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Circ-DB participates in the progression of gastric cancer by competitively binding microRNA-34a to regulate the expression of MET

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Abstract. – OBJECTIVE: To figure out the possible role and mechanism of circ-DB in the pathogenesis of gastric cancer (GCa).

PATIENTS AND METHODS: 32 cases of post-operative GCa tissue samples and adjacent ones were collected and divided into groups of ≥ 5 cm and < 5 cm according to tumor diameter. Circ-DB, microRNA-34a, and MET expressions were detected by real time-quantitative PCR (RT-qPCR) in GCa tissues and adjacent tissues. To determine the main mode of action of circ-DB, the subcellular localization of circ-DB was examined by dividing the cells into the nucleus and cytoplasmic fractions. The binding of microRNA-34a to circ-DB was demonstrated by a Dual-Luciferase reporter gene assay. The expression of circ-DB in HGC-27 and AGS cells was overexpressed and knocked down to evaluate the migration function of the cells by transwell. The protein expression of MET, as well as the target gene of microRNA-34a, was detected by Western blot.

RESULTS: The expression of circ-DB and MET in GCa tissues was significantly higher than that in the corresponding adjacent tissues. Circ-DB was positively correlated with MET expression, while microRNA-34a expression was negatively correlated with circ-DB and MET expression. Circ-DB was mainly located in the cytoplasm, and the Dual-Luciferase reporter gene demonstrated that microRNA-34a can bind to circ-DB. The down-regulation of circ-DB expression inhibited the migration of HGC-27 and AGS cells. *In vitro* cell experiments showed that low expression of circ-DB inhibited cell migration, which could be recovered by the co-transfection with microRNA-34a inhibitor.

CONCLUSIONS: Circ-DB may regulate MET level through microRNA-34a and affect the proliferative ability and migration of GCa cells.

Key Words:
GCa, Circular RNA, Competitive RNA, Proliferation, Migration.

Introduction

Gastric cancer (GCa) is one of the most common malignant tumors in human beings, and the variation of molecular signaling pathway plays a pivotal role in the occurrence and development of GCa. Currently, the research on the molecular mechanism and pathway of GCa has made some progress, but the specific pathogenesis is still not completely clear, and there are still many questions to be solved[1,2]. In recent years, non-coding RNA has been the focus of molecular research, which is closely related to the occurrence, development, prevention, and treatment of tumors by regulating the gene expression at epigenetic level, transcriptional level, and post-transcriptional

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level. In addition to the confirmation of multiple lncRNAs related to GCa[3,4], evidence showed that circRNA directly participates in the disease process of GCa through the regulation of tumor cell growth, metastasis, and invasion.

CircRNA plays a pivotal role at post-transcriptional level, such as precursor RNA splicing, regulation of RNA expression, protein translation, protein activity, and protein interaction. Adsorption of non-coding short RNA is a common biological function of circRNAs. In addition, the IRES inserted circRNAs can be translated into cells, and the m6a-enriched circRNAs can also be translated[5]. Hong et al[6] have found that circFNDC3B promotes the migration and invasion of GCa cells by regulating the expression of E-cadherin and CD44. CircAKT3 up-regulates PIK3R1 expression by inhibiting mir-198 expression, thereby increasing cisplatin resistance in GCa cells[7]. The latest meta-analysis[8] showed that microRNA-34a can be an important biomarker for the progression and prognosis of GCa. Circ-DB has been detected to activate USP7 by regulating the expression of microRNA-34a, thereby promoting the growth of liver cancer cells. This study mainly discussed the possible roles of circ-DB in the pathogenesis of GCa and the underlying mechanism.

Patients and Methods

Case Collection

Specimens of 36 patients (including 20 males and 12 females) diagnosed with postoperative GCa by pathology in our hospital were selected. No radiotherapy or chemotherapy or other anti-tumor treatment was performed before the operation. The ages of the patients ranged from 36 years old to 86 years old, and the para-membrane tissue other than 5 cm from the edge of the tumor was taken as the control group. This study was approved by the Ethics Committee of The First Hospital of Jilin University. Signed written informed consents were obtained from all participants before the study.

