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# Effects of circular ribonucleic acid G-protein subunit beta 1 on migration, invasion and apoptosis of colon cancer cells

Guangwei Zheng[a], Jiantao Zheng[b], Lin Zhang[b], Yi Zhou[a], Yuanfeng Yang[a], Zhenlv Lin[a*]

**Abstract**

***Objective:*** To explore the effects of circular ribonucleic acid G-protein subunit beta 1 (circGNB1) on the migration, invasion and apoptosis of colon cancer cells and its molecular mechanism.

***Methods:*** The small-interfering RNA-negative control (si-NC) group, si-circGNB1 group, pcDNA-NC group, pcDNA-circGNB1 group, miR-NC group, miR-432-5p group, si-circGNB1 + anti-miR-NC group, and si-circGNB1 + anti-miR-432-5p group were set up. The expression levels of circGNB1 and miR-432-5p were determined via real-time fluorescence quantitative polymerase chain reaction (RT-qPCR), and the protein expressions of matrix metalloproteinase-2 (MMP2), MMP9 and cleaved-caspase-3 were determined via Western blotting. The cell migration and invasion were detected using Transwell assay, and the apoptosis was detected using flow cytometry. The targeting relationship between circGNB1 and miR-432-5p was verified through dual-luciferase reporter assay.

***Results:*** Compared with normal human colonic epithelial cells FHC, colon cancer cell lines HCT116, HT29 and SW480 had a significantly increased expression of circGNB1 and a significantly decreased expression of miR-432-5p ($P<0.05$). After low expression of circGNB1 or high expression of miR-432-5p, the expression levels of MMP2 and MMP9 significantly declined, the expression level of cleaved-caspase-3 significantly rose, the number of migrating and invading cells was significantly decreased, and the apoptosis rate was significantly increased ($P<0.05$). CircGNB1 regulated miR-432-5p in a targeted manner, and lowly-expressed miR-432-5p partially reversed the effects of lowly-expressed circGNB1 on the migration, invasion and apoptosis of HCT116 cells.

***Conclusion:*** Lowly-expressed circGNB1 may inhibit the migration and invasion and promote the apoptosis of HCT116 cells through up-regulating miR-432-5p.

**Key words:** CircGNB1, miR-432-5p, colon cancer, migration, invasion, apoptosis.

## 1. Introduction

Colon cancer is a common malignant tumor, and its metastasis is an important cause of deaths in patients. It has important clinical significance to deeply study the molecular mechanism of colon cancer metastasis and search for definite tumor markers for improving the early diagnosis rate of colon cancer (Nayak K.B. et al., 2018) (Juan T.K. et al., 2018). Circular ribonucleic acids (circRNAs) are a class of newly-discovered endogenous non-coding RNAs, with a closed circular structure, high conservation and stability. Abnormally expressed circRNAs are involved in the occurrence and development of cancer, which are expected to

*a.Department of Surgical Emergency, The First Affiliated Hospital of Fujian Medical University, Fuzhou, Fujian,350005, P.R. China*
*b.Department of Gastrointestinal Surgery, The First Affiliated Hospital of Fujian Medical University, Fuzhou, Fujian,350005, P.R. China*
**Corresponding Author: Zhenlv Lin*
*Address: Department of Surgical Emergency, The First Affiliated Hospital of Fujian Medical University, Fuzhou, Fujian,350005, P.R. China*
*Email: loubo26991@163.com*

become new biomarkers for the diagnosis and prediction of tumor occurrence and development (Meng S. et al., 2017). It has been reported that circGNB1 is overexpressed in triple-negative breast cancer cell lines, and its high expression is related to poor clinical features, survival outcome, tumor size and clinical stage. Moreover, circGNB1 is also an independent risk factor for patients with triple-negative breast cancer. Knockout of circGNB1 can significantly inhibit tumor cell proliferation and migration and tumor growth (Liu P. et al., 2020). G-protein subunit beta 1 (GNB1) may be the core gene of colon cancer, which plays an important role in the development and prognosis of stage IIA colon cancer (Dong Z. et al., 2019). However, the effects of circGNB1 on the migration, invasion and apoptosis of colon cancer cells remain unclear. In lung adenocarcinoma, miR-432-5p has a low expression, and Ophiopogonin B up-regulates the expression of miR-432-5p through Linc00668, thus inhibiting the epithelial-mesenchymal transition of human lung adenocarcinoma cells, and suppressing the metastasis of A549 cells (Hu C. et al., 2019). Overexpression of circ_001569 promotes the growth and metastasis of hepatocellular carcinoma cells through sponging miR-411-5p and miR-432-5p. However, the effects of miR-432-5p on the migration, invasion and apoptosis of colon cancer cells and whether circGNB1 affects the progression of colon cancer through regulating miR-432-5p are still unclear. Therefore, this experiment aims to investigate the effects of circGNB1 on the migration, invasion and apoptosis of colon cancer cells and whether its mechanism is related to miR-432-5p.

