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Targeting AURKA by microRNA-490-3p suppresses gastric cancer cell growth

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Summary. Objective. To illustrate the molecular mechanism of microRNA-490-3p regulating gastric cancer (GC) cells by targeting AURKA.

Methods. Genes with significantly different expression in GC and normal tissue in TCGA-STAD dataset were analyzed by bioinformatics. Expression levels of genes and proteins in GC cells were measured by qRT-PCR and western blot. The interaction between microRNA-490-3p and AURKA was verified by dual luciferase assay. Proliferation, migration, invasion and apoptosis of GC cells were evaluated through a set of cell function assays.

Results. MicroRNA-490-3p was significantly less expressed in GC, while AURKA was significantly highly expressed. Dual luciferase reporter gene assay proved that microRNA-490-3p targeted AURKA. Up-regulation of microRNA-490-3p restrained proliferation, migration, invasion and stimulated apoptosis of GC cells, which was attenuated by overexpression of AURKA.

Conclusions. MicroRNA-490-3p was likely to restrain the development of GC cells by inhibiting AURKA, and it may be an underlying target for GC treatment.

Key words: microRNA-490-3p, AURKA, Proliferation, Gastric cancer, Invasion, Migration

Introduction

Gastric cancer (GC) is among the most frequent malignant tumors worldwide, with over 70% of cases in developing countries (Ferlay et al., 2010). In the United States and some European countries, GC is frequently diagnosed in the middle and advanced stages (Digklia and Wagner, 2016). Despite great improvements in diagnosis and treatment of GC, the 5-year survival of GC patients is extremely low (Catalano et al., 2009). Today, surgery is still the primary treatment for GC, but more than 50% of patients are still likely to relapse after radical resection (Sathy et al., 1989). Therefore, exploring biomarkers for diagnosis of GC and then constructing early screening methods is the optimal way to reduce the mortality rate of GC.

Studies have indicated that microRNAs can regulate a variety of physiological activities of cells (Croce, 2009). For instance, microRNA-211 suppresses the invasion and proliferation of GC cells by modulating SOX4 (Wang et al., 2015). MicroRNA-324-3p accelerates development of GC by mediating the Smad4-mediated Wnt/β-catenin signaling pathway (Sun et al., 2018). MicroRNA-23a/b facilitates tumorigenesis and inhibits cell apoptosis of GC by mediating PDCD4 (Hu et al., 2017). These studies all demonstrate that it is of importance to study the function of microRNAs in GC.

MicroRNA-490, a member of microRNAs, is located on chromosome 7q33, and the microRNA-490 family includes microRNA-490-5p and microRNA-490-3p (Yang et al., 2018). MicroRNA-490-3p has previously been proved to be prominently associated with the development of multiple cancers. Zhang et al. (2013) discovered that microRNA-490-3p affects epithelial-mesenchymal transition and cell growth by mediating ERGIC3 in hepatocellular carcinoma. Chen et al. (2015) discovered that microRNA-490-3p hampers development of ovarian epithelial cancer cells by targeting CDK1. Liu et al. (2018) demonstrated that microRNA-490-3p serves as an inhibitor by restraining expression of VDAC1 in colorectal cancer. However, few studies on microRNA-490-3p in GC cells are reported, and its molecular mechanism requires further research.

The Aurora kinase family is comprised of serine/threonine kinases, which exerts a vital role in the cell cycle and mitotic spindle assembly (Bavetsias and Linardopoulos, 2015). AURKA has been found to modulate development of different cancers. It mediates cell migration and adhesion in epithelial ovarian cancer (Do et al., 2014). Additionally, it is found that the interaction of AURKA with Wnt and the Ras-MAPK

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signaling pathway can promote the occurrence of colorectal cancer (Jacobsen et al., 2018). AURKA is also a biomarker for bladder cancer diagnosis (Mobley et al., 2017). However, AURKA has been rarely studied in GC.

In our current study, microRNA-490-3p expression in GC was detected. The function of microRNA-490-3p in regulating GC cell growth could be further understood through overexpressing microRNA-490-3p. In addition, we explored the downstream target of microRNA-490-3p, which enables us to investigate the mechanisms underlying development of GC more comprehensively.

