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# FBXO17 promotes malignant progression of hepatocellular carcinoma by activating wnt/β-catenin pathway

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**Abstract. – OBJECTIVE: This study was to investigate the expression of FBXO17 in hepatocellular carcinoma (HCC) and its relationship with clinical HCC features and patient prognosis.**

**PATIENTS AND METHODS: The expression of FBXO17 at mRNA level and protein level in tumor tissues and paracancerous tissues of 45 patients with HCC was respectively detected by quantitative Real Time-Polymerase Chain Reaction (qRT-PCR) and Western blot. Besides, FBXO17 expression and its pathological characteristics of HCC, as well as the prognosis of patients, were also analyzed. Then, the expression level of FBXO17 in HCC cell lines was further verified using qRT-PCR assay. In addition, FBXO17 overexpression and knockdown models were constructed using lentivirus in HCC cell lines including Bel-7402 and HepG2. Cell counting kit-8 (CCK-8), 5-Ethynyl-2'-deoxyuridine (EDU), cell clone experiment, flow cytometry, and transwell assay were used to explore the effect of FBXO17 on the biological function of HCC cells. Finally, whether FBXO17 could exert its biological characteristics through wnt/β-catenin pathway was determined.**

**RESULTS: Results showed that FBXO17 expression in tumor tissues of HCC patients was markedly higher than that in adjacent tissues. Meanwhile, compared with patients with low FBXO17 expression, the pathological grade was higher and the overall survival rate was lower in patients with high expressed FBXO17. In vitro experiments showed that the cell proliferation and metastasis ability in the Anti-FBXO17 group was markedly decreased, and the apoptosis was significantly enhanced compared with the NC group. In contrast, overexpression of FBXO17 markedly increased cell proliferation and metastasis ability while decreased cell apoptosis. Finally, Western blot results indicated that silencing FBXO17 might function through downregulating the expression of proteins in wnt/β-catenin pathway such as c-Myc, MMP-9, and MMP-2 while upregulating GSK-3β level, thereby promoting the malignant progression of HCC.**

**CONCLUSIONS: FBXO17 was significantly increased in tumor tissues of HCC patients, which was significantly associated with pathological stage and poor prognosis of these patients. In addition, FBXO17 might promote the malignant progression of HCC by inhibiting wnt/β-catenin pathway.**

*Key Words:*
FBXO17, Wnt/β-catenin pathway, Hepatocellular carcinoma, Malignant progression.

## Introduction

As one of the most common malignant tumors in the world, primary hepatocellular carcinoma (HCC) is also the third leading cause of death in cancer[1,2]. The incidence of HCC worldwide averages about 5.5-14.9 per 100,000 people, but the incidence of HCC in Africa and Southeast Asia is as high as 100/100,000[3,4]. Previous studies[5-7] have concluded that complex interactions between viral, host and environmental factors ultimately lead to the occurrence and development of HCC. The hepatitis B virus (HBV) core protein is a multifunctional protein produced by the virus, which can transactivate a variety of transcription factors and induce abnormalities in certain important cell signal transduction and transcription factor. It may lead to imbalance of cell proliferation and differentiation and weaken the immune defense function, which is conducive to the establish-

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ment of chronic persistent infection and ultimately participates in the incidence of HCC[7]. The long-term survival rate of patients with liver cancer is extremely low. Current treatment methods include surgery, chemotherapy, targeted therapy, and symptomatic treatment. Among these treatment methods, only surgical resection may cure liver cancer[8-10]. Unfortunately, only 10-15% of patients have the possibility of receiving surgery, and most patients have lost the opportunity when diagnosed with HCC[10]. Since the pathogenesis of HCC is not clear at present, in-depth study of the pathogenesis of HCC, searching for molecular markers of HCC with good specificity and sensitivity, and finding effective therapeutic targets are the current priority in liver cancer research[11,12].

FBXO17, a negative regulator of glycogen synthase kinase-3β (GSK-3β), was identified by polyubiquitination and targeting of kinases to proteasomal degradation[13-15]. The wnt/β-catenin pathway is an evolutionarily highly conserved signaling pathway with high homology from lower organisms to higher mammals[11,16]. Wnt signaling pathway participate in varieties of normal human physiological processes such as embryonic development, cell adhesion, proliferation, regeneration, differentiation, etc. The abnormal regulation of its pathway is also closely in relation with the occurrence and development of various human tumors[16]. Without stimulation of wnt, the wnt/β-catenin pathway is inactivated. β-catenin is the main effector molecule of this pathway, and its serine/threonine residue is phosphorylated by the protein degradation complex composed of GSK-3β, Axin, APC, etc., which is finally degraded by the proteasome[16,17]. When the pathway is activated, the wnt molecule binds to the Frizzled receptor and the LRP5/6 co-receptor to phosphorylate the unkempt protein. And then, the phosphorylated unkempt protein can inhibit GSK-3β activity and prevent phosphorylation of β-catenin, which accumulates in the cytosol and then transfers into the nucleus to bind to Tcf/Lef to initiate the expression of downstream genes including c-myc, cyclin D1, MMP-9, and MMP-2[17,18].

