Original Article

CAP2 contributes to tumorigenesis in gastric cancer by targeting transcription factor SOX9

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Background: Gastric cancer (GC) is one of the most common tumors and the major cause of cancer-related mortality in the world. The purpose of this study is to identify new biomarker and reveal its potential molecular mechanism in GC.

Methods: The expression of CAP2 was observed by the bioinformatics analysis and western blot assays. The effects of CAP2 on cell proliferation and growth were tested by MTT assay, EdU assay, colony formation assay, and flow cytometric assay, respectively. ChIP and dual-luciferase assays were confirmed that SOX9 binding sites were putative regulatory elements in the transcriptional activation of CAP2. Furthermore, western blot and xenograft assays were applied to examine whether SOX9 was involved in the regulation of CAP2 expression.

Results: We reported that CAP2 is overexpressed in GC cells and tissues and related to a poorer prognosis for GC patients. Moreover, we found that knockdown of CAP2 suppressed the proliferation, growth, and cell cycle of GC cells. Besides, the transcription factor SOX9 participated in the CAP2-mediated proliferation of GC cells *in vitro* and *in vivo*.

Conclusions: Our results provide novel evidence that CAP2 plays an essential role in the genesis and development of GC, thus potentially highlighting this gene as a therapeutic target.

Keywords: CAP2; gastric cancer (GC); cell proliferation; SOX9

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Introduction

Gastric cancer (GC) is part of the main causes of cancer-related death in the world (1). Over the last decades, despite advances in the surgical techniques and therapeutic strategies, the 5-year survival rate of severe GC patients is still very low (2), and one of the reasons for the high mortality rate is that most patients are diagnosed with advanced tumor grades and cancer metastasis, losing the optimal treatment time (3). Moreover, genetic mutations, epigenetic changes, and abnormal molecular signaling pathways are implicated in the occurrence, spread, and metastasis of GC (4). Thus, understanding the pathogenesis of GC at the molecular level and identifying potential molecular targets in the process of metastasis is important for diagnosis, prognosis, and GC therapy.

Cyclase-associated proteins (CAPs) are evolutionally conserved proteins that belong to the actin monomer-binding protein family and were thought to regulate actin cytoskeleton assembly (5). Accumulating evidence

reveals that the actin cytoskeleton can play vital roles in cell morphogenesis, cytokinesis, and cell migration, and an abnormal actin cytoskeleton is usually the basis of tumorigenesis and metastasis (6). Therefore, CAPs play an important role in cell division and cell motility through its action on actin filament dynamics and the cytoskeleton. Previously, we reported that CAP2, a homolog of CAP (7), has been implicated in several types of cancers, including hepatocellular carcinoma (8), malignant melanoma (9), epithelial ovarian cancer (10), breast cancer (11), glioma (12), however, the biological function and precise mechanism of CAP2 in GC are not understood.

Herein, we aimed to estimate the role of CAP2 in GC, and then we further evaluated the molecular mechanisms whereby CAP2 could influence GC through *in vitro* and *in vivo* experiments in which we estimated the functions of CAP2 on cell proliferation. In addition, we showed that CAP2 is transcriptionally activated by SOX9, while SOX9 was proved to mediate the CAP2-regulated cell proliferation of GC *in vitro* and tumor growth *in vivo*. Finally, the above results supported an oncogenic activity for CAP2 in GC tumorigenesis, which can act as a therapeutic potential biomarker in GC.

We present the study in accordance with the ARRIVE reporting checklist (available at http://dx.doi.org/10.21037/jgo-20-234).

Methods

Clinical specimens and cell culture

Fresh GC tissues and corresponding peritumor tissues were obtained from 24 patients who experienced surgical resection at the Affiliated Hospital of Nantong University. None of these patients received any preoperative anticancer treatment. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013), and was approved by Ethics the Committee of Affiliated Hospital 2 of Nantong University (ID: 2020KT042). Informed consent was provided by all participants.

The MKN45, BGC823, AGS, and SGC7901 GC cell lines and gastric epithelial cell (GES) line were obtained from the Chinese Academy of Sciences. These cell lines were cultured with DMEM containing 10% FBS in a humidified incubator at 37 7 with 5% CO_2.