Materials and methods

Bioinformatics approaches

Differentially expressed mature microRNAs (normal: 45, tumor: 446) and mRNAs (normal: 32, tumor: 373) were offered by The Cancer Genome Atlas (TCGA) (https://portal.gdc.cancer.gov/). MicroRNA-490-3p level was analyzed based on the downloaded mature microRNA data with normal samples as the control. R package "edgeR" was utilized to carry out differential expression analysis on mRNAs in TCGA with the normal group as the control to obtain differentially expressed mRNAs (DEmRNAs). TargetScan (http://www.targetscan.org/vert_72/) and Starbase (http://starbase.sysu.edu.cn/) were utilized for target prediction of microRNA-490-3p. The up-regulated DEmRNA with the most significant negative correlation with microRNA-490-3p was selected as the study object.

Culture and transfection of cells

Human gastric mucosa cells GES 1 (BNCC337970) and GC cells BGC-823 (BNCC337689), SGC-7901 (BNCC100674), MKN-28 (BNCC102156) and MGC-803 (BNCC100665) were bought from BeNa Culture Collection (Beijing, China). MGC-803 cell line was grown in DMEN (Thermo Scientific, USA) with 10% fetal bovine serum (FBS; Thermo Scientific HyClone, Beijing, China), while the rest cell lines were placed in RPMI-1640 medium plus 10% FBS. The cells were kept at 37°C and 5% CO_2.

oe-AURKA and its control (oe-NC) were designed by Invitrogen (Shanghai, China). MicroRNA-490-3p mimic and the corresponding control (NC mimic) were synthesized from GenePharma (Shanghai, China). Cell transfection was carried out using Lipofectamine 2000 (Life Technologies, San Diego, CA, USA).

qRT-PCR

Total RNA extraction was done using RNAiso Plus (Takara, Japan). Based on the obtained RNA, cDNA was reversely transcribed using PrimeScript RT kit (Takara, Japan) and qRT-PCR was conducted on the Quantstudio™DX system (Applied Biosystems, Singapore) using TB Green Premix Ex Taq II (Takara, Japan). U6 and GAPDH served as internal references. Information of Primer sequences was as follows: microRNA-490-3p forward: 5'-TGCGGTTCAAG TAATTCAGGA-3', reverse: 5'-CCAGTGCAGGGT CCGAGGT-3'; U6 forward: 5'-TGCGGGTGCTCG CTTCGGCAGC-3', reverse: 5'-CCAGTGCAGGGTC CGAGGT-3'; AURKA forward: 5'-CTGAGGAGGAAC TGGCATCAA-3', reverse: 5'-ATTAGGTAGACT CTGGTAGCATCAT-3'; GAPDH forward: 5'-CGGAGTCAACGGATTTGGTCGTAT-3', reverse: 5'-AGCCTTCTCCATGGTGGTGAAGAC-3'. $2^{-\Delta\Delta Ct}$ method was applied to analyze the relative expression.

Western blot

Cell lysates were obtained from the cells by RIPA (Thermo Fisher, USA). Protein samples were separated by SDS-PAGE and transferred onto a PVDF membrane (Millipore). After blocking the membrane in 5% skimmed milk powder for 1 h, it was incubated with primary antibodies of AURKA (1:4000, ab1287, Abcam, UK) or GAPDH (1:10,000, ab180630, Abcam, UK) overnight at 4°C. HRP-conjugated secondary antibody IgG (1:2000, ab6721, Abcam, UK) was utilized to incubate the membrane and protein imprints were examined by ECL Plus (Millipore).

CCK-8 assay

Cell proliferative abilities were examined by Cell Counting Kit-8 (Beyotime Inst Biotech, China). In brief, 5×10^3 cells/well were inoculated into a 96-well plate to grow for 24 h at 37°C. Then, corresponding vectors were transfected into cells. The absorbance value at 450 nm was read by a microplate reader (Bio-Rad, Hercules, CA, USA) to quantify the cell proliferative abilities.

Cell wound healing and Transwell assays

A wound was scratched in the middle of a six-well plate using a 200 μL pipette at 0 h. After 48 h, cell migration status was observed, and the wound width was measured. Wound width at 0 h was taken as the control. The relative migrating rate was calculated.