## 2. Materials and methods

### 2.1. Materials

Normal human colonic epithelial cells FHC, and colon cancer cell lines HCT116, HT29 and SW480 were purchased from Shanghai Guandao Biological Engineering Co., Ltd., TRIzol reagent and one-step real-time fluorescence quantitative polymerase chain reaction (RT-qPCR) kits were purchased from Beijing BioLab Technology Co., Ltd., and RIPA protein lysis buffer and bicinchoninic acid (BCA) kits were purchased from Shanghai Yanjin Biotechnology Co., Ltd. Transwell chambers and Matrigel were bought from Shanghai Yanhui Biotechnology Co., Ltd., Annexin V-fluorescein isothiocyanate (FITC)/propidium iodide (PI) apoptosis assay kits were bought from Shanghai Jingke Chemical Technology Co., Ltd., and dual-luciferase reporter assay kits were purchased from Beijing Solarbio Co., Ltd.

### 2.2. Cell culture and grouping

FHC, HCT116, HT29 and SW480 cells were cultured with RPMI-1640 medium containing 10% fetal bovine serum under 5% $CO_2$ at 37°C.

HCT116 cells in logarithmic growth phase were taken and transfected with small-interfering RNA-negative control (si-NC group), si-circGNB1 (si-circGNB1 group), pcDNA-NC (pcDNA-NC group), pcDNA-circGNB1 (pcDNA-circGNB1 group), miR-NC (miR-NC group) and miR-432-5p (miR-432-5p group). Besides, HCT116 cells were co-transfected with si-circGNB1 and anti-miR-NC (si-circGNB1 + anti-miR-NC group) and anti-miR-432-5p (si-circGNB1 + anti-miR-432-5p group), respectively.

### 2.3. Measurement of circGNB1 and miR-432-5p expression levels by real-time quantitative PCR (RT-qPCR)

The cells in each group were cultured for 48 h, from which the total RNA was extracted. One-step RT-qPCR was performed in accordance with the instructions of kits, with 3 replicates for each sample, and the cyclic conditions were as follows: 40 cycles of 95℃ for 3 min, 95℃ for 30 s, 60℃ for 30 s, and 72℃ for 30 s, and extension at 60℃ for 5 min. The relative expressions of circGNB1 and miR-432-5p were detected through $2^{-\triangle\triangle Ct}$ method, with GAPDH and U6 as internal controls, respectively. Upstream primer sequence for CircGNB1: 5'-CTTAAGAACCAGATTCGAACAAAT-3, downstream primer sequence: 5'-TGGTCAAGCTCACTCATCTT-3'. Upstream primer sequence for GAPDH: 5'-GCACCGTCAAGGCTGAGAAC-3', downstream primer sequence: 5'-TGGTGAAGACGCCAGTGGA-3'. Upstream primer sequence for miR-432-5p: 5'-GCTCTTGGAGTAGGTCATTGGGTG-3, downstream primer sequence: 5'-CAGTGCGTGTCGTGGAGT-3'. Upstream primer sequence for U6: 5'-GTGCTCGCTTCGGCAGCACATATAC-3', downstream primer sequence: 5'-AAAATATGGAACGCTTCACGAATTTGC-3'.

### 2.4. Measurement of MMP2, MMP9 and cleaved-caspase-3 protein expressions by Western blot

The total protein was extracted from cells using RIPA lysis buffer, and quantified using BCA kits. After SDS-PAGE, the protein was transferred onto a

membrane, blocked and incubated with primary

antibodies (diluted at 1:500) at 4°C overnight. After the membrane was washed, the protein was incubated with HRP-labeled secondary antibodies (diluted at 1:3,000) at room temperature for 2 h on a shaker, and the membrane was washed again, followed by color development with ECL, image development and fixation in a dark room. Then the gray value of protein bands was analyzed using Quantity-One software, and the relative protein expression was expressed as the ratio of gray value of target protein to that of internal control GAPDH. The assay was repeated for 3 times.

