FOXK2 is highly expressed in gastric carcinoma, and facilitates cells proliferation through transcriptional inhibition of CHEK2 and promotes metastasis

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Abstract: FOXK2, as a transcription factor, plays crucial function in multiple cancers, but its role in gastric carcinoma (GC) is still unknown. We aim to evaluate the function of FOXK2 in GC. In this study, we first performed qRT-PCR and western blotting to detect the expression of FOXK2 in GC. The results indicated that FOXK2 was highly expressed in GC. Moreover, high expression of FOXK2 was positively correlated with tumor size, clinical stages, metastasis and poor prognosis. Several functional experiments, including colony formation assay and CCK-8 assay, revealed that FOXK2 can promote cell proliferation in GC. In addition, cell cycle analysis demonstrated FOXK2 also regulated cell cycle through regulation of CHEK2. Luciferase reporter analysis and ChIP analysis confirmed that FOXK2 transcription suppressed CHEK2. Western blot and qRT-PCR showed FOXK2 promoted EMT, high expression of FOXK2 was correlated with loss of E-cadherin expression, and gain of N-cadherin and Vimentin expression. Our work showed as an oncogene, FOXK2 facilitated cell proliferation and metastasis through regulation of cell cycle and EMT in GC, and we provided FOXK2 as a novel molecular therapy target.

Keywords: FOXK2, proliferation, metastasis, gastric cancer

Introduction

Gastric cancer (GC), a typical epithelium-originated malignant cancer, has become the second most common cancer in the world [1]. Over the past decades, although the diagnosis and treatment methods have been developed, there are almost 50% of gastric cancer patients finally developed distant metastasis after surgical treatment [2]. The distant metastasis is the main cause of death in more than 90% of gastric carcinoma patients [3]. Metastasis is a complex biological program that starts with local invasion by cancer cells, and then continues with migration to distant tissues. However, the detail molecular mechanisms of gastric carcinoma are still unknown.

The forkhead transcription factors family is highly evolutionarily conserved [4, 5]. In human, there are almost 40 forkhead transcription factors. The character of forkhead transcription factors family is a forkhead winged helix DNA binding domain. According to overall sequence conservation and other additional domains, there are multiple subfamilies, including FOXO, FOXK and so on. FOX family plays a crucial function in several cellular processes, such as cell cycle, metastasis and apoptosis [5, 6].

FOXK1 and FOXK2 belongs to FOXK family, they have a FHA domain which other FOX subfamily don’t contain. Forkhead box K2 (FOXK2) was first discovered as a regulator of IL-2 transcription, where FOXK2 serves as a transcriptional inhibitor [7]. FOXK2 has been reported to regulate a wide range of cellular processes, including cell cycle, DNA repair and survival [8, 9]. Several previous works reveal that FOXK2 is phosphorylated by the CDK1/Cyclin B kinase complex which regulates FOXK2 stability and activity [10]. During cell division, FOXK2 also interacts with AP-1, and facilitates the binding of AP-1 to chromatin, thereby mediates transcriptional activation [10, 11]. FOXK2 also facilitates cell survival and activates Wnt signal by...
enhancing DVL nuclear translocation in colorectal carcinoma [12, 13]. It also interacts with BRCA1/BARD1 and promotes the degradation of ERα in breast carcinoma, leading to cellular suppression [14]. Whereas, the function and molecular mechanism of FOXK2 in gastric carcinoma are still largely unknown.

Epithelial-mesenchymal transition (EMT) is a main cause of cancer metastasis. The main character of EMT is that epithelial cells switch to mesenchymal cells. The epithelial marker proteins, including E-cadherin, is significant decreased, and the mesenchymal markers, including N-cadherin, is obviously increased [15-17]. Multiple evidence reveals that EMT plays a key function during embryonic development, tumor invasion, metastasis, senescence resistance and apoptosis [18-20]. EMT is regard as a sign of invasion and metastasis of cancer [18, 21, 22]. The relationship between EMT and FOXK2 in gastric cancer still unknown.