Transfection

Specific or scrambled siRNAs (GenePharma) were applied to transfect cell lines by Lipofectamine 2000 (Invitrogen). The targeting sequence of CAP2 and SOX9 was as follows: CAP2-siRNA1: CCTGTAGCATCCACAGTAT, CAP2-siRNA2: GCGCCAAGTCATCTGAAAT, CAP2-siRNA3: GGATGGTGATTATAGAGAA, siSOX9: GCAGCGACGUCAUCUCCAA.

Western blot analysis

Tissues and cells were lysed using RIPA buffer (Promega). Proteins were separated using SDS-PAGE and transferred into a PVDF membrane. Subsequently, the membranes were blocked for 2 h with 5% non-fat milk and then incubated with primary antibodies CAP2 (ab236590, Abcam)and SOX9 (ab3697, Abcam) at 4 ℃ overnight. Then, horseradish peroxidase-conjugated secondary antibodies were used to incubate the membrane at room temperature for 2 hours after three washes with TBST. The protein bands were visualized by ECL kits (Millipore, MA, USA).

MTT assay

Cells were grown in 96-well plates (2×10^3 cells/well) for 24 h. Cell viability and proliferation assay were carried out using the MTT kit (Beyotime) after transfection or Cell-Light^{TM} EdU Apollo567 *in vitro* kit (Ribo). For the MTT assay, the absorbance was measured at 490 nm. For the EdU assay, positive cells in each group were recorded under the fluorescence microscope.

Colony formation assay

Cells were plated in a 12-well plate at a density of 1×10^3 cells/well, with media changed every third day. After two weeks, cells were fixed with methanol and stained with crystal violet (Sigma). Subsequently, the number of colonies was counted.

Flow cytometric analysis

The cells were collected and fixed. Cell apoptosis was stained through using Annexin V- FITC/propidium iodide

(PI) apoptosis kit (Invitrogen) and the percentage of cells was stained via a PI-based cell cycle kit (Invitrogen). The stained cells were detected by Attune Acoustic Focusing Cytometer (Invitrogen).

Chromatin immunoprecipitation assay (ChIP)

In brief, the protein-DNA complexes were cross-linked with 1% formaldehyde, followed by nuclear fractionation and DNA shearing by sonication. The immunoprecipitation was applied with an anti-SOX9 antibody (ab3697, Abcam) or IgG (negative control). Then, the antibody-protein-DNA complex was eluted from the beads and reversed cross-linked after washing. PCR primers: Site-1-F: 5'-TGTGGCTCATCCACTCTTAG-3', Site-1-R: 5'-TTCCAAGCATCCATTCATAT-3', Site-2-F: 5'-GATAGGGAGGGTGCTGG-3', Site-2-R: 5'-GCTGACAGTAATGAGGTGCA-3', Site-3-F: 5'-TATTGGCCTTTAAGAAATTC-3', Site-3-R: 5'-GGAAAATAATTGCAGAAAAG-3', Site-4-F: 5'-TTGATGAAAATTGAAAATCA-3', Site-4-R: 5'-CACTTGGCTTCTTAAGATGT-3'.

Animal study

The 5-week-old BALB/c nude mice were divided into four groups (n=5). Cells (1×10^6) with transfection were resuspended in 200 mL PBS and subcutaneously injected into the flanks of the mice. The lengths and widths of tumors were detected every week. Tumor volume was calculated as = width^2 × length/2. At 28 days, these tumors were excised and weighted. Experiments were performed under a project license (No. 2020KT042) granted by institutional/regional/national ethics/committee/ethics board of Affiliated Hospital 2 of Nantong University, in compliance with institutional guidelines for the care and use of animals.

Statistical analysis

Statistical analyses were conducted by SPSS 19.0. A student's *t*-test was implemented to analyze the differences between the two groups. Multiple comparisons between groups were employed by using ANOVA analysis. P value <0.05 was statistically significant.