However, there are no relevant research reports on whether and how FBXO17 can activate wnt/β-catenin pathway. Therefore, we intended to investigate the biological behavior of FBXO17 and the activation of wnt/β-catenin pathway in HCC by *in vitro* FBXO17 overexpression and knockdown cell model, and to further explore the underlying mechanism of FBXO17 function in the molecular pathogenesis of HCC.

## Patients and Methods

### Patients and HCC Samples

Forty-five cases of HCC tumor tissue specimens and adjacent tissues were obtained from specimens of biopsy or surgical resection of general surgery and oncology in our hospital and stored in a refrigerator at -80°C. The 45 patients with hepatocellular carcinoma were 64.2 (56.3-78.4) years old in average, ranging from 30 to 78 years old. All cases were diagnosed by two senior directors of pathology and the results were accurately evaluated. This study was approved by the Ethics Committee of Liaocheng People's Hospital. The signed written informed consents were obtained from all participants before the study.

### Cell Lines and Reagents

Six human HCC cell lines (MHCC88H, SMMC-722, Bel-7402, HepG2, Hep3B, Huh7) and one human normal liver cell line (LO2) were purchased from American Type Culture Collection (ATCC; Manassas, VA, USA). Cells were cultured in a Dulbecco's Modified Eagle's Medium (DMEM) high glucose medium (Gibco, Rockville, MD, USA) containing 10% fetal bovine serum (FBS; Gibco, Rockville, MD, USA). All cells were cultured in an incubator with 5% $CO_2$ at 37°C. In addition, cells were passaged with 1% trypsin when grown to 80%-90% of confluence.

### Transfection

The negative control (NC or Anti-NC) and FBXO17 (FBXO17 or anti-FBXO17) lentiviral sequence were purchased from Shanghai Jima Company (Shanghai, China). Cells were seeded in 6-well plates, and then, lentiviral transfection was performed according to the instructions. Cells were harvested for further experiments 48 hours later.

### Cell Counting Kit-8 (CCK-8) Assay

After 48 h of transfection, cells were collected and seeded into 96-well plates at 2000 cells per well. After cultured for 24 h, 48 h, 72 h, and 96 h, the cells were added with CCK-8 reagent (Dojindo, Molecular Technologics, Kumamoto, Japan) and incubated for 2 hours; then, the optical density (OD) value was measured at 490 nm using a microplate reader.

### Colony Formation Assay

After transfection for 48 h, cells were digested and 200 cells were seeded in each well of a 6-well

plate and cultured for 2 weeks. The medium was changed after one week and then twice a week. When cloned after 2 weeks, the cells were fixed in 2 ml of methanol for 20 minutes and then aspirated and stained with 0.1% crystal violet staining solution for 20 minutes. After washed 3 times with phosphate-buffered saline (PBS), the cells were photographed under a light-selective environment.

### EdU (5-Ethynyl-2′-Deoxyuridine) Proliferation Assay

To demonstrate the effect of FBXO17 on cell proliferation, the EDU proliferation assay (RiboBio, Guangzhou, China) was performed. After transfection for 24 h, the cells were incubated with 45 μm EDU for 2 h, then stained with AdoLo and DAPI (4',6-diamidino-2-phenylindole), and the number of EDU-positive cells was analyzed using a fluorescence microscopy. The display rate of EDU positive was shown as the ratio of the number of EDU positive cells to the total DAPI chromogenic cells (blue cells).

### Flow Cytometry

The bind of Annexin V-FITC (Merck, Billerica, MA, USA) and Propidium Iodide (PI) was used to detect cell apoptosis by flow cytometry. Cells were adjusted to about $1\times10^6$ cells/mL and gently resuspended with 0.5 mL of pre-cooled 1× binding buffer, then 1.25 Ul Annexin V-FITC was added. After incubated for 15 min in the dark, cells were centrifuged, resuspended with 0.5 mL of pre-cooled l×binding buffer, and then 10 Ul PI was added. Next, flow cytometry was applied to analyze the cell samples immediately in the dark (BD, Franklin Lakes, NJ, USA).