Quantitative Real Time-Polymerase Chain Reaction (qRT-PCR)

The total RNA in tissues and cells was extracted through the TRIzol method (Invitrogen, Carlsbad, CA, USA). The reverse transcription reaction was carried out according to the instructions of the PrimeScript RT reagent Kit (TaKaRa, Otsu, Shiga, Japan). The complementary deoxyribose nucleic acid (cDNA) obtained by reverse transcription was diluted to an appropriate multiple and then subjected to qRT-PCR experiments according to the instructions of the real time-quantitative premix. The sequences of the primers of circ-DB, MET, microRNA-34a, and glyceraldehyde 3-phosphate dehydrogenase (GAPDH) were listed in Table I. In brief, an appropriate amount of cDNA, the primers, the premix, and the ultrapure water were mixed into a 20-liter system and applied for qPCR with the ABI 7900 Fast PCR real time-PCR instrument (Applied Biosystems, Foster City, CA, USA), according to the recommended parameters. Then, the fluorescence signal was collected and analyzed. GAPDH was selected as the internal reference gene, and the expression level of the target gene was calculated based on the $2^{\Delta\Delta CT}$ method.

Cell Culture and Transfection

GCa cell lines were subcultured in Dulbecco's Modified Eagle's Medium (DMEM; Gibco, Rockville, MD, USA) supplemented with 10% fetal bovine serum (FBS; Gibco, Rockville, MD,

Table I. Primer sequences.

Gene	Primer sequences
circ-DB	F: 5'-CTGCTCCTCCAGCTCTT-3' R: 5'-AGTGATCTTGAACCCCAAAG-3'
MET	F: 5'-AGCGTCAACAGAGGGACCT-3' R: 5'-GCAGTGAACCTCCGACTGTATG-3'
hsa-microRNA-34a	F: 5'-CTCAACTGGTGTCGTGGAGTCGGCAATTCAGTTGAGACAACCAG-3' R: 5'-ACACTCCAGCTGGGTGGCAGTGTCTTAGCT-3'
GAPDH	F: 5'-GCACCGTCAAGGCTGAGAAC-3' R: 5'-GGATCTCGCTCCTGGAAGATG-3'
U6	F: 5'-CTCGCTTCGGCAGCACA-3' R: 5'-AACGCTTCACGAATTTGCGT-3'

USA) and double antibody at 37°C in a 5% CO_2 incubator. The circ-DB siRNA and overexpression plasmids, the microRNA-34a mimics and inhibitors, as well as the corresponding negative controls, were constructed. The cells were planted in a 6-well plate, and when the cells grew up to 50%-70%, the transfections were performed respectively by using Lipofectamine 2000 (Invitrogen, Carlsbad, CA, USA) according to the manufacturer's instructions. After 24 to 48 h of transfection, the cells were collected for further experiments.

Western Blot

Total cellular proteins were collected by using the radioimmunoprecipitation assay (RIPA) cell lysis buffer added with a protease inhibitor cocktail (Sigma-Aldrich, St. Louis, MO, USA). The bicinchoninic acid (BCA) method (Pierce, Rockford, IL, USA) was used to quantify the protein concentration. An equal amount of protein sample was loaded onto a 10% sodium dodecyl sulphate-polyacrylamide gel electrophoresis (SDS-PAGE) gel and transferred to a polyvinylidene difluoride (PVDF) membrane (Millipore, Billerica, MA, USA) after the electrophoresis. After blocking with a skim milk shaker for 1 h, the membrane was incubated with the primary antibody MET (Abeam, Cambridge, MA, USA, ab51067) diluted in Tris Buffered Saline and Tween 20 (TBST) buffer overnight at 4°C and then, incubated with a secondary antibody for 2-3 h at room temperature. Finally, an image was obtained by exposure through a Tanon (Shanghai, China) detection system using enhanced chemiluminescence (ECL) reagent.

Dual-Luciferase Reporter Gene

HGC-27 cells cultured in 24-well plates were transfected with microRNA-34a mimics and pGL3-circ-DB wild-type plasmids or the pGL3-circ-DB mutant plasmids, respectively. If microRNA-34a activated the promoter of circ-DB, then, the luciferase gene could be expressed, and the amount of luciferase expression could be directly proportional to the intensity of microRNA-34a mimics.