Materials and methods

Patients and samples

The Clinical Research Ethics Committee of The First Affiliated Hospital of University of South China has approved our human tissue study, and all participants have known and provided informed consent. 52 pairs’ gastric carcinoma tissue samples and adjacent normal tissues were obtained from The First Affiliated Hospital of University of South China during the period 2014 to 2016.

Cell culture

Gastric cell lines, CTC-141 and MNK45 cells and the normal bronchial epithelial cell line (GES-1) were purchased from American Type Culture Collection (ATCC). Cells were grown in RPMI-1640 medium which contain 10% fetal bovine serum (FBS) and 1% Penicillin-Streptomycin at 37°C with 5% CO2.

Cell transfection

FOXK2 small interfering RNA (siRNA) was purchased from Sigma. According to the manuscript’s protocol, lipofectamine RNAiMAX (Invitrogen, USA) was used to transfect 25 nM siRNA into cells, after transfection for 48 h, cells were collected for further experiments.

qRT-PCR

Total RNA was isolated with TRizol reagent (Invitrogen, Carlsbad, CA, USA) followed by the manufacturer’s instruction and next was resolved in diethylpyrocarbonate (DEPC)-treated water. The cDNA was synthesized by RevertAid First Strand cDNA Synthesis Kit (Thermo Scientific Fermentas, USA). Finally, FastStart Universal SYBR Green Master (Roche, USA) was utilized for qRT-PCR. GAPDH was used as an internal control and calculated as the fold change of gene by using the 2ΔΔCt methodology. The primers as followed: FOXK2 forward primer 5’-CAGTCTTTAACGCTGGCAG-3’; reverse primer 5’-GCTCTACCTTTCCATTTGACTTCC-3’; GAPDH forward primer 5’-TCTGATTTGGTCGTATTTGG-3’; reverse primer 5’-CTGGTTAACCCATGGATTGAGGGTG-3’; E-cadherin forward primer 5’-AGATGATTCTTGGAGAAGG-3’; α-catenin forward primer 5’-AACACACAAGTAAACTCGGC-3’; reverse primer 5’-ATGGATTCTTGGACAGACG-3’; N-cadherin forward primer 5’-AAAGACCTCTGAACTATGGT-3’; reverse primer 5’-GGATTGTCATTGACATCTGG-3’; Vimentin forward primer 5’-TAAAGGAACCAATGAGTCCC-3’; reverse primer 5’-AGTGAATCCAGATGGAGAAG-3’; CHEK2 forward primer 5’-TGTTGACTGCCTTGAATTTCC-3’; reverse primer 5’-ACCACTGATACCCCTGAAAC-3’.

Western blotting

Whole cells were lysed in RIPA buffer (1% NP-40, 50 mM Tris-HCl PH 7.4, 150 mM NaCl, 1 mM deoxycholic acid, 1 mM phenylmethylsulfonfyl fluoride, 1 mM EDTA and 1 μg/ml leupeptin) containing a phosphatase inhibitors and protease inhibitors (Pierce, USA). Protein concentration was measured by a BCA Protein Assay Kit (Pierce, USA). Equal amounts of protein sample (40-60 μg) were separated via 10% SDS-PAGE gel. Subsequently, Bio-Rad semidry transfer system was used to transfer the protein to Polyvinylidene Fluoride (PVDF) membrane (Millipore, USA). The membranes were blocking by 5% non-fat milk and washed by PBST solution, follow by incubated with indicated antibody at 4°C overnight. The antibodies as followed: FOXK2 (1:2000; Abcam, Cambridge, MA, USA;
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Figure 1. FOXK2 is high expressed in GC and correlates with poor prognosis. A. Total mRNA was extracted from gastric cancer tissues and normal tissues, respectively. qRT-PCR was performed to detect the relative mRNA level of FOXK2 in gastric cancer tissues and normal tissues. B. Whole protein was lysed from gastric cancer tissues and normal tissues, respectively. Western blotting was performed to detect the relative protein level of FOXK2 in gastric cancer tissues and normal tissues. Quantification of the protein level was measured as FOXK2/β-actin ratio. C. Survival curve was analyzed by Kaplan-Meier method. High expression of FOXK2 was correlated with poor prognosis. D. Total mRNA was extracted from GES-1, CTC-141 and MNK45 cells, respectively. qRT-PCR was performed to detect the relative mRNA level of FOXK2 in normal bronchial epithelial cell line and gastric carcinoma cell lines. E. Whole protein was lysed from GES-1, CTC-141 and MNK45 cells, respectively. Western blotting was performed to detect the relative protein level of FOXK2 in normal bronchial epithelial cell line and gastric carcinoma cell lines. Quantification of the protein level was measured as FOXK2/β-actin ratio.