### Transwell Cell Migration and Invasion Assay

Cells were seeded into a 6-well plate with the cell density adjusted to $3.0\times10^5$/mL and liposomal transfection experiment was performed when cell density reached 80%. Positive clones were selected for expanded culture for subsequent transwell experiments. Transwell chamber containing Matrigel and no Matrigel was placed in culture plate. 200 μL of cell suspension was added to the upper chamber, and 500 μL of medium was added to the lower chamber. After 48 hours, the chamber was removed, fixed with 4% paraformaldehyde for 30 minutes, stained with the crystal violet for 15 minutes and then washed with the PBS. The inner surface of the basement membrane of the chamber was carefully cleaned to remove the inner layer cells. The transmembrane cells stained in the outer layer of the basement membrane of the chamber were observed under the microscope, and 5 fields of view were randomly selected for counting.

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

TRIzol (Invitrogen, Carlsbad, CA, USA) was used to extract total RNA. The initially extracted RNA was treated with DNase I to remove genomic DNA and repurify the RNA. RNA reverse transcription was performed according to the Prime Script Reverse Transcription Kit (TaKaRa, Otsu, Shiga, Japan) instructions while Real-Time PCR was performed according to the SYBR Premix kit instructions using the StepOne Real-time PCR System. Primers were listed below. FBXO17: f: 5'-TGGGGAAGATTGGGAAAGGC-3', r: 5'-TCGCCCATTGGCTACATCTC-3'; β-actin: f: 5'-CCTGGCACCAGCACAATT-3', r: 5'- TGCCGTAGGTGTCCCTTTG-3'. Data analysis was performed using ABI Step One software (Applied Biosystems, Foster City, CA, USA).

### Western Blot Assay

The transfected cells were lysed while total protein concentration was determined. Western blot analysis was performed according to standard procedures. The primary antibodies were FBXO17, β-catenin, GSK-3β, c-Myc, cyclin D1, MMP-2, MMP-9, and glyceraldehyde 3-phosphate dehydrogenase (GAPDH), and the secondary antibodies were anti-mouse and anti-rabbit, which were all purchased from Cell Signaling Technology (Danvers, MA, USA).

### Statistical Analysis

Statistical analysis was performed using the GraphPad Prism 5 V5.01 software (La Jolla, CA, USA). Statistical differences between the two groups were analyzed using the Student's *t*-test, and one-way ANOVA for more groups followed by the Post-Hoc test (Least Significant Difference), respectively. Independent experiments were repeated at least three times for each experiment and data were expressed as mean ± standard deviation ($\bar{x}\pm s$). $p<0.05$ was considered statistically significant.

## Results

### Expression of FBXO17 in HCC

To determine the difference in the expression levels of FBXO17 in tumor tissues and paracan-

cerous tissues of patients with HCC, we detected FBX017 expression and performed qRT-PCR and Western blot analysis. The results displayed that FBXO17 expression was higher in tumor tissues than in paracancerous tissues in HCC patients (Figure 1A, B), suggesting FBXO17 might play a role as a cancer-promoting gene in HCC. At the same time, we also detected the FBXO17 expression in common HCC cell lines by qRT-PCR, which showed that FBXO17 had the highest expression in Bel-7402 and HepG2 cell lines, so we selected these two cell lines for follow-up study (Figure 1C).

According to the FBXO17 mRNA levels in tumor tissues and paracancerous tissues of 45 pairs of HCC patients, patients were divided into high FBXO17 expression group and low FBXO17 group, with the number of each group counted. Chi-square test was performed to analyze the relationship between the expression level of FBXO17 mRNA and age, clinical stage, lymph node or distant metastasis of HCC patients. Table I showed that high expression of FBXO17 was positively in correlation with clinical stage of HCC. In addition, in order to explore the relationship between the FBXO17 expression and the prognosis of patients with HCC, we collected relevant follow-up data. Kaplan-Meier survival curves suggested that high expression of FBXO17 was significantly in association with poor prognosis of HCC, and the higher the level of FBXO17, the worse the prognosis of patients with HCC ($p<0.05$; Figure 1D).