**2.5. Detection of cell migration and invasion by Transwell assay**

After serum-free culture, 200 μL of cells in each group were inoculated into the upper Transwell chamber and cultured for 24 h. After the culture solution was aspirated, the upper-layer cells were gently wiped off with cotton swabs, washed with phosphate buffered saline (PBS), fixed with 4% paraformaldehyde for 30 min, and stained with 0.1% crystal violet for 10 min, followed by photography and counting of migrating cells under a microscope. In cell invasion assay, 100 μL of Matrigel was added into the upper Transwell chamber, and then the cells were inoculated after Matrigel coagulation, and the remaining operations were the same as those of cell migration assay. Finally, the invading cells were photographed and counted in 5 randomly-selected fields under an inverted microscope for 3 times in each group.

**2.6. Detection of cell apoptosis by flow cytometry**

The cells in each group were cultured for 48 h, rinsed twice with pre-cooled PBS, and mixed evenly with 500 μL of binding buffer. Then the cells were added with 10 μL of Annexin V-FITC first and then 5 μL of PI, mixed evenly and incubated in the dark for 10 min. The apoptosis rate was determined using flow cytometry. Three replicates were set in each group, and the assay was repeated for 3 times.

**2.7. Verification of targeting relationship between circGNB1 and miR-432-5p by dual-luciferase reporter assay**

The circGNB1 wild-type and mutant reporter vectors containing miR-432-5p binding sites were constructed, and HCT116 cells were transfected with miR-432-5p mimics and the circGNB1 wild-type and mutant reporter vectors. After 48 h, the luciferase activity was determined according to the instructions of the dual-luciferase reporter assay kit.

**2.8. Statistical analysis**

All data were statistically analyzed by SPSS 20.0 software. The quantitative data were expressed as mean ± standard deviation ( $\bar{x}$ ± s). The comparisons between two groups were performed by the t test, and those among multiple groups were conducted with one-way analysis of variance. Pairwise comparisons were carried out by the LSD-t test. $P<0.05$ was considered statistically significant.

**3. Results**

**3.1. CircGNB1 and miR-432-5p expressions in colon cancer cell lines**

Compared with normal human colonic epithelial cells FHC, colon cancer cell lines HCT116, HT29 and SW480 had a significantly increased expression of circGNB1 and a significantly decreased expression of miR-432-5p ($P<0.05$) (Table 1).

*Table 1:* **CircGNB1 and miR-432-5p expressions in colon cancer cell lines ( $\bar{x}$ ± s, n=9)**

| Group | CircGNB1 | miR-432-5p |
|---|---|---|
| FHC | 1.00±0.11 | 1.02±0.12 |
| HCT116 | 2.35±0.23* | 0.34±0.03* |
| HT29 | 2.07±0.20* | 0.42±0.04* |
| SW480 | 1.76±0.15* | 0.45±0.04* |
| F | 95.708 | 180.418 |
| P | 0.000 | 0.000 |

Compared with FHC (human normal colon epithelial cells), *$P<0.05$.

**3.2. Effects of low circGNB1 expression on HCT116 cell migration, invasion and apoptosis**

Compared with si-NC group, after low expression of circGNB1, the expression levels of MMP2 and MMP9 significantly declined, the expression level of cleaved-caspase-3 significantly rose, the number of migrating and invading cells was significantly decreased, and the apoptosis rate

was significantly increased (P<0.05) (Figure and Table 2).

*Figure 1:* **Effects of low circGNB1 expression on HCT116 cell migration, invasion and apoptosis. A: Cell apoptosis detected by flow cytometry; B: MMP2, MMP9 and cleaved-caspase-3 protein expressions detected by Western blot.**

*Table 2:* **Effects of low circGNB1 expression on HCT116 cell migration, invasion and apoptosis ( $\bar{x}$ ± s, n=9)**

| Group | CircGNB1 | MMP2 | MMP9 | Cleaved-caspase-3 | Number of migrating cells | Number of invasive cells | Apoptosis rate (%) |
|---|---|---|---|---|---|---|---|
| si-NC | 1.00±0.12 | 0.88±0.08 | 0.80±0.07 | 0.38±0.03 | 161.22±16.11 | 131.11±13.01 | 8.27±0.82 |
| si-CircGNB1 | 0.39±0.04* | 0.30±0.03* | 0.35±0.04* | 0.93±0.09* | 81.29±8.10* | 69.08±6.21* | 29.03±2.76* |
| t | 14.467 | 20.365 | 16.745 | 17.393 | 13.298 | 12.908 | 21.631 |
| P | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 |

Compared with si-NC group, *P<0.05.