Transwell assays

To measure cell invasion, transwell chamber (Corning Costar, USA) was coated with Matrigel (BD Biosciences, USA). In brief, almost $3 \times 10^4$ cells were placed in transwell chamber with 300 μl serum-free RPMI-1640 medium, and then transwell chambers were transferred to wells, which contained 500 μl RPMI-1640 medium supplemented with 10% FBS. After incubation cells for 24 h, the cells on the upper membrane were removed by cotton swab. Invading cells were fixed in 4% paraformaldehyde, subsequently, cells were stained with 0.5% crystal violet. Finally, the number of invasion cells was counted under a light microscope.

Wound healing assays

To determine the effect of FOXK2 on cell migration, wound healing assay was performed. Briefly, approximately $3 \times 10^4$ cells were placed in six-well plates and transfected with vector, FOXK2 or SCR, siFOXK2, respectively. When cells density was almost 100%, cells were scratched with 20 μl peptide tip. Then detached cells were removed by cold-PBS solution. Cell migration ability was evaluated by the ratio of wounded area at time points of 48 h and 0 h after the scratch.

Colony formation assay

To detect the function of FOXK2 on cell proliferation, colony formation assay was performed. In brief, CTC-141 and MNK45 cells were transfected with empty vector, FOXK2, Scramble si-RNA (SCR) or siFOXK2 for 48 h, next 5,000 cells were placed into 6-well plates and cultured with serum-free RPMI-1640 medium for 14 days. Next, cells were fixed with methanol and stained with 0.5% crystal violet. Finally, the number of colonies were counted under a light microscope.

Cell viability assay

Cell Counting Kit-8 (Sigma, USA) was used to measure the relative cell growth in GC cells.
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| Table 1. Clinic pathologic variables in 52 gastric carcinoma patients |
|-----------------------------|-----------------------------|-----------------------------|
| Variables                  | No. (n=52)                  | FOXK2 protein expression    | P value |
|                            |                             | Low (n=18)                  | High (n=34) |
| Gender                     |                             |                             |           |
| Male                       | 28 (53.8%)                  | 10 (55.6%)                  | 18 (52.9%) | 0.857 |
| Female                     | 24 (46.2%)                  | 8 (44.4%)                   | 16 (47.1%) |
| Age                        |                             |                             |           |
| < 60                       | 21 (40.4%)                  | 9 (50%)                     | 12 (35.3%) | 0.304 |
| ≥60                        | 31 (59.6%)                  | 9 (50%)                     | 22 (64.7%) |
| Tumor Size (diameter)      |                             |                             |           |
| Small (≤3 cm)              | 20 (38.5%)                  | 11 (61.1%)                  | 9 (26.5%) | 0.015 |
| Large (≥3 cm)              | 32 (61.5%)                  | 7 (38.9%)                   | 25 (73.5%) |
| Pathological stage         |                             |                             |           |
| I-II                       | 27 (51.9%)                  | 13 (72.2%)                  | 14 (41.2%) | 0.033 |
| III-IV                     | 25 (48.1%)                  | 5 (27.8%)                   | 20 (58.8%) |
| Drink status               |                             |                             |           |
| Yes                        | 23 (44.2%)                  | 8 (44.4%)                   | 15 (44.1%) | 0.982 |
| No                         | 29 (55.8%)                  | 10 (55.6%)                  | 19 (55.9%) |
| Metastasis                 |                             |                             |           |
| Yes                        | 29 (55.8%)                  | 6 (33.3%)                   | 23 (67.6%) | 0.018 |
| No                         | 23 (44.2%)                  | 12 (66.7%)                  | 11 (32.4%) |

Chromatin immuno-precipitation (ChIP)

The ChIP analysis was performed according to previously described [10]. In brief, EZ ChIP Kit (Millipore, USA) was used to perform ChIP analysis, cells were lysed and sonicated until the fragments of chromatin were from almost 200 to 1000 bp. Subsequently, FOXK2 antibody was utilized to immunoprecipitate chromatin. After collected and purified chromatin fragments, target genes were amplified through specific primer. The negative control was the normal IgG group.