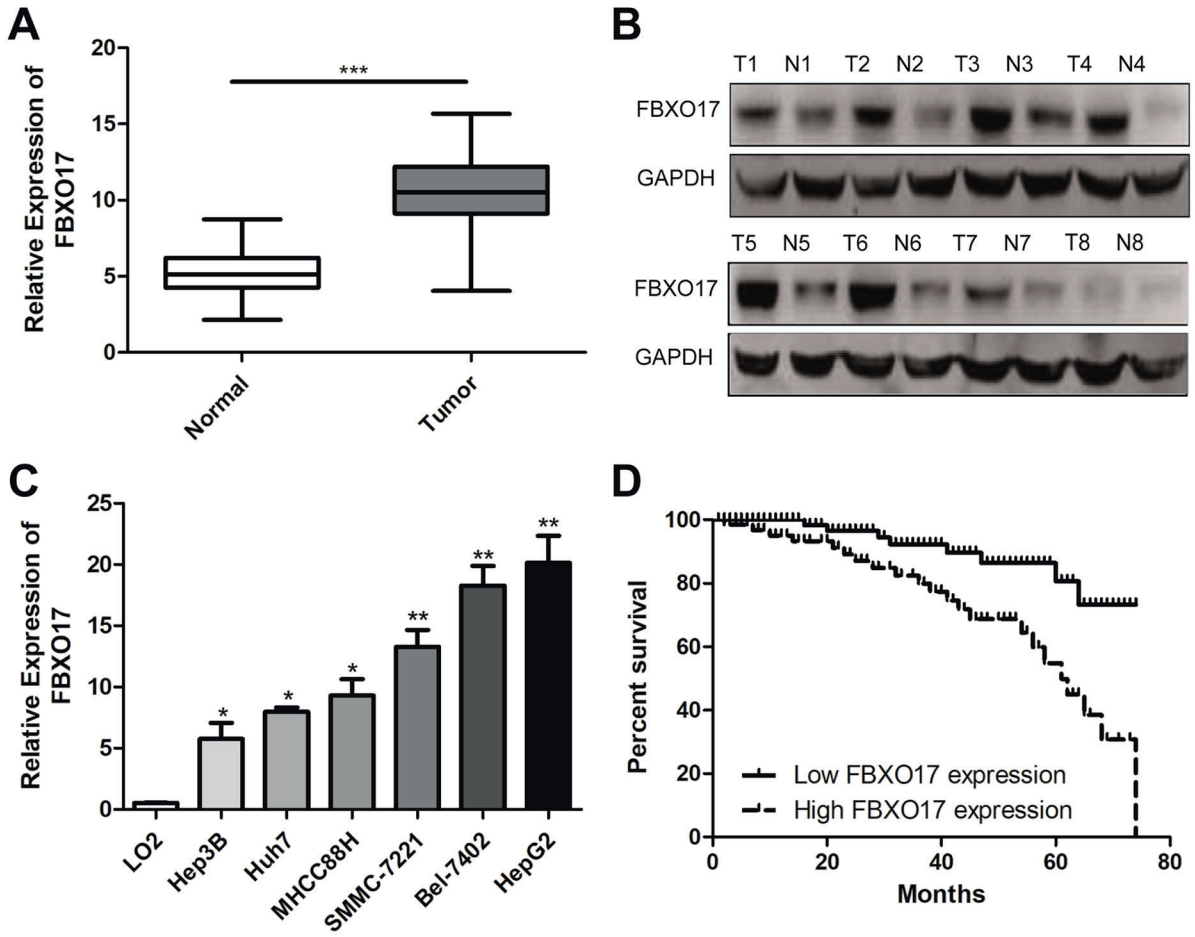


**Figure 1.** FBXO17 is highly expressed in hepatocellular carcinoma tissues and cell lines. ***A, B,*** qRT-PCR and Western blot detection of differential expression of FBXO17 in hepatocellular carcinoma tumor tissues and adjacent tissues. ***C,*** qRT-PCR detection of FBXO17 expression levels in hepatocellular carcinoma cell lines. ***D,*** Kaplan Meier survival curve of patients with hepatocellular carcinoma based on FBXO17 expression: the prognosis of patients with high expression was significantly worse than that of low expression group. Data are mean ± SD, *$p<0.05$, **$p<0.01$, ***$p<0.001$.