Results

Identification of clinical significance and expression of CAP2 in GC

According to the criteria for screening DEGs, 642 genes that exhibited over-expression status in GC tissues were identified through the bioinformatics analysis of GSE84437 datasets. Among these genes, we included 172 candidate genes that were significantly connected with survival outcomes (log-rank P<0.001). Besides, univariate and multivariate Cox analysis was employed to select out 82 hub genes from these candidates, which can be performed to independently predict the survival time of GC patients. Then, we screened out the CAP2 gene from all hub genes and observed that the mRNA expression of CAP2 was increased in tumor tissues compared to the normal tissues (*Figure 1A*). Moreover, Kaplan-Meier plots showed that high CAP2 expression had a notably shorter overall survival time than GC patients in low CAP2 expression (*Figure 1B*). Also, elevated expression of CAP2 markedly associated with the tumor clinical stage (*Figure 1C,D*), suggesting that GC samples with high expression of CAP2 are prone to progress to a higher stage. Furthermore, we constructed the forest plot of univariate and multivariate analyses to assess the independent prognostic factors of CAP2. Cox's proportional hazards model demonstrated that CAP2 expression, T stage, and N stage were notably associated with the survival of GC patients (*Figure 1E,F*). CAP2 expression was further measured by western blot. Our results exhibited that the CAP2 protein level in tumor tissues was dramatically higher than that in matched normal tissues (*Figure 2A*). Taken together, our data identified that CAP2 could act as an oncogene and associated with GC patients' prognosis.

Effects of CAP2 expression on the proliferation of GC cells

To investigate the roles of CAP2 on GC cell proliferation, we performed the MTT and colony formation assays. Firstly, western blot analysis detected that CAP2 expression in MKN45 and BGC823 cells were higher than other GC cells and GES cells (*Figure 2B*). After transfected with three different CAP2 siRNA, we observed that siRNA1 had the highest knockdown efficiency compared with siRNA2 and siRNA3 by western blot (*Figure 2C*). Besides, the results indicated that the cell viability and the number of colonies