A Transwell chamber (8 μm pore size, Costar) with Matrigel (BD Science, USA) was prepared for cell invasion. 5×10^4 cells were resuspended in serum-free medium and plated onto the upper chamber. The cell culture medium with 10% FBS was supplemented in the lower chamber as a chemical attractant. After incubation for 48 h, cells failing to pass through the membrane were gently removed, and cells in the lower chamber were treated with methanol, dyed with 0.1% crystal violet, photographed and counted.

Cell apoptosis assay

FITC/Annexin V kit (BD, USA) was applied to stain cells in line with the manufacturer's guidelines and cell

apoptosis was evaluated utilizing flow cytometry (FACS Calibur, BD Biosciences).

Dual luciferase assay

SGC-7901 cells were inoculated into a 24-well plate and co-transfected with corresponding psiCHECK™-2 vectors and microRNA mimics. 48 h later, the luciferase viabilities of Firefly and Ranilla were assessed using a dual luciferase reporter gene assay system (Promega, USA).

Statistical analysis

Data from 3-repeated experiments were analyzed by t-test for two-group comparisons or one-way analysis of variance for multi-group comparisons, and the results were expressed as mean ± standard deviation. $P<0.05$ was regarded as statistically significant. All statistical tests were processed by SPSS 19.0 software (SPSS Inc., Chicago, IL, USA) and Graph Pad Prism 6 software (San Diego, CA).

Results

MicroRNA-490-3p is significantly less expressed in GC

MicroRNA levels in tumor and normal samples from TCGA-STAD dataset were analyzed with "edgeR" package in R language. $|logFC|>1.5$ and adj.pvalue<0.05 were screening standards for identifying differentially expressed microRNAs (DEmiRNAs), and 39 DEmiRNAs were obtained (Fig. 1A). MicroRNA-490-3p was notably less expressed in GC tissue compared to normal tissue (Fig. 1B) with a statistically significant FDR value. Hence, microRNA-490-3p was selected as the research object. Then, the qRT-PCR result also displayed that microRNA-490-3p expression in GC cells was remarkably lower than that in normal cells (Fig. 1C). SGC-7901 and BGC-823 with relatively low microRNA-490-3p expression were utilized for subsequent functional experiments.

Upregulation of microRNA-490-3p hampers GC cell processes

To investigate the effects of microRNA-490-3p on progression of GC cells, NC mimics or microRNA-490-3p mimics were transfected into GC cell lines SGC-7901 and BGC-823, respectively. Expression levels of microRNA-490-3p in cells transfected with NC mimics and microRNA-490-3p mimics were measured using qRT-PCR. It could be observed that the transfection of microRNA-490-3p was effective (Fig. 2A). To evaluate the functions of microRNA-490-3p in GC cell growth, cell proliferation level was assessed by CCK-8 assay. The result implied that up-regulation of microRNA-490-3p significantly hampered proliferation of BGC-823 and SGC-7901 cells (Fig. 2B). Then, the wound healing assay showed that microRNA-490-3p overexpression dramatically the reduced migratory ability of GC cells (Fig. 2C). The Transwell results exhibited that up-regulating microRNA-490-3p remarkably hindered the invasive ability of SGC-7901 and BGC-823 cells (Fig. 2D). Finally, the flow cytometry result displayed that compared with control group, up-regulation of microRNA-490-3p significantly enhanced apoptosis of cancer cells (Fig. 2E).

AURKA is a target of microRNA-490-3p in GC

We adopted R package "edgeR" first to analyze the differential expression of mRNAs from TCGA-STAD dataset in tumor samples and normal samples ($|logFC|>1$, adj.pvalue<0.05), and a total of 2,375 up-regulated DEmRNAs were obtained (Fig. 3A). Then,