**Table I.** Association of FBXO17 expression with clinicopathologic characteristics of hepatocellular carcinoma.

| | | FBXO17 expression | | |
|---|---|---|---|---|
| Parameters | Number of cases | Low (%) | High (%) | *p*-value |
| Age (years) | | | | 0.592 |
| <60 | 20 | 12 | 8 | |
| ≥60 | 25 | 13 | 12 | |
| T stage | 0.023 | | | |
| T1-T2 | 22 | 16 | 6 | |
| T3-T4 | 23 | 9 | 14 | |
| Lymph node metastasis | | | | 0.540 |
| No | 27 | 16 | 11 | |
| Yes | 18 | 9 | 9 | |
| Distance metastasis | | | | 0.577 |
| No | 29 | 17 | 12 | |
| Yes | 16 | 8 | 8 | |

### *Upregulation of FBXO17 Contributed to Cell Proliferation and Apoptosis in HCC In Vitro*

To explore the effects of FBXO17 on HCC cell function, we first constructed a FBXO17 overexpression and knockdown expression model by lentivirus and examined its transfection efficiency by qRT-PCR (Figure 2A). Subsequently, CCK8, cell clone and EDU assay were used to detect the cell proliferation. These results showed that the proliferation rate of cells in anti-FBXO17 group was markedly lower than that in anti-NC group. However, compared with NC group, the proliferation rate of cells in FBXO17 overexpression group was notably increased (Figure 2B, 2C, and 2D).

Subsequently, to further figure out the effect of FBXO17 on the apoptosis of HCC cells, we used flow cytometry to detect apoptosis in each treatment group. The Annexin V-FITC/PI double staining results showed that the apoptosis of cells in FBXO17 silencing group was markedly higher than that in anti-NC group; however, FBXO17 overexpression markedly downregulated the apoptosis of HCC cells (Figure 2E). Those above results showed that upregulation of FBXO17 contributed to cell proliferation and cell apoptosis in HCC *in vitro*.

### *Knockdown of FBXO17 Inhibited Cell Migration and Invasion in HCC In Vitro*

We subsequently performed transwell migration assay to explore the effect of FBXO17 on migration and invasion of HCC cells. The results showed that the number of HCC cells transmembrane in the transwell chamber was markedly reduced after FBXO17 silencing, suggesting that the invasive ability was inhibited. However, FBXO17 overexpression markedly increased number of transmembrane HCC cells, suggesting a significant increase in cell invasiveness (Figure 3A and 3B). Those results demonstrated that knockdown of FBXO17 inhibited cell migration and invasiveness in HCC *in vitro*.

### *Upregulation of FBXO17 Contributed to the Expression of Wnt/β-Catenin Pathway*

To further explore how FBXO17 promoted malignant progression of HCC, we detected the expression levels of key proteins in the wnt/β-catenin pathway after knockdown of FBXO17. Results showed that the expressions of key proteins including β-catenin, cyclin D1, c-Myc, MMP-9, and MMP-2 in wnt/β-catenin pathway were significantly decreased, while the expression level of GSK-3β was up-regulated, which promoted the malignant progression of HCC (Figure 4). These results suggested that FBXO17 might promote the malignant progression of HCC by inhibiting wnt/β-catenin pathway.

## Discussion

In the present time, surgical resection and liver transplantation are still the most effective treatment methods for liver cancer, but only 10%-20% of patients with liver cancer have surgical indications, and the recurrence rate is high. The 5-year survival rate is only 30% to 40%[5,7,10]. The reason why liver cancer patients