**3.3. Effects of high miR-432-5p expression on HCT116 cell migration, invasion and apoptosis**

Compared with miR-NC group, after high expression of miR-432-5p, the expression levels of MMP2 and MMP9 significantly decreased, the expression level of cleaved-caspase-3 significantly increased, the number of migrating and invading cells was significantly reduced, and the apoptosis rate was significantly elevated (P<0.05) (Figure 2 and Table 3).

*Figure 2:* **MMP2, MMP9 and cleaved-caspase-3 protein expressions detected by Western blot.**

*Table 3:* **Effects of high miR-432-5p expression on HCT116 cell migration, invasion and apoptosis ( $\bar{x}$ ± s, n=9)**

| Group | miR-432-5p | MMP2 | MMP9 | Cleaved-caspase-3 | Number of migrating cells | Number of invasive cells | Apoptosis rate (%) |
|---|---|---|---|---|---|---|---|
| miR-NC | 1.00±0.14 | 0.85±0.08 | 0.78±0.06 | 0.40±0.04 | 159.86±15.80 | 134.27±13.40 | 8.09±0.81 |
| miR-432-5p | 3.27±0.32* | 0.40±0.04* | 0.31±0.03* | 0.83±0.08* | 90.11±9.02* | 60.24±6.01* | 24.01±2.36* |
| t | 19.497 | 15.093 | 21.019 | 14.423 | 11.501 | 15.123 | 19.141 |
| P | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 |

Compared with miR-NC group, *P<0.05.

**3.4. CircGNB1 targeted miR-432-5p to regulate its expression**

It was predicted using the starBase database that there were binding sites between circGNB1 and miR-432-5p (Figure 3). The results of luciferase reporter assay showed that compared with that in miR-NC group, the luciferase activity of cells transfected with the circGNB1 wild-type vectors significantly declined in miR-432-5p group (P<0.05), while that of cells transfected with the circGNB1 mutant vectors had no significant difference (Table 4). The expression level of miR-432-5p was significantly lower in pcDNA-circGNB1 group than that in pcDNA-NC group (P<0.05), while it was significantly higher in si-circGNB1 group than that in si-NC group (P<0.05) (Table 5).

*Figure 3:* **Prediction of binding between circGNB1 and miR-432-5p by starBase database.**

*Table 4:* **Dual luciferase activity after co-transfection of miR-NC or miR-432-5p with CircGNB1 wild-type and mutant reporter plasmids in HCT116 cells ( $\bar{x}$ ± s, n=9)**

| Group | Dual luciferase activity | |
|---|---|---|
| | WT | MUT |
| miR-NC | 1.00±0.11 | 1.03±0.12 |
| miR-432-5p | 0.44±0.04* | 0.99±0.10 |
| t | 14.353 | 0.768 |
| P | 0.000 | 0.454 |

Compared with miR-NC group, *P<0.05.

**Table 5.** MiRT-432-5p expression detected by qRT-PCR

| Group | miR-432-5p |
|---|---|
| pcDNA-NC | 1.02±0.11 |
| pcDNA-CircGNB1 | 0.42±0.04* |
| si-NC | 1.03±0.10 |
| si-CircGNB1 | 2.01±0.21# |
| F | 230.124 |
| P | 0.000 |

Compared with pcDNA-NC group, *P<0.05; compared with si-NC group, #P<0.05.

**3.5. Low miR-432-5p expression partly reversed the effects of low circGNB1 expression on HCT116 cell migration, invasion and apoptosis**

Compared with si-circGNB1 + anti-miR-NC

group, si-circGNB1 + anti-miR-432-5p group had a significantly decreased expression of miR-432-5p in HCT116 cells, significantly increased expressions of MMP2 and MMP9, a significantly decreased expression of cleaved-caspase-3, significantly enhanced cell migration and invasion, and significantly weakened apoptosis (P<0.05) (Figure 4 and Table 5).