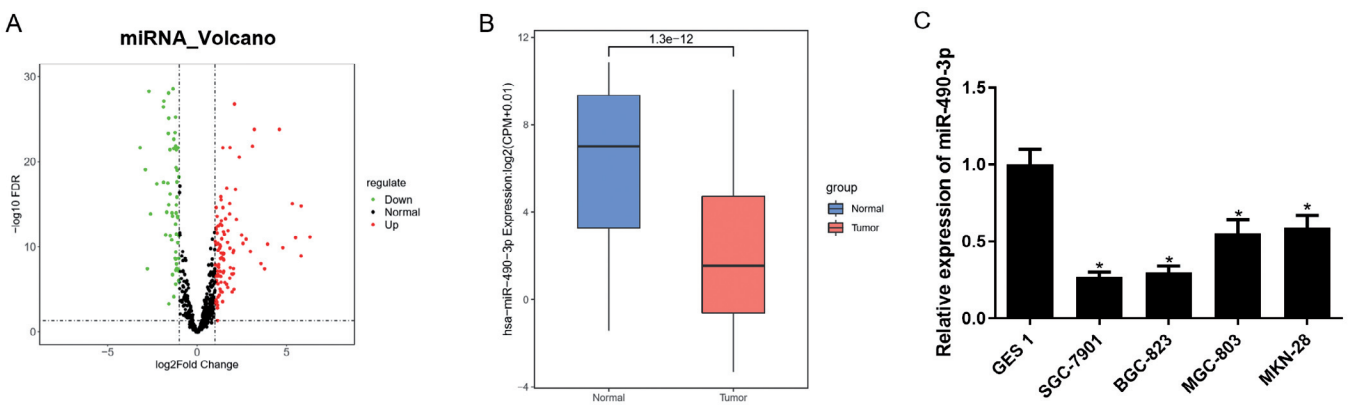

Fig. 1. MicroRNA-490-3p is significantly down-regulated in GC cells. **A.** Volcano map of DEmiRNAs in normal and tumor groups from TCGA dataset. Red: significantly up-regulated microRNAs, green: significantly down-regulated microRNAs. **B.** Boxplot of microRNA-490-3p expression in normal (blue) and tumor (red) groups. **C.** Relative expression level of microRNA-490-3p in human gastric mucosa cell lines GES 1 and GC cell lines SGC-7901, BGC-823, MGC-803 and MKN-28. * $P<0.05$.

target gene prediction of microRNA-490-3p was performed using Starbase and TargetScan databases. Target gene AURKA with binding sites of microRNA-490-3p was acquired by interacting predicted target genes with up-regulated DEmRNAs (Fig. 3B). The expression data of samples in TCGA database indicated that AURKA was expressed significantly highly in GC tissue (Fig. 3C). Meanwhile, correlation analysis pointed out that microRNA-490-3p expression negatively correlated with AURKA expression (Fig. 3D). In addition, AURKA expression was markedly higher in GC cells than in normal cells (Fig. 3E,F).

Next, we predicted the targeted binding sequences of microRNA-490-3p on AURKA 3'UTR using TargetScan database (Fig. 3G) and hypothesized that AURKA was a molecular target of microRNA-490-3p in GC cells. Dual luciferase assay result showed that luciferase activity of AURKA-WT decreased after upregulation of microRNA-490-3p (Fig. 3H). In addition, compared with GC cells transfected with NC mimics, AURKA mRNA and protein levels were prominently reduced after transfection of microRNA-490-3p mimics into GC cells (Fig. 3I,J). These experimental results demonstrated that microRNA-490-3p targeted AURKA