After 48 h of incubation, the cells were lysed with the Dual-Glo® Luciferase Reagent (Promega's Dual-Glo® Luciferase Assay System kit, Madison, WI, USA) for about 10 min. A specific luciferase substrate was added, and the luciferase reacted with the substrate to generate the fluorescence. The activity of the luciferase was determined by detecting the intensity of the fluorescence, thereby determining whether microRNA-34a can interact with circ-DB.

Cytoplasm and Nuclear Separation

The treated cells were collected and incubated with 100 μL of Buffer A (10 mM HEPES, pH 7.9, 10 mM KCl, 0.1 mM EDTA, 0.1 mM EGTA, 0.15% NP-40) for 15 min, and centrifuged at 12,000 rpm for 4 min at 4°C. Then, the supernatant was taken like the plasma, and the pellet was washed with 1 mL Buffer A and resuspended in 150 μL Buffer B (20 mM HEPES, pH 7.9, 0.4 mM NaCl, 1 mM EDTA, 1 mM EGTA, 0.5% NP-40) at 12,000 rpm for 30 min at 4°C. The supernatant was nuclear extraction.

Statistical Analysis

The data processing were processed by Stata 9.0 Statistical Software (Calgary, TX, USA). The measurement data were compared by the *t*-test, which was expressed as the mean ± standard deviation ($\bar{x} \pm s$). The classification data were analyzed by the Chi-square test. $p<0.05$ was considered statistically significant; $*p<0.05$, $**p<0.01$, $***p<0.001$.

Results

Expression and Correlation of Circ-DB, MET, and MicroRNA-34a in GCa

To determine the correlation between the expression of circ-DB and GCa, we detected the expression of circ-DB in 32 pairs of GCa cancer tissues and adjacent tissues and found that circ-DB was significantly overexpressed in GCa tissues ($p<0.001$) (Figure 1A). In details, in 12 GCa tissue samples with tumor diameter ≥ 5 cm and 20 tumor diameter < 5 cm, circ-DB was significantly highly expressed in the group of ≥ 5 cm in diameter ($p<0.05$) (Figure 1B). Besides, circ-DB was also highly expressed in GCa cell lines including the BGC-823, HGC-27, AGS, MGC-803, and MKN-7 relative to that of the normal gastric mucosal epithelial cell line GES1, among which the expression of circ-DB was the circ-DB in HGC-27 and AGS cell lines. Therefore, we could suggest that circ-DB was highly expressed in GCa.

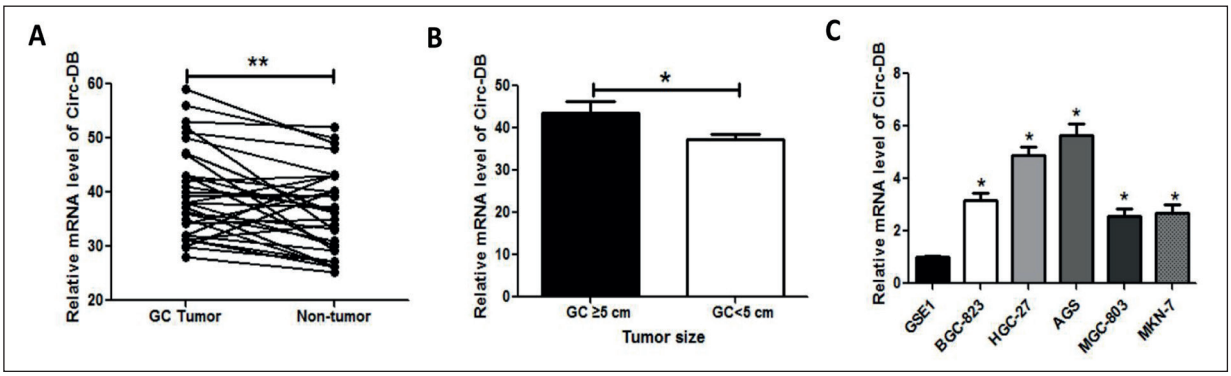

Figure 1. Circ-DB expression in GCa and adjacent tissues and GCa cell lines. **A,** In 32 cases of GCa and adjacent tissues, circ-DB was highly expressed in GCa tissues ($p<0.001$). **B,** In 12 GCa tissue samples with tumor diameter ≥ 5 cm and 20 tumor diameter < 5 cm, circ-DB was significantly expressed in the group of ≥ 5 cm in diameter ($p<0.05$). **C,** Circ-DB is highly expressed in GCa cell lines BGC-823, HGC-27, AGS, MGC-803, and MKN-7 relative to the normal gastric mucosal epithelial cell line GES1, with the most prominent in HGC-27 and AGS cell lines.

