into the above chamber of transwell chamber. In the bottom compartment, complete medium was used as a chemoattractant. After 24 h, the invaded/migrated cells were fixed using methanol and dyed using crystal violet (Beyotime Biotechnology), and then counted with a microscope (Olympus).

2.7 | Glycolysis metabolism analysis

Glucose uptake and lactic acid level in the cell culture medium were determined using the glucose assay kit (Biovision) and lactic assay kit (Biovision) to assess the glycolysis metabolism of the cells. The absorbance was detected using a microplate reader (Molecular Devices).

2.8 | Western blot (WB)

After extracting by RIPA lysis buffer (Solarbio), protein was electrophoresed by SDS-PAGE gel and then transferred to the PVDF membrane (Merck). Then, the membrane was incubated with the antibodies against HK2 (ab209847: 1:1000; Abcam), N-cadherin (N-cad, ABP51903; 1:1000; Abbkine), E-Cadherin (E-cad, ab212059; 1:1000; Abcam), Lactate Dehydrogenase (LDHA, ab134187; 1:500; Abcam), Glucose Transporter (GLUT1, ab115730; 1:1000; Abcam), and β-actin (ABP0593; 1:2000; Abbkine) overnight at 4°C. Then, membrane was hatched with secondary antibody (ab205718; 1:5000; Abcam) for 2 h. All membranes were incubated with ECL reagent (Abcam) and photographed in a gel imaging analyzer (UVITEC).

2.9 | Dual-luciferase reporter assay

The fragments of hsa_circ_0045932 and HK2 3’UTR containing miR-873-5p binding sequence region and the corresponding mutated region were synthesized and individually cloned into the psiCHECK2 vector (YouBia), thereby generating hsa_circ_0045932-WT/MUT and HK2 3’UTR-WT/MUT vectors. MiR-NC/miR-873-5p and these vectors were co-introduced into SW480 and HCT116 cells, respectively. The luciferase activities were measured using the Dual Luciferase Reporter Gene Assay Kit (Yeasen).

2.10 | RNA immunoprecipitation (RIP) assay

EZ-Magna RIP Kit (Millipore) was used for RIP assay. Cell extracts were treated with magnetic beads coupled anti-IgG or anti-Ago2. Then, the enrichments of hsa_circ_0045932 and miR-873-5p in extracted RNAs were quantified by RT-qPCR.

2.11 | Tumor xenograft mice model construction

Five-week-old nude mice (n = 10) were purchased from Vital River. A total of 1 × 10⁵ SW480 cells (transfected with sh-hsa_circ_0045932 or sh-NC) were subcutaneously injected into the mice. After 1 week, the volume of tumor was surveyed every 7 days in according with the equation: volume = width² × length/2. Twenty-eight days later, the mice were killed for subsequent analysis. Our research was approved by the Animal Welfare and Research Ethics Committee of the Number Two Hospital of Shanxi Medical University.

2.12 | Immunohistochemistry assay

Tumor tissue was fastened with paraformaldehyde (4%; Solarbio) and encapsulated in paraffin to prepare paraffin sections. The slices were treated with diluted Ki67 antibody (1:300, ab16667, Abcam) at 4°C all night long and hatched with the secondary antibody for 30 min. After staining with diaminoniline (DAB; Maxim) and counterstaining with hematoxylin (Maxim), the samples were observed and photographed under a microscope (Olympus).

2.13 | Statistical analysis

Graphpad Prism 7.0 software was serviced for data analysis. The Student’s t test was used for comparing the diversities between two groups, and ANOVA was employed to compare the discrepancies among multiple groups. Results were displayed as mean ± standard deviation, and p < 0.05 indicated statistically significant differences.