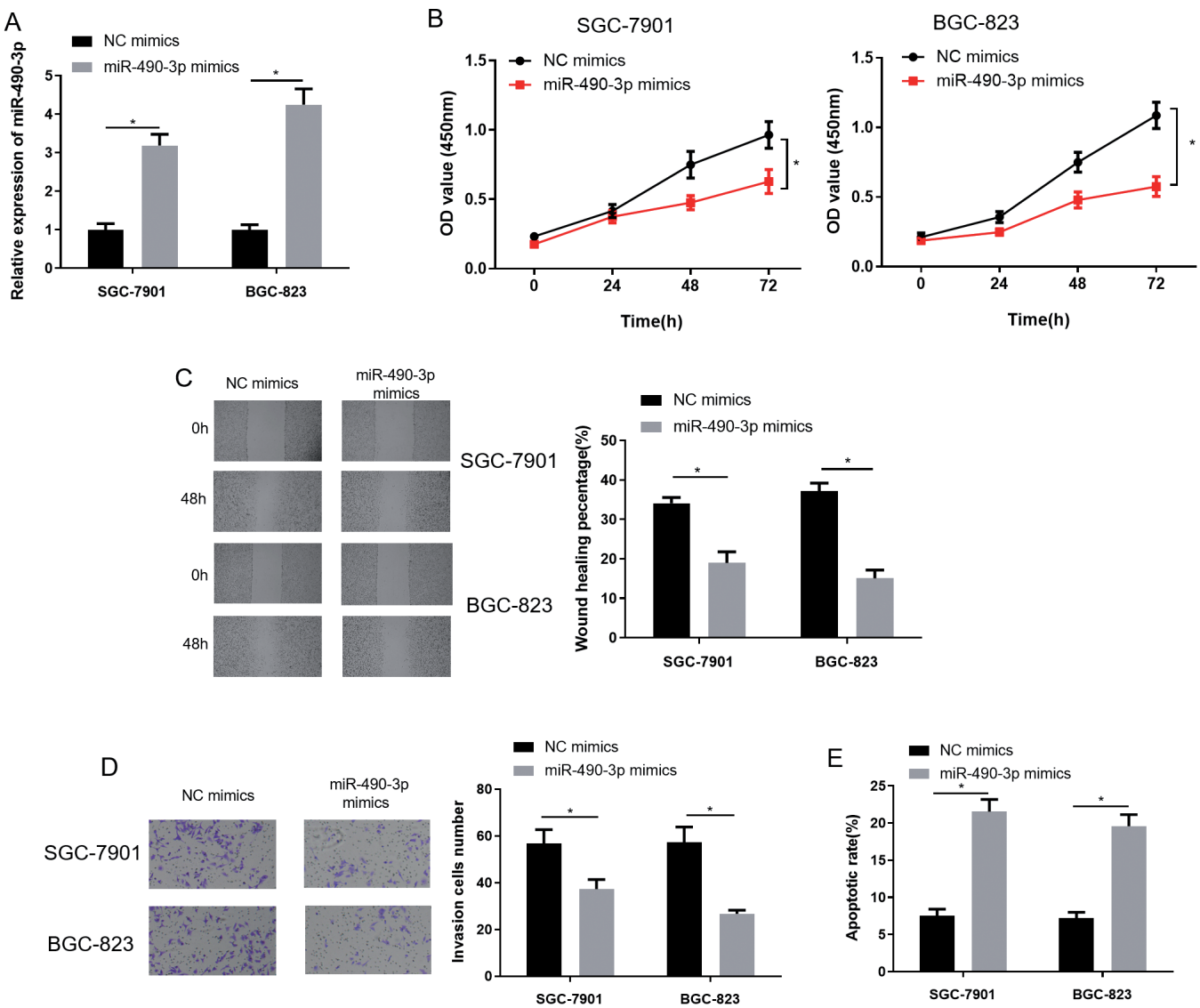

Fig. 2. Up-regulation of microRNA-490-3p inhibits proliferation, migration and invasion of GC cells and facilitates apoptosis. **A.** The transfection efficiency of microRNA-490-3p in GC cells. **B.** Proliferation level of GC cells after upregulation of microRNA-490-3p. **C.** The migratory ability of GC cells upon microRNA-490-3p overexpression. **D.** Invasive ability of GC cells after upregulating microRNA-490-3p. **E.** Apoptosis of GC cells after up-regulating microRNA-490-3p. * P<0.05. C, x 40; D, x 100.