Statistical analysis

Each independent experiment was performed at least three times. Statistical analysis was performed by SPSS19.0 software. The factors associated with OS, including age, gender, smoking, tumor size, metastasis, tumor stage and FOXK2 expression, were analyzed by uni-variant and multi-variant analyses. Variables were adopted for their prognostic significance (p < 0.05) in univariate analysis using forward, stepwise selection (forward likelihood ratio), multivariate analysis was analyzed by a Cox proportional hazards regression model. Survival curve was calculated by the Kaplan-Meier method, and then used log-rank test to analyze. The correlation between FOXK2 and the clinic pathological features of GC was analyzed by Spearman test. Student’s t-test was used to analyze the differences between two groups, ANOVA followed by Tukey’s was used to assess the differences between multiple groups. *P < 0.05 and **P < 0.01 was regarded as significant.

Result

FOXK2 is high expressed in GC and correlates with poor prognosis

In order to decipher the function of FOXK2 in GC, we first collected 52 pairs of GC tissue samples and adjacent normal tissue samples, and detected the mRNA and protein levels of...
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FOXK2 by qRT-PCR and western blotting, respectively. We found that FOXK2 was up-regulated in GC tissues compared with adjacent normal tissues (Figure 1A and 1B). To further investigate the clinical significance of FOXK2 in GC, we detected the relationship between FOXK2 expression and clinicopathological variables. As shown in Table 1, high expression of FOXK2 was closely correlated with tumor size, clinical stages and metastasis. However, there were no correlation between FOXK2 and gender, age and drinking (p > 0.05). Next, we divided the 52 patients into two groups: the mean value of FOXK2 content in tumor cells as the standard, the higher values than the standard values as high expression, the lower values than the standard values as low expression, those with a lower expression of FOXK2 (FOXK2low) and those with a higher expression of FOXK2 (FOXK2high). Univariate analysis showed that tumor size (≥3 cm, p < 0.001), advanced tumor stage (p < 0.001), metastasis (p < 0.001) and high FOXK2 expression (p=0.005) were associated with overall survival (OS) (Table 2). Moreover, we performed multivariate Cox proportional hazards model to analysis high FOXK2 expression was an independent prognostic predictor for OS (p=0.007, Figure 1C, Table 2). In addition, we determined the expression of FOXK2 in GC cell lines, CTC-141 and MNK45. The normal bronchial epithelial cell lines (GES-1) was used to as a control group. As shown in Figure 1D and 1E, compared with GES-1, FOXK2 was highly expressed in CTC-141 and MNK45 cell lines. Base on above works, we hypothesize FOXK2 might play a crucial function in GC.

Up-regulation of FOXK2 promotes the migration of GC cells

Metastasis always leads to poor prognosis in multiple cancers; we then explored the function of FOXK2 in GC metastasis. We first over-expressed or knocked down FOXK2 in CTC-141 cells. The protein and mRNA levels of FOXK2 were determined by western blotting and qRT-PCR, respectively. As shown in Figure 2A, we chose siFOXK2#1 for the further investigation. Subsequently, we performed wound healing assay in CTC-141 cells, the results showed that over-expression of FOXK2 increased the distance of wound healing, however, FOXK2 inhibition significantly decreased the distance of wound healing (Figure 2B). Moreover, transwell assay also confirmed that when we over-expressed FOXK2 in CTC-141 cells, the number of migrated cells was increased, compared with control groups. On the contrary, when we knocked down FOXK2 in CTC-141 cells, the number of migrated cells was decreased (Figure 2C). EMT has been found to play a key role during cancer cells metastasis. Therefore, we next investigated whether the effect of FOXK2 on GC cells migration was correlated with EMT. To assess our hypothesis, we used qRT-PCR and western blotting analysis. As shown in Figure 2D, we found that the ectopic expression of FOXK2 reduced the expression of epithelial markers, including E-cadherin and α-catenin, and the mesenchymal markers were increased, such as N-cadherin and vimentin. On the contrary, opposite results were observed when FOXK2 was silenced. To sum up, our works suggested that FOXK2 suppressed GC cells metastasis through partially reversing its EMT.