3 | RESULTS

3.1 | Hsa_circ_0045932 was overexpressed in CRC

Hsa_circ_0045932 expression in normal adjacent tissues and CRC tissues was measured by RT-qPCR. As displayed in Figure 1A, hsa_circ_0045932 expression in CRC tissue specimens and non-cancer...
**FIGURE 1** High expression of hsa_circ_0045932 was observed in CRC. (A) Hsa_circ_0045932 expression in normal and CRC tissues from GSE142837 was shown. (B) Hsa_circ_0045932 expression in normal ($n = 80$) and tumor tissue samples ($n = 80$) was detected using RT-qPCR. (C) Kaplan–Meier overall survival curve was used for evaluating the overall survival rate in CRC patients with high and low hsa_circ_0045932 expression. (D) Hsa_circ_0045932 expression was examined in HCoEpic and CRC cells (HCT116, SW480, SW620, and LoVo). *$p < 0.05$*

**FIGURE 2** Hsa_circ_0045932 knockdown could suppress CRC cell malignant behaviors. HCT116 and SW480 cells were transfected with sh-hsa_circ_0045932 or sh-NC. (A) RT-qPCR was performed for detecting the efficiency of sh-hsa_circ_0045932. (B and C) MTT assay was used to test cell viability. (D and E) Detection of DNA synthesis was performed using EdU assay. (F–H) Transwell assay was employed for assessing cell migratory and invasive abilities. (I and J) Glucose uptake and lactic acid level were determined by glucose assay kit and lactic assay kit. (K) E-cad, N-cad, GLUT1, and LDHA protein expression were measured using WB assay. *$p < 0.05$*
tissue specimens was shown by GEO database (GSE142837), and it was found that hsa_circ_0045932 was high-expressed in CRC tissue samples. Hsa_circ_0045932 was increased in CRC tissues ($n = 80$) in contrast to normal adjacent tissues ($n = 80$) (Figure 1B). The overall survival of CRC patients with low hsa_circ_0045932 expression group ($n = 40$) was higher than these patients with high expression group ($n = 40$) (Figure 1C). Compared with the normal cells, hsa_circ_0045932 expression was elevated in CRC cells, especially in HCT116 and SW480 cells (Figure 1D). Hence, HCT116 and SW480 cells were selected for subsequent experiments.

3.2 | Deficiency of hsa_circ_0045932 repressed CRC cell growth, metastasis, and glycolysis

Hsa_circ_0045932 expression was decreased in CRC cells after sh-hsa_circ_0045932 transfection (Figure 2A). MTT and EdU analyses demonstrated that hsa_circ_0045932 silencing decreased cell viability and DNA synthesis in SW480 and HCT116 cells (Figure 2B–E), revealing that hsa_circ_0045932 might promote CRC cell proliferative ability. At the same time, CRC cell migration and invasion abilities were distinctly restrained after hsa_circ_0045932 knockdown (Figure 2F–H). Moreover, hsa_circ_0045932 silencing drastically repressed glucose uptake and lactic acid level (Figure 2I–J), indicating that hsa_circ_0045932 might enhance CRC cell glycolysis. E-cad, N-cad, GLUT1, and LDHA protein expression levels were tested using WB, and the results indicated that hsa_circ_0045932 knockdown increased E-cad protein expression, while decreased N-cad, GLUT1, and LDHA protein levels in CRC cells (Figure 2K).

3.3 | Hsa_circ_0045932 was a miR-873-5p sponge

To study the mechanism of hsa_circ_0045932 in CRC progression, we screened and determined the target miRNA of hsa_circ_0045932. MiR-873-5p was eventually predicted as the target of hsa_circ_0045932 using CircBank and circinteractome (Figure 3A,B). MiR-873-5p level was elevated in SW480 and HCT116 cells after miR-873-5p overexpression (Figure 3C). Up-regulation of miR-873-5p decreased the luciferase intensity of hsa_circ_0045932-WT (Figure 3D,E). The enrichments of miR-873-5p and hsa_circ_0045932 were obviously elevated in Ago2 complexes group (Figure 3F,G). A down-regulation of miR-873-5p was found in CRC tissue specimens and cell lines (Figure 3H,I).
3.4 | Hsa_circ_0045932 knockdown repressed CRC cell malignant features via targeting miR-873-5p