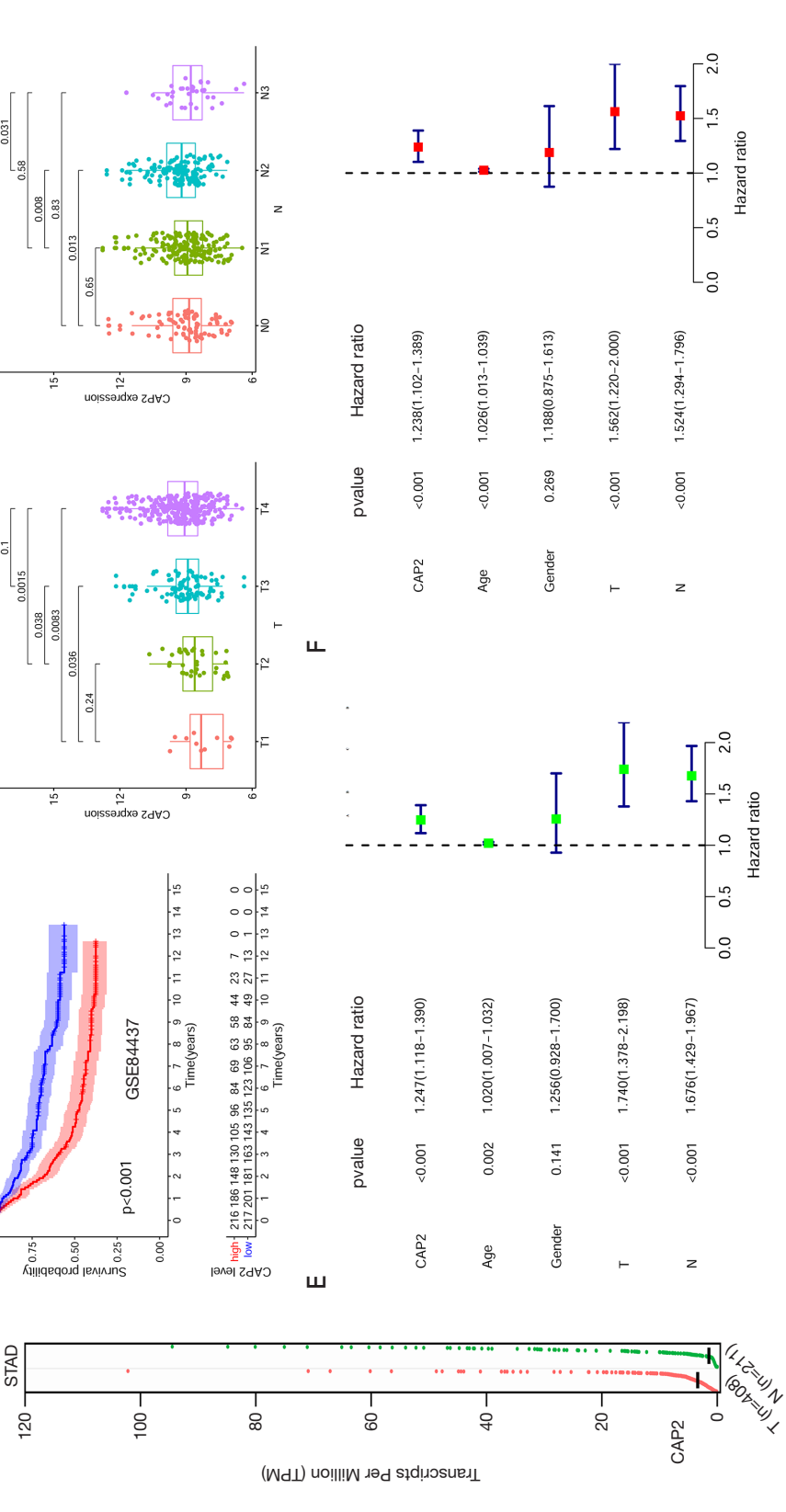

Figure 1 Identification of clinical significance of CAP2 in the GSE84437 cohort. (A) GEPIA database validated that CAP2 expression in GC and normal tissues; (B) Kaplan-Meier survival curves of CAP2 expression based on GSE84437 datasets; (C,D) Boxplot representation of association with CAP2 expression and clinical stage (T and N stage) in the GSE84437 cohort; (E) univariate and multivariate (F) Cox analysis for independent CAP2 expression was presented in the forest plot.