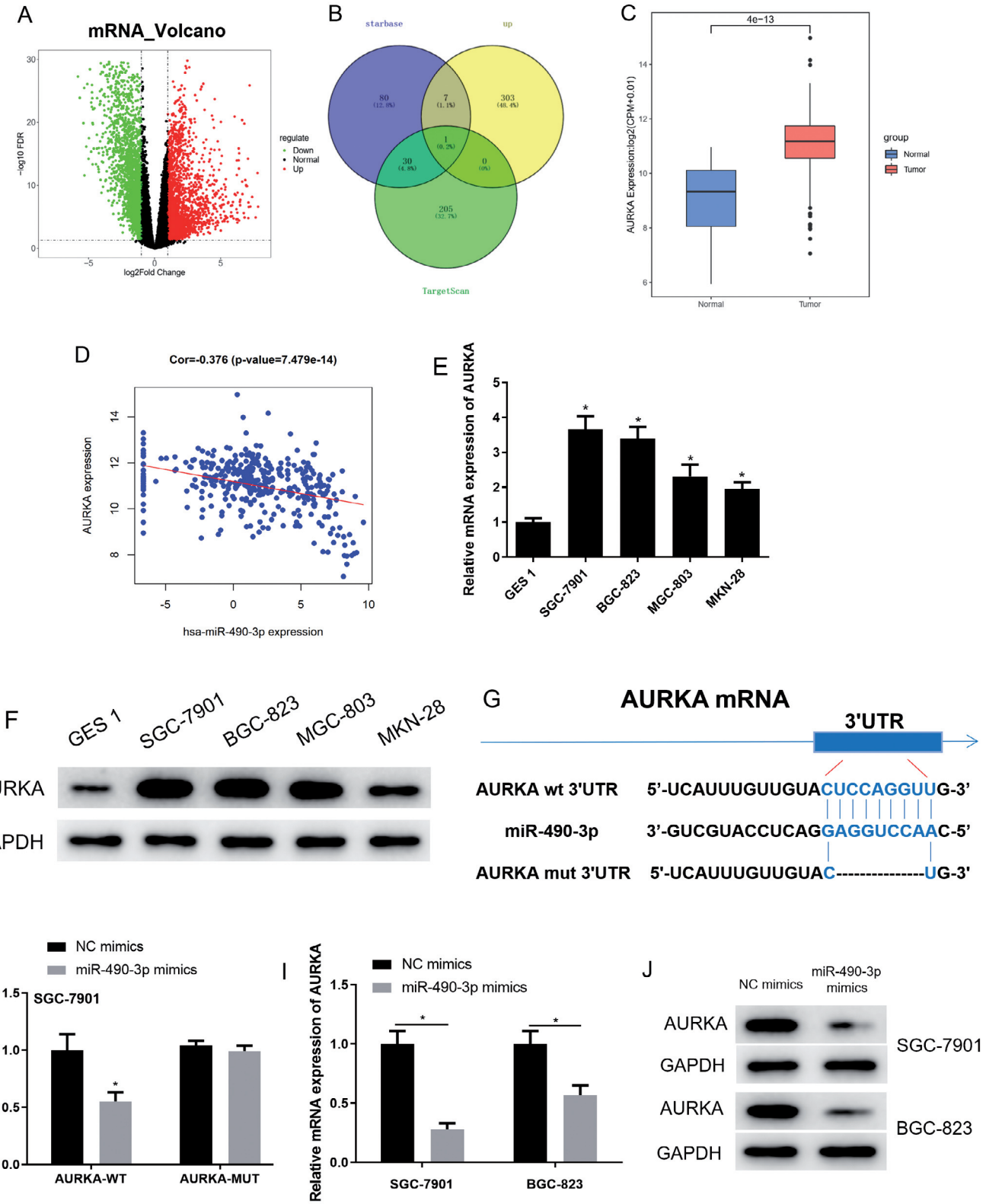

Fig. 3. AURKA is targeted by microRNA-490-3p in GC. **A.** Volcano map of DEmRNAs from TCGA-STAD data set in normal group and tumor groups. Red: up-regulated DEmRNAs, green: down-regulated DEmRNAs. **B.** Venn diagram of the intersection of database-predicted target genes of microRNA-490-3p and up-regulated DEmRNAs. **C.** Boxplot of AURKA expression from TCGA database in normal group (blue) and tumor group (red). **D.** Expression correlation analysis of microRNA-490-3p and AURKA. **E, F.** Relative mRNA and protein expression levels of AURKA in gastric mucosa cell line and GC cell lines. **G.** The targeted binding sites of microRNA-490-3p on AURKA 3'UTR were predicted by bioinformatics analysis. **H.** The targeted binding relationship between AURKA and microRNA-490-3p. **I, J.** AURKA mRNA and protein expression levels after up-regulating microRNA-490-3p in GC cells. * P<0.05.

and significantly suppressed AURKA expression in GC.

Overexpression of AURKA attenuates the impact of up-regulating microRNA-490-3p on GC cells