In vitro recovery experiments were conducted for exploring the interaction between miR-873-5p and hsa_circ_0045932. MiR-873-5p expression was reduced in SW480 and HCT116 cells transfected with anti-miR-873-5p (Figure 4A). Silence of hsa_circ_0045932 repressed CRC cell viability, while anti-miR-873-5p reversed this effect (Figure 4B). Down-regulating miR-873-5p alleviated the suppressing impact of sh-hsa_circ_0045932 on DNA synthesis, migration, and invasive abilities in CRC cells (Figure 4C–E). MiR-873-5p knockdown mitigated the reduction effect of sh-hsa_circ_0045932 on glucose uptake and lactic acid level in CRC cells (Figure 4F,G). The impacts of sh-hsa_circ_0045932 on E-cad, N-cad, GLUT1, and LDHA were overturned by inhibiting miR-873-5p (Figure 4H).

3.5 | MiR-873-5p directly targeted HK2

Starbase software was utilized to explore the genes targeted by miR-873-5p. HK2 had binding sites with miR-873-5p (Figure 5A). We expounded that miR-873-5p up-regulation remarkably hindered HK2 3’UTR-WT luciferase activity, but did not influence the luciferase activity of HK2 3’UTR-MUT (Figure 5B,C). HK2 protein expression was found to be up-regulated in CRC tissue specimens and cells (Figure 5D–F). HK2 protein expression was strikingly decreased by miR-873-5p overexpression, while was improved by anti-miR-873-5p (Figure 5G,H). Besides, HK2 protein expression was reduced in SW480 and HCT116 cells after hsa_circ_0045932 down-regulation, and anti-miR-873-5p co-transfection triggered HK2 expression (Figure 5I).

3.6 | HK2 up-regulation reversed the function of hsa_circ_0045932 down-regulation in CRC cells

RT-qPCR and WB assays were performed for detecting HK2 expression following transfection of pcDNA-HK2. The expression of HK2 was obviously multiplied after overexpression of HK2 (Figure 6A). The suppressing effects of sh-hsa_circ_0045932 on cell proliferation, migration, invasion, glucose uptake, and lactic acid level were recovered by pcDNA-HK2 (Figure 6B–H). The impact of sh-hsa_circ_0045932 on the protein expression of E-cad, N-cad, GLUT1, and LDHA in CRC cells was regained by pcDNA-HK2 transfection (Figure 6I).
3.7  |  Hsa_circ_0045932 deficiency reduced tumor growth in vivo

The xenotransplantation model was established to evaluate whether hsa_circ_0045932 served as a tumor-promoting circRNA in vivo. Tumor volume and weight in sh-hsa_circ_0045932 group were markedly reduced compared with the sh-NC group (Figure 7A,B). Furthermore, hsa_circ_0045932 was reduced, while miR-873-5p level was increased in the tumor tissues of sh-hsa_circ_0045932 group (Figure 7C). HK2 protein level in sh-hsa_circ_0045932 tumor tissues was obviously decreased (Figure 7D). Ki67 expression was examined by immunohistochemistry assay, and the data determined that hsa_circ_0045932 knockdown significantly decreased Ki67 expression in tumor tissues (Figure 7E).

4  |  DISCUSSION

CRC is a deadly tumor with complex pathogenesis. More and more researchers have found that genetic factors can regulate the occurrence of CRC. Increasing studies confirmed circRNAs serve as the sponges for miRNAs in several cancers. In this study, we pointed out that hsa_circ_0045932 suppressed CRC cell migration, invasion, proliferation, and glycolysis through miR-873-5p/HK2 pathway.