FOXK2 promotes GC cells proliferation through regulating cell cycle

Since high expression of FOXK2 was associated with tumor size, next we detected whether FOXK2 regulated GC cell proliferation. We performed colony formation assay and CCK-8 assay to determine the function of FOXK2 in cell proliferation. Colony formation analysis

Table 2. Univariate and multivariate analysis of factors associated with OS

<table>
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<tr>
<th>Variables</th>
<th>Univariate analysis</th>
<th>p value</th>
<th>Multivariate analysis</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (≥60 versus &lt; 60)</td>
<td>1.698 (0.882-3.267)</td>
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<td>Gender (female versus male)</td>
<td>0.695 (0.403-1.198)</td>
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<td>Drinking status (no versus yes)</td>
<td>0.610 (0.362-1.028)</td>
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<tr>
<td>Tumor size (≥3 cm versus &lt; 3 cm)</td>
<td>2.864 (1.708-4.802)</td>
<td>&lt; 0.001</td>
<td>2.467 (1.333-4.600)</td>
<td>0.004</td>
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<tr>
<td>Metastasis (yes versus no)</td>
<td>2.989 (1.730-5.166)</td>
<td>&lt; 0.001</td>
<td>2.244 (1.247-4.040)</td>
<td>0.007</td>
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<tr>
<td>Tumor stage (III-IV versus I-II)</td>
<td>3.285 (1.952-5.530)</td>
<td>&lt; 0.001</td>
<td>1.031 (0.535-1.987)</td>
<td>0.927</td>
</tr>
<tr>
<td>FOXK2 expression (high versus low)</td>
<td>2.854 (1.622-5.022)</td>
<td>0.005</td>
<td>2.319 (1.297-4.147)</td>
<td>0.032</td>
</tr>
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</table>
FIGURE 2. Up-regulation of FOXK2 promotes the migration of GC cells. A. CTC-14 cells were transfected with vector, FLAG-FOXK2 or scramble siRNA (SCR), FOXK2 siRNA (siFOXK2). After transfection 48 h, total mRNA and whole protein were extracted, then qRT-PCR and western blotting were performed to detect the relative mRNA level and protein level of FOXK2, respectively. B. CTC-14 cells were transfected with vector, FLAG-FOXK2 or scramble siRNA (SCR), FOXK2 siRNA (siFOXK2). After transfection 48 h, cells were draw with a wound by a 200 μl pipette tip. The wound distance was measured at different time point (0 h, 24 h). The chart indicated the ratio of wound closure. C. CTC-14 cells were transfected with vector, FLAG-FOXK2 or scramble siRNA (SCR), FOXK2 siRNA (siFOXK2). After transfection 48 h, transwell analysis was used to determine the effect of FOXK2 on metastasis. The chart indicated the relative invaded cells. D. CTC-14 cells were transfected with vector, FLAG-FOXK2 or scramble siRNA (SCR), FOXK2 siRNA (siFOXK2). After transfection 48 h, total mRNA and whole protein were extracted, then qRT-PCR and western blotting were performed to detect the relative mRNA level and protein level of EMT associated protein, respectively.

Discussion

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suggested that over-expression of FOXK2 significantly promoted colony formation, whereas FOXK2 inhibition suppressed colony formation in CTC-141 cells (Figure 3A). The similar results were observed in MNK45 cells (Figure 3A). CCK-8 assay also revealed that ectopic expression of FOXK2 increased the proliferation rate, however, FOXK2 inhibition decreased cells proliferation rate in CTC-141 and MNK45 cells (Figure 3B). To further decipher the detail mechanism, we explored cell cycle by flow cytometry. The results demonstrated that ectopic expression of FOXK2 increased the percentage of S+G2/M phase, whereas FOXK2 inhibition arrested cells in the G0/G1 cells (Figure 3C). Our works reveal that FOXK2 regulates the proliferation of GC cells through regulation of cell cycle.