*Figure 4:* **MMP2, MMP9 and cleaved-caspase-3 protein expressions detected by Western blot.**

*Table 5:* **Low miR-432-5p expression partly reversed the effects of low circGNB1 expression on HCT116 cell migration, invasion and apoptosis ( $\bar{x}$ ± s, n=9)**

| Group | miR-432-5p | MMP2 | MMP9 | Cleaved-caspase-3 | Number of migrating cells | Number of invasive cells | Apoptosis rate (%) |
|---|---|---|---|---|---|---|---|
| si-CircGNB1+anti-miR-NC | 1.00±0.12 | 0.33±0.03 | 0.38±0.04 | 0.90±0.09 | 80.66±8.05 | 65.96±6.60 | 30.05±3.12* |
| si-CircGNB1+anti-miR-432-5p | 3.27±0.32* | 0.75±0.07* | 0.69±0.06* | 0.46±0.04* | 142.16±14.22* | 119.25±10.96* | 11.66±1.15* |
| t | 19.926 | 16.545 | 12.897 | 13.403 | 11.291 | 12.496 | 16.592 |
| P | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 |

Compared with si-CircGNB1 + anti-miR-NC group, *P<0.05.

**4. Discussion**

Colon cancer is a common tumor in the digestive tract, with a higher incidence rate. At present, it is still mainly treated with surgery supplemented by chemoradiotherapy, but patients are prone to recurrence after surgery and have a low survival rate due to metastasis (Cao D.Z. et al., 2017)(Zippi M. et al., 2017). It is of great significance to study the molecular mechanism of occurrence and development of colon cancer, and search for diagnostic and prognostic markers for colon cancer for its treatment. It is reported that a variety of circRNAs are involved in regulating the occurrence and development of colon cancer. For example, circ-0001313 up-regulates the expression of Akt2 through sponging miR-510-5p, thereby facilitating the development and progression of colon cancer (Tu F.L. et al., 2020). Overexpression of circCDYL inhibits miR-150-5p, thus suppressing the growth and migration of colon cancer cells (Cui W. et al., 2019). CircPIP5K1A promotes the development of colon cancer *via* inhibiting miR-1273a (Zhang Q. et al., 2019). In this experiment, the expression level of circGNB1 greatly rose in colon cancer cell lines HCT116, HT29 and SW480, and circGNB1 promoted the progression of colon cancer by regulating miR-141-5p (Liu P. et al., 2020). To study the effects of circGNB1 on the migration, invasion and apoptosis of colon cancer cells, si-circGNB1 vectors were transfected into cells. The results manifested that the expression levels of MMP2 and MMP9 were remarkably decreased, the expression level of cleaved-caspase-3 was remarkably increased, the number of migrating and invading cells was greatly reduced, and the apoptosis rate was greatly raised. It can be seen that the low expression of circGNB1 can inhibit the migration and invasion, and promote the apoptosis of colon cancer cells.

A previous study indicated that circRNAs can act as competitive endogenous RNAs and bind to miRNAs, and play as miRNA sponge in cells, thereby relieving the inhibitory effect of miRNAs on target

genes, and regulating tumor progression (Liu K. et al., 2020). In this experiment, to explore whether circGNB1 affects the migration, invasion and apoptosis of colon cancer cells through miRNA sponge, the miRNA that may bind to circGNB1 was predicted using starBase software. It was found that there were binding sites between miR-432-5p and circGNB1. Furthermore, the results of dual-luciferase reporter assay showed that circGNB1 could regulate the expression of miR-432-5p. It was reported that the overexpression of miR-432-5p regulated by p53 can inhibit the proliferation of neuroblastoma cells (Rihani A. et al., 2015). MiR-432-5p affects the apoptosis of bladder cancer cells (Zhang Y.P. et al., 2019). Hsa_circ_0008039 promotes the proliferation and migration of breast cancer cells through regulating the miR-432-5p/E2F3 axis (Liu Y. et al., 2018). In this experiment, it was confirmed that the expression of miR-432-5p significantly declined in colon cancer cell lines. After overexpression of miR-432-5p, the expression levels of MMP2 and MMP9 obviously declined, the expression level of cleaved-caspase-3 obviously rose, the number of migrating and invading cells was greatly decreased, and the apoptosis rate was greatly increased. It can be seen that overexpression of miR-432-5p can suppress the migration and invasion, and enhance the apoptosis of colon cancer cells. Moreover, lowly-expressed miR-432-5p partially reversed the effects of lowly-expressed circGNB1 on the migration, invasion and apoptosis of HCT116 cells, indicating that circGNB1 may affect the migration, invasion and apoptosis of colon cancer cells through regulating the expression of miR-432-5p.

In conclusion, lowly-expressed circGNB1 may inhibit the migration and invasion and promote the apoptosis of HCT116 cells through up-regulating miR-432-5p.

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