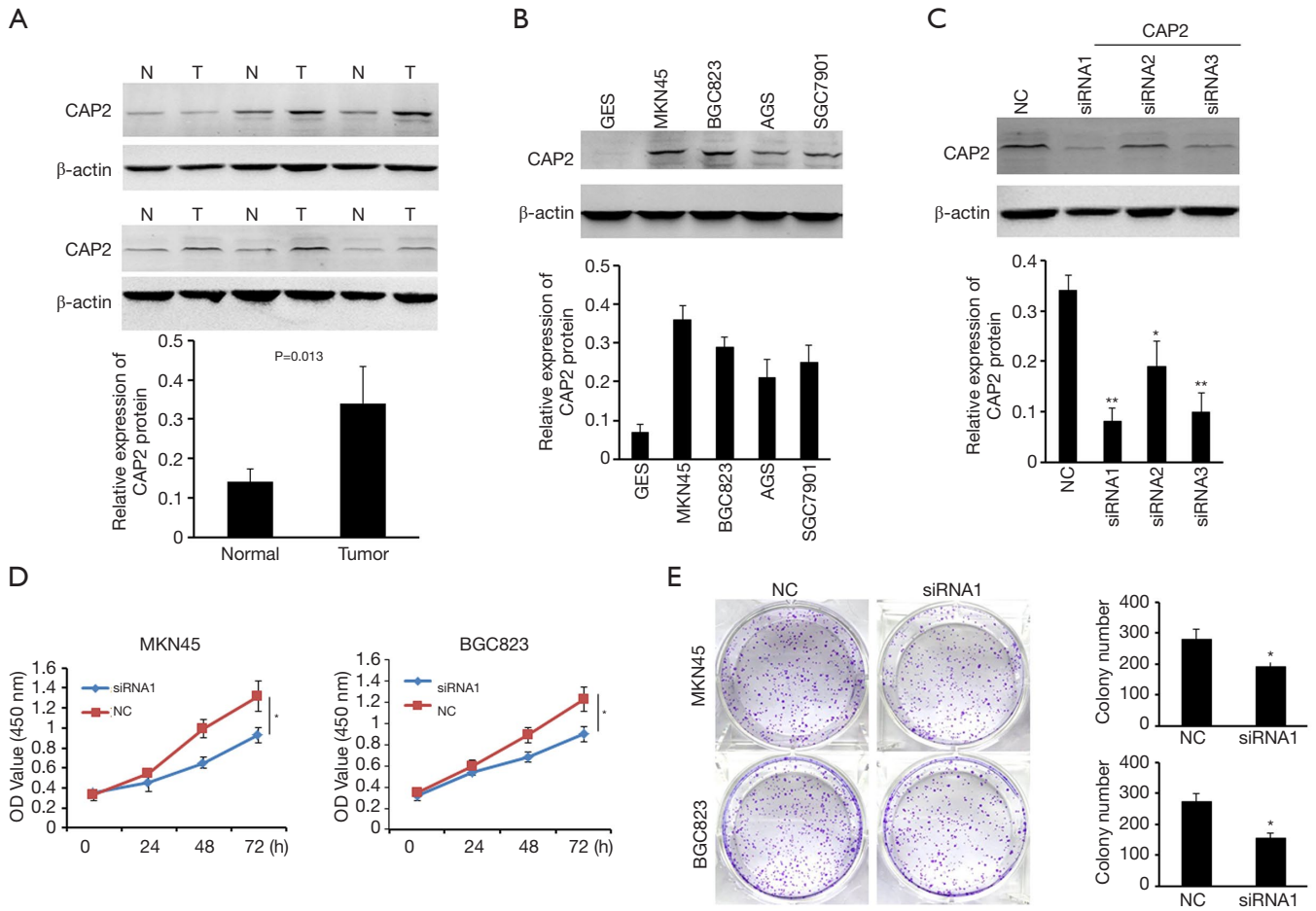

Figure 2 The expression of CAP2 is elevated in GC tissues and cells. (A) Representative western blot results of the protein levels of CAP2 in six pairs of GC tissues (T) and matched normal tissues (N); (B) the protein expression levels of CAP2 in GC cell lines and GES cell lines were detected by western blot; (C) Western blot analysis indicated the CAP2 expression level with three different CAP2 siRNA transfectants (siRNA1, siRNA2, and siRNA3) and the empty vector transfectant (NC); (D) effects of CAP2 expression on the cell viability of MKN45 and BGC823 cells transfected with CAP2 siRNA1 or sh-NC; (E) colony numbers of the treated GC cell lines were measured by colony formation assay. The colonies were stained with 1% crystal violet. *, P<0.05; **, P<0.01.

on MKN45 and BGC823 cells in the siRNA1 treated group was dramatically reduced compared to the NC group (*Figure 2D,E*). Also, the EdU staining assay was utilized to assess the role of CAP2 on DNA replication of GC cells. The results showed that cell proliferation was observably suppressed in MKN45 and BGC823 cells transfected with the siRNA1 treated group (*Figure 3A,B*).

To further determine the effects of CAP2 on cell proliferation, we employed flow cytometry analysis to measure the cell cycle and apoptosis of GC cells after transfection with siRNA1. The results demonstrated that the percentage of cells in the G1 phase observably increased and the percentage of cells in the S phase dramatically decreased in MKN45 and BGC823 cells transfected with siRNA1 (*Figure 3C*). Besides, cell apoptosis analysis demonstrated that the apoptosis rate of cells was increased in MKN45 and BGC823 cells transfected with siRNA1 (*Figure 3D*). Therefore, these above results revealed that CAP2 could contribute to GC tumorigenesis.