We carried out cell functional experiments in three transfection groups: NC mimics+oe-NC, microRNA-490-3p mimics+oe-NC and microRNA-490-3p mimics+oe-AURKA. First of all, qRT-PCR and western blot results indicated that up-regulated microRNA-490-3p suppressed AURKA expression, while AURKA expression in GC cells was significantly increased after overexpressing microRNA-490-3p and AURKA, compared with overexpression of microRNA-490-3p alone (Fig. 4A,B). Then, the CCK-8 assay result manifested that up-regulation of microRNA-490-3p dramatically reduced the proliferative ability of GC cells, while overexpressing microRNA-490-3p and AURKA simultaneously attenuated the inhibitory effect of overexpressed microRNA-490-3p on GC cell proliferation (Fig. 4C). Besides, GC cell migratory and invasive abilities decreased significantly after upregulation of microRNA-490-3p, but the suppressive effect of overexpressed microRNA-490-3p on GC cells was weakened by upregulation of microRNA-490-3p and AURKA (Fig. 4D,E). Finally, the flow cytometry result showed that overexpression of microRNA-490-3p promoted apoptosis of GC cells. However, compared with microRNA-490-3p overexpression alone, overexpression of microRNA-490-3p and AURKA

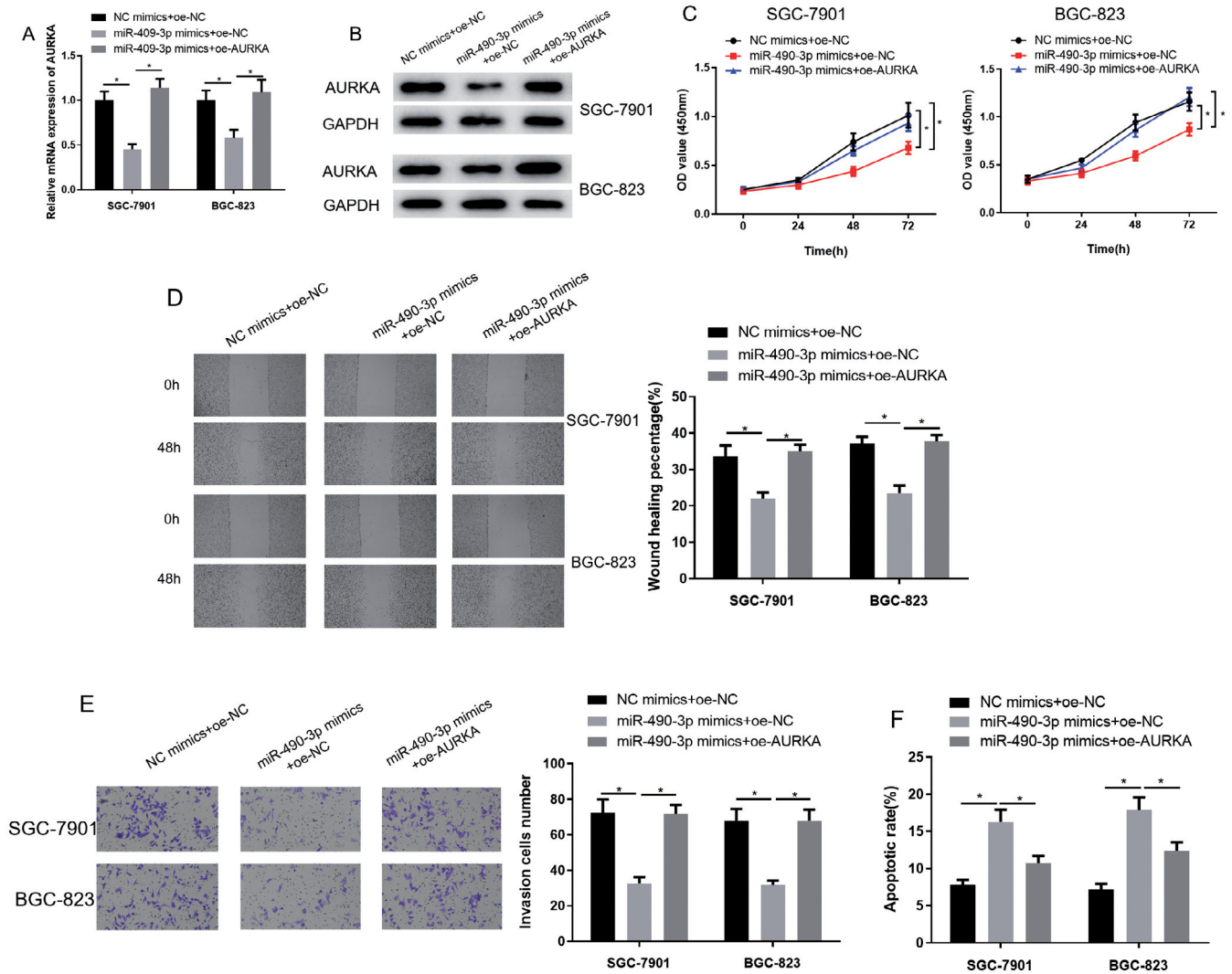

Fig. 4. AURKA overexpression is able to attenuate the impact of up-regulated microRNA-490-3p on GC cells. **A, B.** AURKA mRNA and protein levels in each group, respectively. **C.** Cell proliferative ability in different groups. **D.** Cell migratory ability in different groups. **E.** Cell invasive ability in each group. **F.** Cell apoptosis level in different groups. * P<0.05. D, x 40; E, x 100.

significantly reduced the apoptosis level of GC cells (Fig. 4F).

Discussion

GC accounts for one third of all cancers in the world (Torre et al., 2015). As GC is usually diagnosed at advanced stages, its median overall survival is less than 12 months (Jou and Rajdev, 2016). To improve the early diagnosis and prognosis of GC patients, a deeper understanding of genes and mechanisms related to GC progression is needed. Many studies have put forward that microRNAs can be an oncogene or a tumor inhibitor in regulating tumorigenesis and progression (Fang et al., 2017; Mu et al., 2018, Sun et al., 2018a). Studies have confirmed that microRNA-490-3p being a tumor inhibitor is linked with the development of various cancers. For example, microRNA-490-3p is significantly less expressed in esophageal squamous cell carcinoma cells, while overexpressed microRNA-490-3p restrains cancer cell processes (Kang et al., 2018). MicroRNA-490-3p suppresses invasiveness and growth of triple-negative breast cancer by suppressing TNKS2 (Jia et al., 2016). Moreover, the expression of microRNA-490-3p is persistently down-regulated during malignant progression of colorectal cancer, and artificial overexpression of microRNA-490-3p in colorectal cancer represses cell migratory and invasive abilities (Xu et al., 2015). Similarly, herein, we also found that microRNA-490-3p presented low expression in GC tissue and cells. Further studies clarified that up-regulating microRNA-490-3p prominently suppressed growth of GC cells and promoted apoptosis. These results further illustrated that microRNA-490-3p was a tumor suppressor in GC.