Circ-DB Promotes Proliferative Ability and Migration of HGC-27 and AGS Cells

To determine the effect of circ-DB on the function of GCa cells, we constructed circ-DB siRNA and overexpression plasmids. After the transfection of circ-DB siRNA, the proliferative and migration abilities of HGC-27 and AGS cells were inhibited, while the overexpression of circ-DB promoted its proliferative ability and migration.

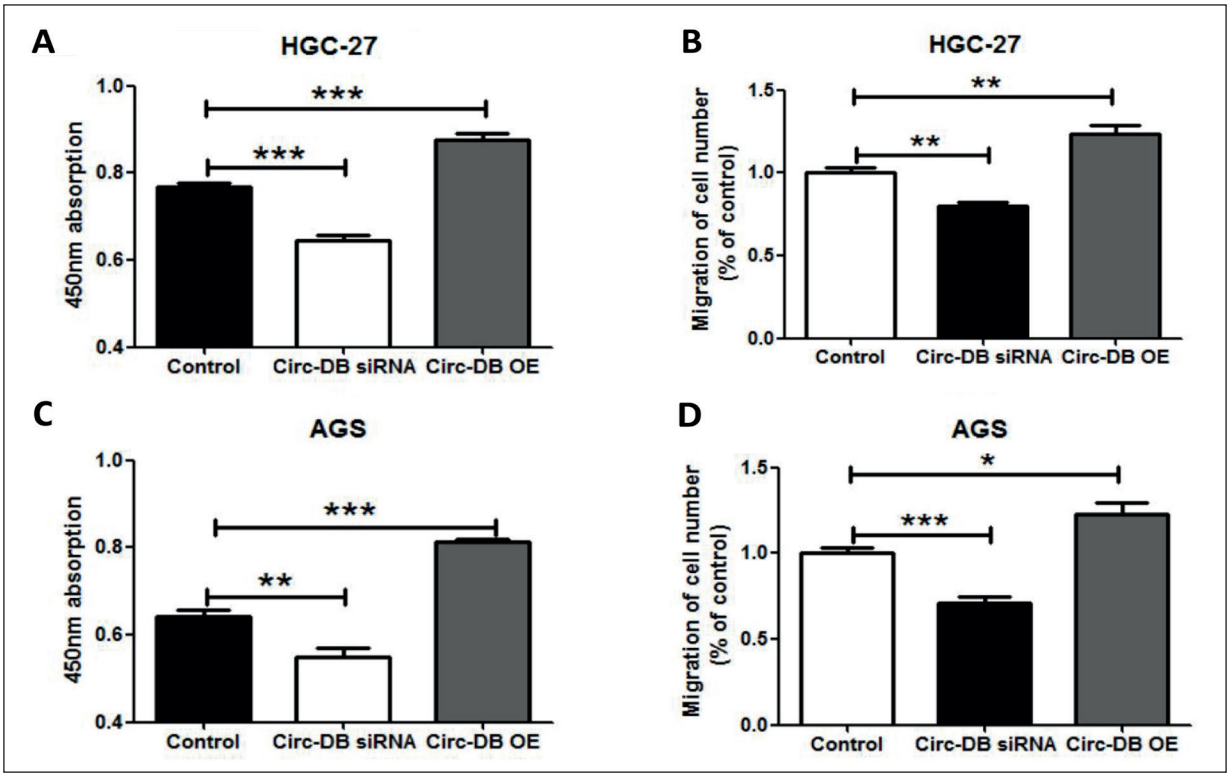

Figure 2. Circ-DB promotes the proliferative ability and migration of HGC-27 and AGS cells. **A, B,** After transfection of circ-DB siRNA, the proliferative ability and migration ability of the HGC-27 cells was inhibited, while the overexpression of circ-DB promoted its proliferative ability and migration. **C, D,** After transfection of circ-DB siRNA, the proliferative ability and migration ability of AGS cells were inhibited, while the circ-DB overexpression promoted proliferative ability and migration.