SOX9 is involved in CAP2-mediated proliferation of GC cells in vitro and in vivo

To further explore the mechanisms that CAP2 is involved

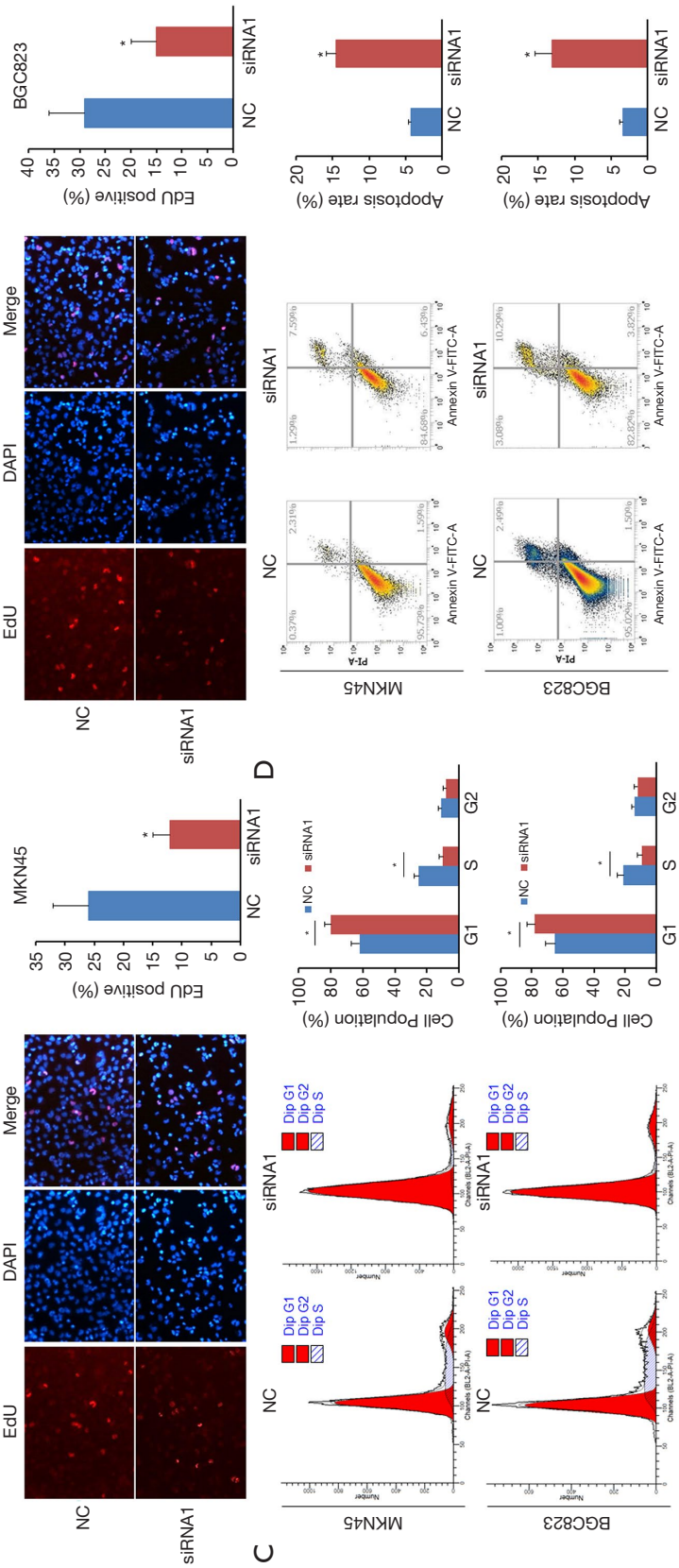

Figure 3 Effects of CAP2 expression on GC cell proliferation. (A,B) EdU staining assays were performed to assess the abilities of DNA replication on treated MKN45 and BGC823 cells. DAPI means the number of cells, and EdU means the number of proliferative cells in the field. Magnification: 200×. (C,D) Flow cytometry assay was applied to detect the effects of CAP2 expression on cell cycle and cell apoptosis of MKN45 and BGC823 cells. *, P<0.05.

in GC tumorigenesis, we utilized the JASPAR database to estimate the possible binding sites of relevant transcription factors in the CAP2 promoter region. Our analysis showed that the possible binding sites for CAP2 within the -1200 to -1192, -941 to -933, -714 to -706, and -567 to -559 regions (*Figure 4A*). ChIP assay was conducted to detect that the transcription factor SOX9 can be bind to the CAP2 promoter at Site-1, Site-2, Site-3, and Site-4 (*Figure 4B*). Then, we constructed serially truncated and mutated CAP2 promoter plasmids and conducted a dual-luciferase assay to present that the region from -1200 to -559 exhibited the strongest promoter activity, which seemed to be the core part explaining for increasing promoter activity (*Figure 4C*). To confirm whether the SOX9 binding sites take effects for CAP2 transcription, we performed substitution mutations of the sites (pGL3-M1, pGL3-M2, pGL3-M3, and pGL3-M4). We found that there was an observable decrease in CAP2 promoter activity when the -1200 to -1192, -714 to -706, and -567 to -559 regions were respectively mutated. These data demonstrated that the SOX9 binding sites (Site-1, Site-3, and Site-4) are putative regulatory elements in the transcriptional activation of CAP2.

To further confirm that SOX9 can regulate the expression of CAP2, the results of western blot demonstrated that CAP2 expression in MKN45 and BGC823 cells transfected with SOX9 overexpression plasmid could notably upregulate the protein expression of CAP2. While silenced SOX9 expression by transfection of siSOX9 significantly downregulated CAP2 expression (*Figure 4D,E*). Next, western blot analysis revealed that overexpression of SOX9 enhanced the protein expression level of CAP2, and the effect was reversed by the siCAP2 transfection (*Figure 4F*). Moreover, we conducted a xenograft assay to determine the effects of SOX9 on CAP2-mediated tumor growth *in vivo*. Tumor xenograft results showed the effects that tumor volume and weight were significantly increased after transfection of SOX9 overexpression plasmid could be reversed by silenced CAP2 expression (*Figure 4G*). These above results suggested that SOX9 could play important roles in CAP2-mediated tumorigenesis in GC.