To elucidate the mechanism of microRNA-490-3p on GC cell progression, we predicted the possible target gene of microRNA-490-3p in GC cells. It was discovered that microRNA-490-3p directly targeted AURKA through bioinformatics analysis and dual luciferase assay. Overexpression of microRNA-490-3p led to a conspicuous reduction in AURKA mRNA and protein levels. AURKA is located on chromosome 20q13.2 (Sen et al., 1997; Tanner et al., 2000). Gene amplification, mRNA and protein overexpression of Aurora-A are frequent in many tumor types, and are related to aneuploidy and redundant centrosomes as well as anti-apoptosis (Nikonova et al., 2013). Thus, AURKA is considered as a target for cancer therapies. This study noted that AURKA mRNA and protein levels were remarkably increased in GC. The same expression trend of AURKA has been reported in other cancers (Yang et al., 2007; Cammareri et al., 2010; Tökés et al., 2015). Growing evidence indicates that AURKA can affect the growth of cancer cells (Xie et al., 2017; Gomaa et al., 2019). In accordance with the above results, we also identified that AURKA was an important regulatory factor in GC. Functional experiments showed that cell processes of GC were prominently reduced upon overexpression of microRNA-490-3p, while simultaneous overexpression of AURKA counteracted the inhibitory effect. These findings suggest that targeting to regulate AURKA may be the primary mechanism by which microRNA-490-3p inhibits GC progression, and AURKA might be a potential new target.

Generally speaking, our study suggested that microRNA-490-3p was less expressed in GC. MicroRNA-490-3p was able to dramatically inhibit progression of GC cells by binding to AURKA, and subsequently played an anticancer role in GC. This work offers a new basis for investigating the pathogenesis of GC. These findings also indicate that microRNA-490-3p is a potent tumor biomarker, and highlight its underlying clinical application as a promising target for diagnosis and treatment of GC.

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Final approval of the version: Pinlu Jiang.
All authors read and approved the final manuscript.
Availability of data and materials. The data used to support the findings of this study are included within the article. The data and materials in the current study are available from the corresponding author on reasonable request.

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