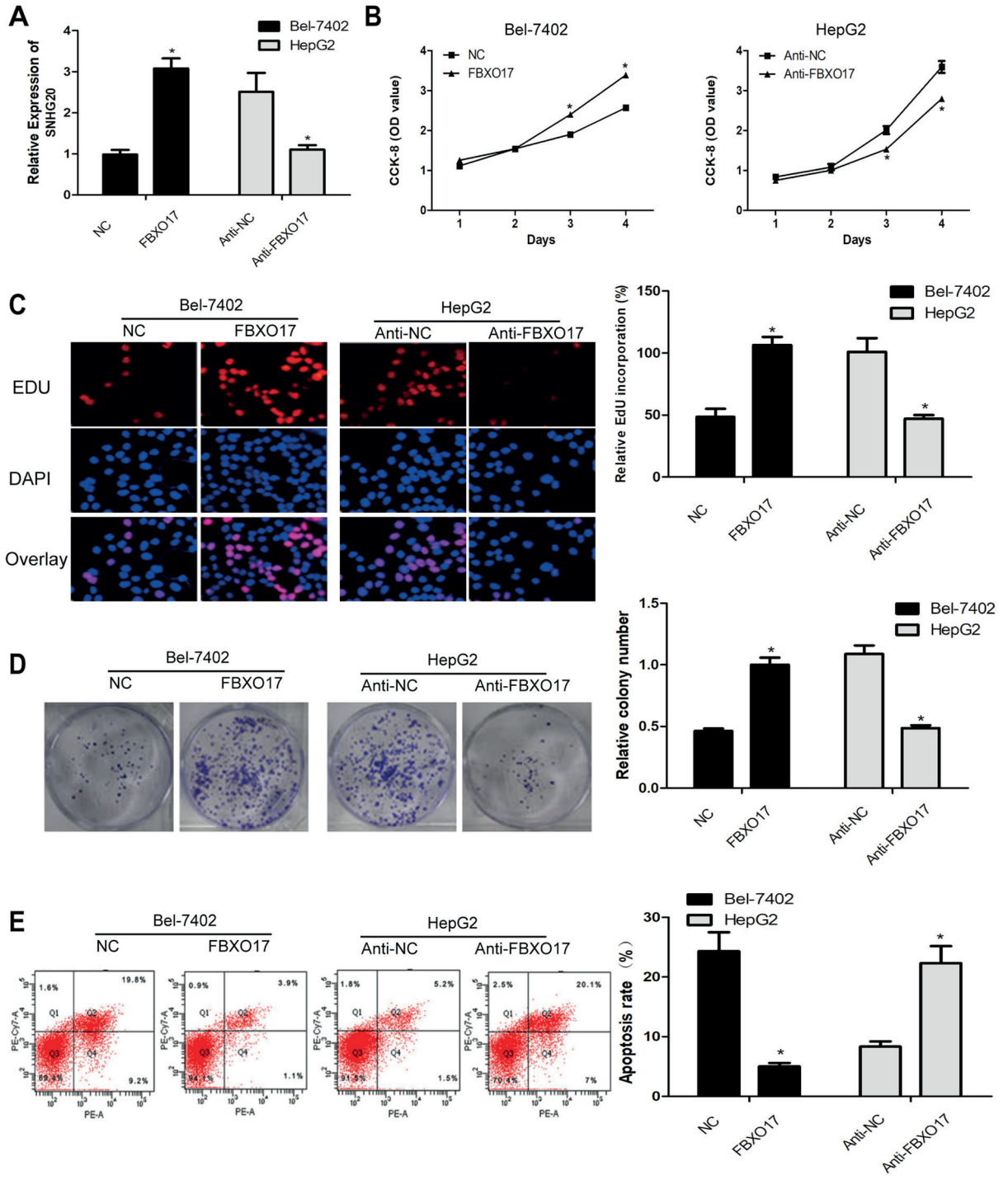


**Figure 2.** Silencing FBXO17 inhibits hepatocyte cancer cell proliferation and promotes its ability to apoptosis. **A,** qRT-PCR verified the interference efficiency of lentiviral transfection of FBXO17 in Bel-7402 and HepG2 cell lines. **B,** CCK-8 assay for hepatocytes after transfection of FBXO17 in Bel-7402 and HepG2 cell lines. **C,** EDU assay (magnification: 100×) and **D,** transwell assay (magnification: 40×) to detect the proliferation of hepatocellular carcinoma cells after transfection of FBXO17 in Bel-7402 and HepG2 cell lines. **E,** Cell flow cytometry assay for detection of apoptosis in Bel-7402 and HepG2 cells after transfection of FBXO17. Data are mean ± SD, *$p<0.05$.