CircRNAs have essential roles in tumor growth and progression. Yang et al. proved that hsa_circ_0043278 was substantially down-regulated in CRC, and its enhancement inhibited CRC cell proliferation and migration. Studies have shown that hsa_circ_0045932 was related to the occurrence of disease. GEO database (GSE142837) showed that hsa_circ_0045932 was
significantly overexpressed in CRC tissues. Based on this, we ex-
pounded that hsa_circ_0045932 was remarkably enhanced in CRC
cells and tissues. At the same time, hsa_circ_0045932 knockdown
restrained CRC cell invasion, migration, and growth in vitro, as
well as reduced CRC tumor growth in vivo. We also confirmed that
hsa_circ_0045932 silencing drastically repressed glucose uptake
and lactic acid level of CRC cells. These data confirmed that hsa_circ_0045932 might promote CRC progression.

FIGURE 6 HK2 overexpression reversed the effect of sh-hsa_circ_0045932 in CRC cells. (A) The expression of HK2 protein was
measured after transfection with pcDNA-NC and pcDNA-HK2 in HCT116 and SW480 cells. (B–I) HCT116 and SW480 cells were
transfected with sh-NC + pcDNA-NC, sh-hsa_circ_0045932 + pcDNA-NC or sh-hsa_circ_0045932 + pcDNA-HK2. (B–D) Cell proliferative
ability was evaluated. (E and F) Cell migratory and invasive capacities were examined. (G and H) Glucose uptake and lactic acid level were
determined. (I) E-cad, N-cad, GLUT1, and LDHA protein levels were tested. *p < 0.05

FIGURE 7 Silenced hsa_circ_0045932 blocked the tumor growth of CRC in vivo. (A) The graft volume was recorded every
7 days. (B) After 28 days of inoculation, tumor weight was examined. (C) Hsa_circ_0045932 and miR-873-5p levels were
examined in in tumor tissues by RT-qPCR. (D) HK2 protein abundance in tumor
tissues was tested using WB. (E) Ki67 expression in tumor tissues was detected
by immunohistochemistry assay. *p < 0.05
To probe the regulatory mechanism of hsa_circ_0045932, miR-873-5p was screened as the target gene of hsa_circ_0045932 by Circinteractome and CircBank. Li et al. displayed that miR-873-5p was low-expressed in CRC cells, and it could limit CRC cell metastasis by negatively modulating the expression of ZEB1. Then, we elucidated that miR-873-5p was remarkably reduced in CRC cells and tissues, which was concurrent with the findings of Wang et al. Besides, the data of rescue experiment in vitro confirmed that the repressive effect of hsa_circ_0045932 interference on CRC cell malignant behaviors were alleviated by anti-miR-873-5p. Collectively, we confirmed that hsa_circ_0045932 sponged miR-873-5p to modulate CRC cell proliferation, glycolysis, and metastasis.

Next, we further explored the possible targets for miR-873-5p, and we found that HK2 was directly targeted by miR-873-5p. HK2 has been suggested to be implicated in the glycolysis process of cancer. CircRNF20 sponged miR-487a to participate in the development of breast cancer through modulating HIF-1α/HK2. Herein, HK2 was detected to be highly expressed in CRC cells and tissue samples, and it could be targeted by miR-873-5p. Besides, we manifested that the down-regulation of hsa_circ_0045932 could reduce HK2 expression, and miR-873-5p inhibition abolished the impact of hsa_circ_0045932 interference on HK2 expression. At the same time, our data illustrated that the repressive impact of hsa_circ_0045932 interference on the malignant behaviors was mitigated after overexpressing HK2. Therefore, our findings manifested that hsa_circ_0045932 facilitated CRC cell proliferation, metastasis, and glycolysis via modulation of miR-873-5p/HK2 axis.

In conclusion, we confirmed that hsa_circ_0045932 was high-expressed in CRC. In vivo and in vitro experiments confirmed that hsa_circ_0045932 promoted CRC migration, invasion, proliferation, and glycolysis through the regulation of miR-873-5p/HK2 axis. The findings revealed the critical function of hsa_circ_0045932 in the treatment of CRC.

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None.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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