Expression of MicroRNA-34a in GCa and Adjacent Tissues and Its Interaction With Circ-DB

In 32 cases of GCa tumor tissues and adjacent tissues, microRNA-34a was significantly downregulated in GCa tissues ($p<0.01$) (Figure 3A). In the GCa tissues of 12 samples with tumor diameters ≥ 5 cm and 20 tumor diameters < 5 cm, microRNA-34a was significantly expressed in the group of ≥ 5 cm in diameter (Figure 3B). In addition, the expression of microRNA-34a was negatively correlated with that of circ-DB in GCa tissues ($R^2=0.3768$, $p=0.0002$) (Figure 3C).

To determine the subcellular localization of circ-DB, we performed the nuclear separation assays on HGC-27 and AGS cells. After RNA extraction, it was found by qRT-PCR that U6 was mainly present in the nucleus, while GAPDH was mainly present in the cytoplasm. Considering this as a reference, circ-DB was mainly present in its cytoplasm (Figure 3D), suggesting that circ-DB was more likely to participate in the development and progression of GCa at the post-transcriptional level. To determine the interaction between microRNA-34a and circ-DB, the HGC-27 cells were co-transfected with microRNA-34a mimics and pGL3-circ-DB wild-type or pGL3-circ-DB mut-type plasmids, respectively, by constructing a Dual-Luciferase reporter plasmid (Figure 3E). It was found that the co-transfected microRNA-34a mimics and circ-DB wild-type plasmids showed a significant decrease in fluorescence ($p=0.009$), while the other groups showed no significant difference (Figure 3F), suggesting that microRNA-34a and circ-DB had a binding relationship.