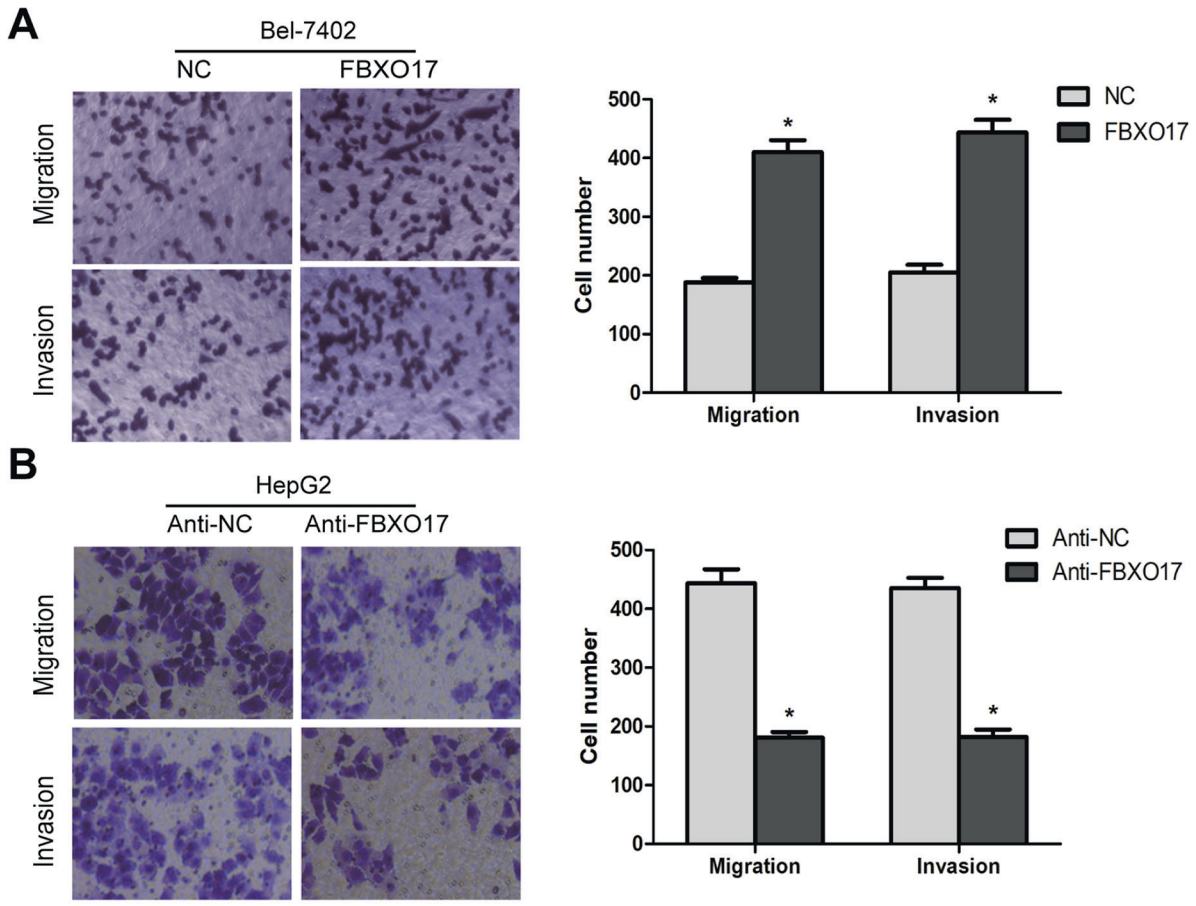


***Figure 3.*** Inhibition of migration and invasion of hepatocellular carcinoma cells after silencing FBXO17. **A,** Transwell assay was performed to detect migration and invasion of hepatocellular carcinoma cells after overexpression of FBXO17 in Bel-7402 cell line (magnification: 40×). **B,** Transwell assay to detect migration and invasion of hepatocellular carcinoma cells after interference with FBXO17 in HepG2 cell lines (magnification: 40×). Data are mean ± SD, *$p<0.05$.

have such an unsatisfied prognosis is that little is known about the molecular pathogenesis of liver cancer and there is no effective treatment. Therefore, it is very urgent and necessary to find a more effective therapeutic target[10]. It has been reported[13,14,19] that FBXO17 can regulate cell proliferation and apoptosis of various cancers such as lung cancer and glioma by regulating the expression of certain proteins involved in cell cycles and apoptosis, but its effect on HCC still remains elusive. In recent years, studies[3,4,9,10] have shown that genetic factors play a pivotal part in the development of HCC. Further research on the etiology of HCC, especially the role of genetic genes in hepatocellular carcinoma, will help to provide new research ideas in the early detection, early diagnosis, and early treatment of HCC, so as to develop some new diagnostics and treatment methods[9,10].

At present, abnormal expression of FBXO17 is found in various tumors of different organs throughout the body, suggesting that it may be associated with malignant progression of the tumor[13,14,19]. In our study, we applied 45 clinical specimens of HCC for the first time to investigate the effect of FBXO17 on the development of HCC. We examined the expression of FBXO17 in fresh HCC tissues as well as cell lines at transcriptional and protein levels and found that FBXO17 expression had an increase to varying degrees. The above experimental results indicated FBXO17 may play an extremely important part in the development of HCC. To further explore the effect of FBXO17 on the biological behavior of HCC cell lines, we investigated the relationship between the level of FBXO17 and age, clinical stage, lymph node or distant metastasis of patients with HCC. The results showed that the highly expressed FBXO17