Discussion

Previously studies have indicated that CAP2 can regulate cellular actin dynamics to control cell migration and cell cycles (13). Overexpression of CAP2 can lead to tumor progression in various cancer types (14). Currently, it was reported that CAP2 was upregulated in breast cancer and was associated with patient survival, which could serve as a prognostic indicator for patients with breast cancer (11). In hepatocellular carcinoma, CAP2 was associated with cellular invasion and metastasis, and its high expression was significantly correlated with poor survival time (15). Moreover, CAP2 might play vital roles in the promotion of cell migration and proliferation of ovarian cancer, indicating that CAP2 could promote the progression of epithelial ovarian cancer (10). Additionally, CAP2 was significantly overexpressed in gliomas, and high CAP2 expression was notably related to the advanced stage (stage III and IV) (12). Furthermore, previous reports showed that CAP2 is overexpressed in malignant melanoma and its expression is linked to increase stepwise during melanoma progression (9). These above studies have demonstrated that CAP2 has been found to play a vital role in tumorigenesis. However, the mechanisms underlying CAP2 promotion of cancer metastasis remain largely unknown in GC.

In the present study, we identified one novel biomarker CAP2 from the GEO database (16), which might function as an oncogene in GC progression and associate with GC patients' prognosis. Subsequently, the expression level of CAP2 in GC tissues and cells was determined by western blot analysis. We further assessed the carcinogenic effects of CAP2 in GC, and our results revealed that the cell growth rate was markedly suppressed by CAP2 knockdown. Besides, by using colony formation assay and EdU assay, the results demonstrated that the number of colonies and the capability of DNA replication in GC cells were significantly decreased and inhibited by CAP2 knockdown. Furthermore, we found that knockdown of CAP2 could arrest cells in the G1 phase and play with the anti-apoptotic effect to regulate the survival of GC cells.

Various factors in the process of development are the key factors of tumorigenesis, including transcription factors (17). SOX transcription factors exert an important influence on tumor progression and metastasis (18). In addition, previous reports have established that as the high mobility group box transcription factor, SOX9 is overexpressed in GC (19), and associated with GC cell survival and promotes proliferation (20). Moreover, the molecular mechanisms for regulating the transcriptional activity of CAP2 by SOX9 to enhance GC cell proliferation have not been elucidated. In this study, we reported that SOX9 promoted the transcription of CAP2 through directly binding to its potential binding site. And SOX9 was demonstrated to be necessary for CAP2-