FOXK2 transcription suppressed CHEK2 in CTC-141 cells

To further explore the detail mechanism of FOXK2 on cell cycle, we next detect whether FOXK2 regulated cell cycle associated proteins, such as CHEK2, cyclin D1 and cyclin E1. We found that the mRNA and protein levels of CHEK2 were increased when FOXK2 was depleted, whereas the mRNA and protein levels of CHEK2 were decreased when FOXK2 was over-expressed (Figure 4A and 4B). So we assumed that FOXK2 might transcriptional suppressed CHEK2. To verify our hypothesis, we performed ChiP assay and luciferase reporter assay. The ChiP assay revealed that FOXK2 bound the promoter region of CHEK2, whereas FOXK2 didn’t bind the promoter region of CCND1 and CCNE1 (Figure 4C). The luciferase reporter assay suggested that CHEK2 was transcriptional suppressed by FOXK2 (Figure 4D).

FOXX2 has been reported to play key functions in colorectal cancer [12, 23]. In the present
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In this study, by western blotting and qRT-PCR, we observed both protein and mRNA levels of FOXK2 were obviously up-regulated in gastric carcinoma tissues compared with normal tissues. Figure 3. FOXK2 promotes GC cells proliferation through regulation cell cycle. A. CTC-14 and MNK45 cells were transfected with vector, FLAG-FOXK2 or scramble siRNA (SCR), FOXK2 siRNA (siFOXK2). After transfection 48 h, 3 × 10^3 cells were placed on the 6-well plates and performed colony formation assay. The chart indicated the relative colony number. B. CTC-14 and MNK45 cells were transfected with vector, FLAG-FOXK2 or scramble siRNA (SCR), FOXK2 siRNA (siFOXK2). After transfection 48 h, 2 × 10^3 cells were placed on the 96-well plates and performed CCK-8 assay. The chart indicated the absorbance at different time point. C. CTC-14 and MNK45 cells were transfected with vector, FLAG-FOXK2 or scramble siRNA (SCR), FOXK2 siRNA (siFOXK2). After transfection 48 h, cells were collected, and cell cycle was detected by flow cytometer. The chart indicated the percentage of cells in each phase.
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Several functional experiments, including colonies formation analysis and CCK-8 assay, indicated that FOXK2 facilitated cell proliferation, which was consistent with previous reports [13]. CHEK2 plays a key function in DNA damage pathway [24-26]. During DNA damage repair, CHEK2 was found to interact with several proteins. Ataxia telangiectasia mutated (ATM) could activate CHEK2 and then CHEK2 phosphorylates many substrates, such as Cdc25A, BRCA1, Cdc25C and p53, leading to cell apoptosis, cell cycle arrest and DNA repair [26]. Here, we found FOXK2 regulated CHEK2, subsequently, we then constructed the luciferase reporter and found that CHEK2 was transcriptional suppressed by FOXK2.

Previous study indicated that FOXK2 directly interacted with the promoter region of FOX-O3a, and interacted with other transcription co-repressor complexes, including REST/Co-REST, SIN3A and NuRD to sensitize cells to drug resistance and inhibit hypoxia response in breast carcinoma [27, 28]. Moreover, several study indicated that SIN3A and NuRD complex were correlated with EMT in cancer [29-31]. Here, we found FOXK2 promoted EMT in gastric carcinoma. But the detail mechanism was still unknown. FOXK2 works as a transcriptional factor, it might promote EMT through transcriptional regulating some EMT associated gene, such as E-cadherin.

In conclusion, our work suggest that FOXK2 transcriptional suppresses CHEK2, thereby regulates cell cycle in gastric carcinoma. Moreover, FOXK2 also promotes cell metastasis through regulation of EMT. Therefore, we provide FOXK2 serves as a potential target for gastric carcinoma and further work is desirable. For instance,
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the detail molecular mechanism of FOXK2 facilitating EMT still needs to be investigated.

Disclosure of conflict of interest

None.

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