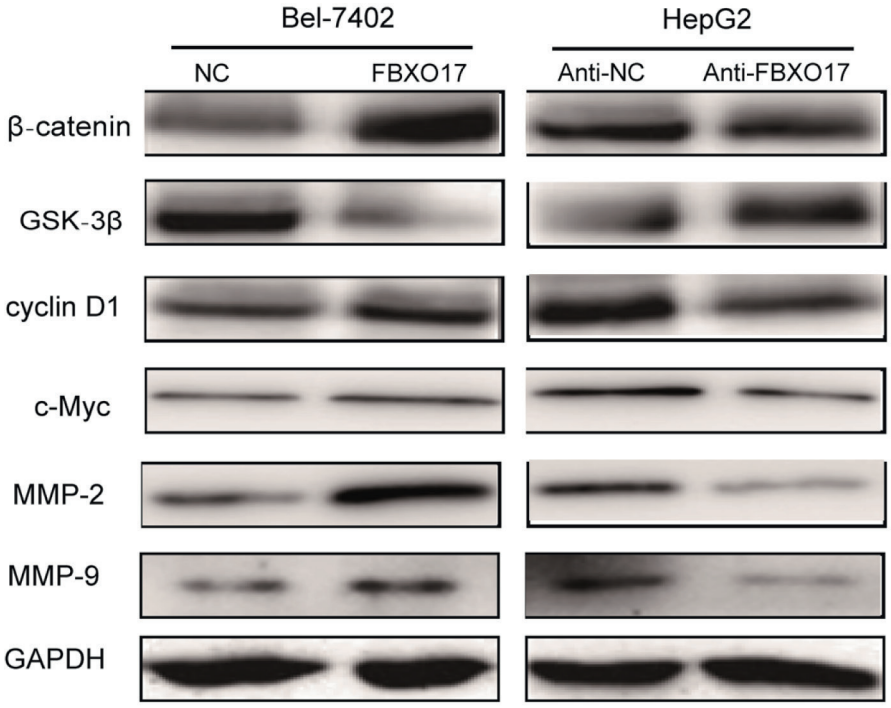


***Figure 4.*** The mechanism of action of FBXO17 in the regulation of wnt/β-catenin pathway in hepatocellular carcinoma cells. Western blotting verified the protein expression levels of β-catenin, cyclin D1, c-Myc, MMP-2, MMP-9, and GSK-3β after overexpression and silencing of FBXO17 in Bel-7402 and HepG2 cell lines.

was positively in correlation with the clinical stage of HCC. Subsequently, we demonstrated that FBXO17 could promote the cell proliferation, migration, and invasiveness of HCC and inhibit its apoptosis. However, its specific molecular mechanism still remained unclear.

The wnt/β-catenin pathway participate in the regulation of important physiological processes in the human body, such as cell adhesion, proliferation, regeneration, and tissue differentiation[16-18]. Abnormal activation of the wnt/β-catenin pathway is closely in relation with the development of various human tumors[16,18]. β-catenin is the main effector of wnt signaling pathway. Under normal conditions, most of β-catenin binds to cadherin to maintain normal adhesion between cells, and a small number of free β-catenin binds to the protein degradation complex composed of GSK-3β, APC, etc. GSK-3β can phosphorylate β-catenin while APC can enhance the affinity of GSK-3β and β-catenin, and promote β-catenin phosphorylation. Phosphorylated β-catenin is recognized by βTrCP and degraded by the proteasome to maintain a low β-catenin level in the cytosol[15-17]. Studies[20,21] have suggested that the increase in the expression level of β-catenin is related to the occurrence of multiple malignant tumors in humans. Current *in vivo* and *in vitro* experimental evidence indicated that wnt/β-catenin plays a pivotal part in primary and secondary metastasis of multiple cancers including rectal cancer and lung cancer[22,23]. Therefore, studying the regulation of wnt/β-catenin is important for finding targets for the treatment of malignant tumors, especially tumor cell metastasis[16-18]. In this work, immunoblots results showed that the expression levels of key proteins in the wnt/β-catenin pathway including β-catenin, c-Myc, cyclin D1, MMP-9, MMP-2 were notably down-regulated while GSK-3β level was markedly increased after knockdown of FBXO17, indicating that FBXO17 may function in HCC through the wnt/β-catenin pathway.

## Conclusions

We showed that the expression of FBXO17 is significantly increased in tumor tissues of HCC patients, which is significantly associated with pathological stage and poor prognosis. Therefore, FBXO17 may promote the malignant progression of HCC by inhibiting wnt/β-catenin signaling pathway.

### Conflicts of interest

The authors declare no conflicts of interest.

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