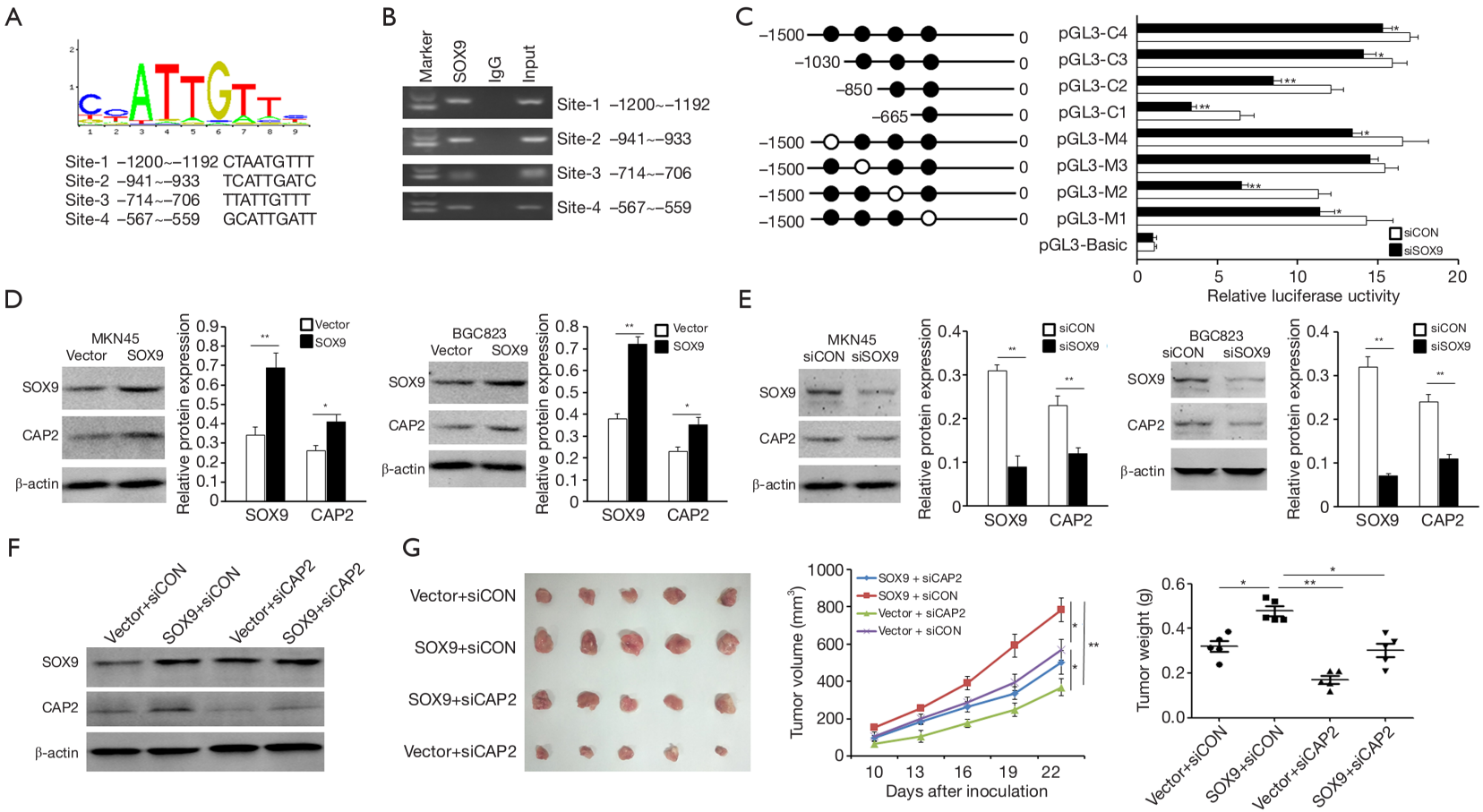

Figure 4 CAP2 is regulated directly by the transcription factor SOX9. (A) Location of the predicted SOX9-binding motif and sites in the promoter region of CAP2. (B) ChIP assay exhibited the direct binding of transcription factor SOX9 to the CAP2 promoter region in GC samples. (C) Sequential deletion and substitution mutation analyses demonstrated SOX9 binding sites in the promoter region of CAP2. Serially truncated and mutated CAP2 promoter constructs were cotransfected with siSOX9 into MKN45 cells. Then, the relative luciferase activities were measured. (D) and (E) After the transfection of the SOX9 overexpression plasmid or siSOX9 into the MKN45 and BGC823 cells, the SOX9 and CAP2 expression levels were determined by western blot. (F) Western blot detected the SOX9 and CAP2 expression in MKN45 cells. (G) Representative photographs of subcutaneous tumors from the nude mice by the treated MKN45 cells. Tumor xenograft results displayed the effects of tumor volume and weight after the different treatments. *, P<0.05; **, P<0.01.

mediated GC proliferation *in vitro* and *in vivo* experiments. The above findings provide strong evidence to support the fact that CAP2 can have a significant impact on the genesis and development of GC.

Conclusions

In summary, our results identified that CAP2 is dramatically overexpressed in GC and involved in GC tumorigenesis. The silencing of CAP2 expression could inhibit the ability of cellular growth *in vitro*. Additionally, the effects of CAP2-mediated promotion of GC cell proliferation were influenced by positive transcriptional regulation of SOX9. So, our results not only provide novel insights into the precise molecular mechanism of CAP2 in GC tumorigenesis but also facilitate the development of future therapeutic strategies for GC.

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Footnote

Reporting Checklist: The authors have completed the ARRIVE reporting checklist. Available at http://dx.doi.org/10.21037/jgo-20-234

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at: http://dx.doi.org/10.21037/jgo-20-234). The authors have no conflicts of interest to declare.

Ethical Statement: 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 study was conducted in accordance with the Declaration of Helsinki (as revised in 2013), and was approved by Ethics the Committee of Affiliated Hospital 2 of Nantong University (ID: 2020KT042). Informed consent was provided by all participants. Experiments were performed under a project license (No. 2020KT042) granted by institutional/regional/national ethics/committee/ethics board of Affiliated Hospital 2 of Nantong University, in compliance with institutional guidelines for the care and use of animals.

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