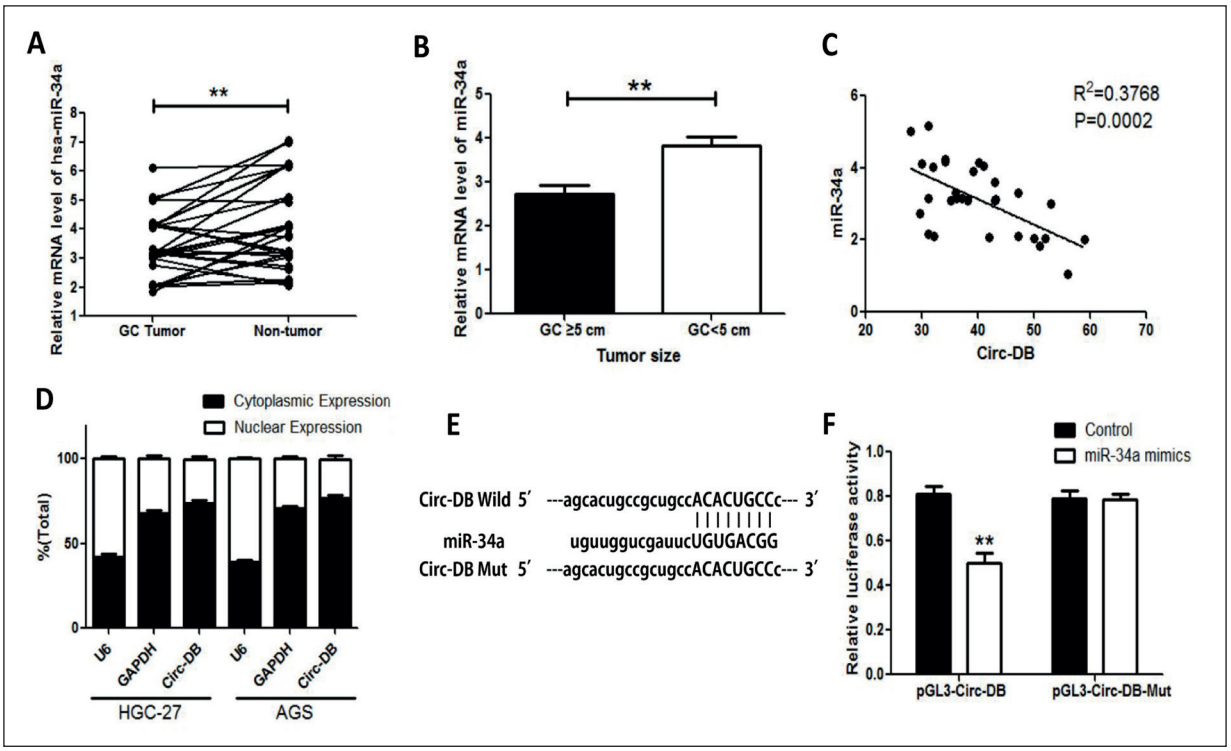

Figure 3. Expression of microRNA-34a in GCa and adjacent tissues and its interaction with circ-DB. **A,** In 32 cases of GCa and adjacent tissues, microRNA-34a was significantly decreased in GCa tissues ($p<0.01$). **B,** In 12 GCa tissue samples with tumor diameter ≥ 5 cm and 20 tumor diameter < 5 cm, microRNA-34a was significantly expressed in the group of ≥ 5 cm in diameter. **C,** The expression of microRNA-34a was negatively correlated with the expression of circ-DB in GCa tissues ($R^2=0.3768$, $p=0.0002$). **D,** It was found by qRT-PCR that U6 was mainly present in the nucleus of HGC-27 and AGS cells, while circ-DB and GAPDH were mainly present in the cytoplasm. **E,** Binding sites for microRNA-34a, circ-DB wild-type, and mutant plasmids. **F,** MicroRNA-34a mimics and pGL3-circ-DB wild type plasmid, microRNA-34a mimics and pGL3-circ-DB mutant plasmid, NC and pGL3-circ-DB wild type plasmid, NC and pGL3-circ-DB mutant plasmid, were co-transfected in HGC-27 cells, respectively. It was found that the co-transfected microRNA-34a mimics and circ-DB wild-type plasmid groups showed a significant decrease in fluorescence values, while the other groups showed no significant difference.

Expression of MET in GCa and Adjacent Tissues and Its Correlation With MicroRNA-34a and Circ-DB

As a target gene of microRNA-34a, MET was highly expressed in GCa tissues ($p<0.01$) (Figure 4A). In GCa tissues, the expression of MET was negatively correlated with the expression of microRNA-34a ($R^2=0.2550$, $p=0.0032$) (Figure 4B), and negatively correlated with the expression of circ-DB ($R^2=0.3045$, $p=0.0011$) (Figure 4C).

Circ-DB-MicroRNA-34a-MET Loop to Regulate Cell Function

To determine whether circ-DB could regulate the cell function and the MET expression by binding to microRNA-34a, we detected some changes in cell proliferation, migration, and MET protein expression after the alteration of the expression of circ-DB and microRNA-34a. After transfection of microRNA-34a mimics in the HGC-27 cells, the proliferative ability and migration of HGC-27 cells were inhibited, and the MET protein levels were significantly reduced, while the co-transfection of circ-DB and microRNA-34a mimics increased the migration ability of cells. Besides, the silence of circ-DB in cells that inhibited microRNA-34a could also promote the tumor cell migration, and the MET protein level was also significantly higher than that of microRNA-34a mimics group (Figures 5A and 5C). Furthermore, the observed phenomenon was consistent with the above results in AGS cell (Figures 5D and 5F). These results demonstrated that the circ-DB-microRNA-34a-MET pathway played a key role in the regulation of GCa cell progression.

Discussion

Gastric cancer (GCa) is one of the most common and malignant tumors of the digestive system. Despite the differences in the incidence of GCa among different regions, its morbidity and mortality rate have been at the forefront of various diseases for long[9,10]. As a new endogenous RNA, circRNA is involved in the process of many diseases, including tumors. The role of the related circRNA in GCa has also become a research hotspot. CircRNA can play an important role in the occurrence, development, invasion, and metastasis of GCa by binding miRNAs. Zhang et al[11] have shown that circ_001569 activates the NRAS/MEK1/erk1/2 pathway by adsorbing miR-502-5p to promote the incidence and metastasis of GCa. Recent studies[12,13] have shown that circRNAs are involved in multiple pathological processes of GCa and are expected to be the diagnostic and prognostic markers of GCa, such as hsa_circ_0000467, circPVT1, etc. The molecular pathogenesis of GCa is complex and heterogeneous, and whether other circRNAs are involved in its molecular pathogenesis remains to be further studied.

MicroRNA-34a is significantly low expressed in GCa, which is related to the progression and prognosis of GCa[14-16]. Cheng et al[15] have shown that circ-DB activates USP7 by inhibiting microRNA-34a expression, thereby promoting the growth of liver cancer cells and reducing DNA damage. MET has been proved to be a target gene of microRNA-34a, which is involved in the pathogenesis of cancer[17]. Therefore, we examined the

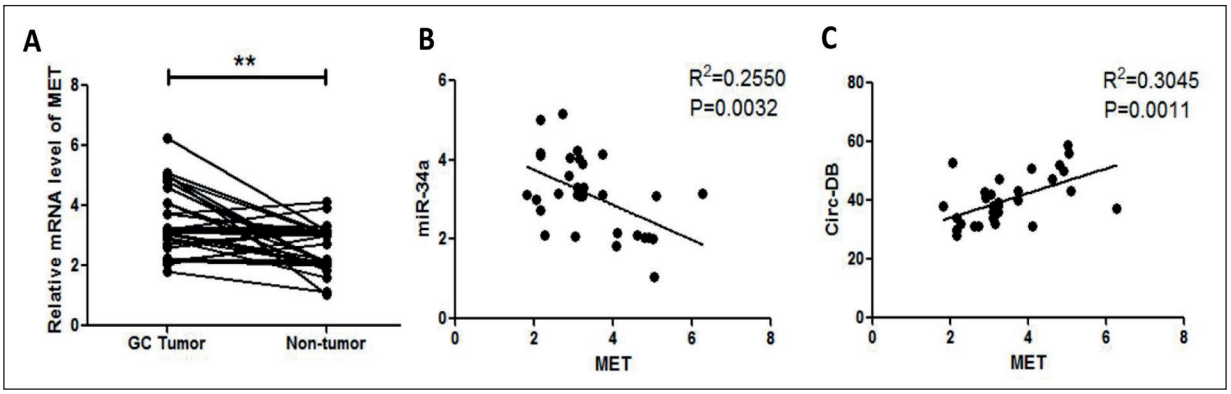

Figure 4. Expression of microRNA-34a target gene MET in GCa and adjacent tissues and its correlation with microRNA-34a, circ-DB. **A,** In 32 cases of GCa and adjacent tissues, MET was highly expressed in GCa tissues ($p<0.01$). **B-C,** In GCa tissues, the expression of MET was negatively correlated with the expression of microRNA-34a ($R^2=0.2550$, $p=0.0032$), and negatively correlated with the expression of circ-DB ($R^2=0.3045$, $p=0.0011$).

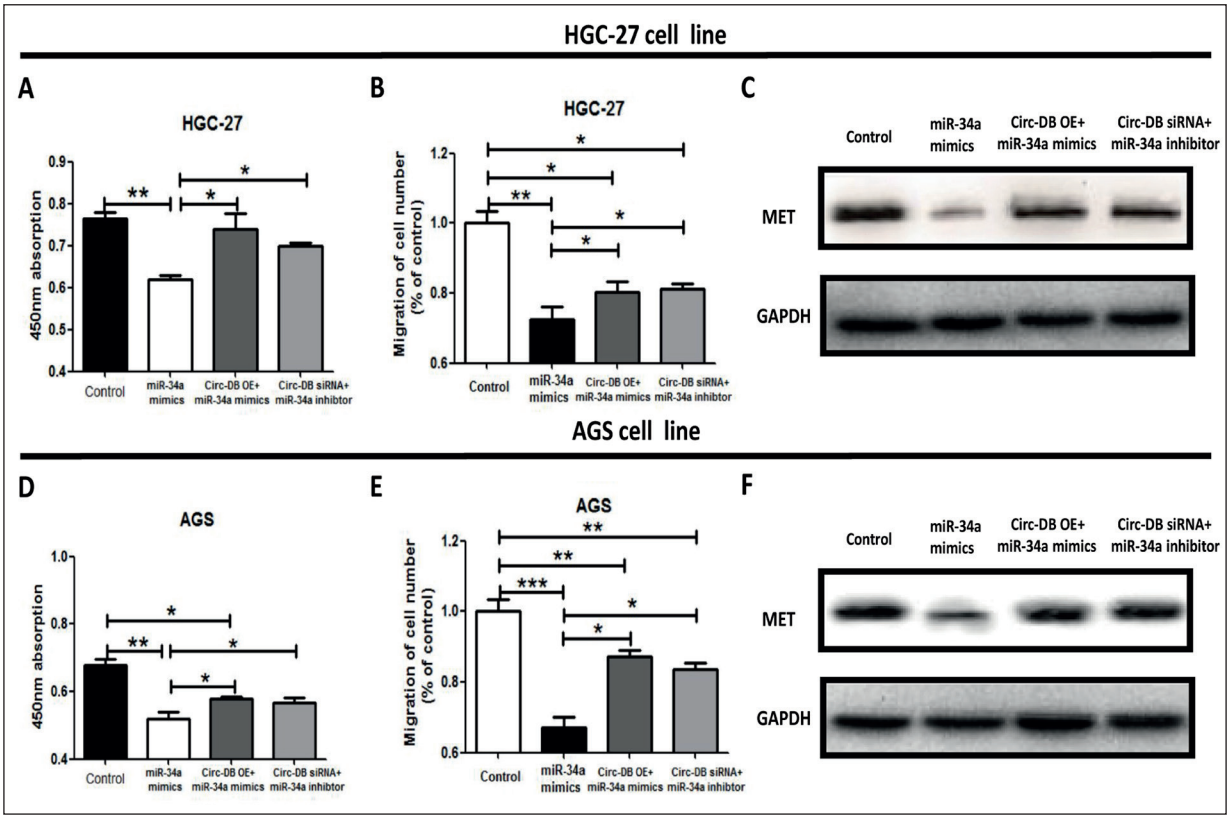

Figure 5. Circ-DB-microRNA-34a- MET loop to regulate cell function. **A-B,** After transfection of microRNA-34a mimics, the proliferative ability and migration ability of HGC-27 cells was inhibited, and the cell migration ability was high after co-transfection of circ-DB OE+microRNA-34a mimics and circ-DB siRNA+microRNA-34a inhibitor. Transfection group in microRNA-34a mimics. **C,** After transfection of microRNA-34a mimics, the expression of MET protein levels in HGC-27 cells was significantly reduced. After co-transfection of circ-DB OE+microRNA-34a mimics and circ-DB siRNA+microRNA-34a inhibitor, MET protein levels were significantly higher than microRNA-34a mimics group. **D-E,** After transfection of microRNA-34a mimics, the proliferative ability and migration ability of AGS cells was inhibited, and the migration ability of the cells was higher than that of miR after the co-transfection of circ-DB OE+microRNA-34a mimics and circ-DB siRNA+microRNA-34a inhibitor. MicroRNA-34a mimics transfection group. **F,** After transfection of microRNA-34a mimics, the expression of MET protein levels in AGS cells was significantly reduced. After co-transfection of circ-DB OE+microRNA-34a mimics and circ-DB siRNA+microRNA-34a inhibitor, the MET protein levels were significantly higher than microRNA-34a mimics group.

expression of circ-DB and MET in GCa tissues, and found that circ-DB may regulate the expression of MET through microRNA-34a. In addition, it plays a role in the occurrence and development of GCa.

In this study, we detected circ-DB expression in 32 postoperative GCa tissues and adjacent tissues, and the results showed that circ-DB expression was significantly higher in GCa tissues, suggesting that the abnormal circ-DB expression may be associated with the development of GCa. This study showed that circ-DB could endogenous competitively binds microRNA-34a. Moreover, the expression of microRNA-34a in GCa cells and its binding relationship with its target gene MET has been observed. We proved that circ-DB played a role as microRNA-34a sponge to positively regulate the expression of its target gene MET, thereby promoting cell proliferative ability and migration, which provides a new possibility to explain the development mechanism of GCa. However, due to experimental limits, we have not proved our results in animal models, which could have further completed this whole research.

Conclusions

These result proved that circ-DB may participate in the occurrence and development of GCa by regulating the proliferative ability and migration of GCa cells through the circ-DB-microRNA-34a-MET pathway.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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