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Basic Transcription Factor 3 Is Required for Proliferation and Epithelial–Mesenchymal Transition via Regulation of FOXM1 and JAK2/STAT3 Signaling in Gastric Cancer

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Gastric cancer (GC) is the most common epithelial malignancy worldwide. Basic transcription factor 3 (BTF3) plays a crucial role in the regulation of various biological processes. We designed experiments to investigate the molecular mechanism underlying the role of BTF3 in GC cell proliferation and metastasis. We confirmed that BTF3 expression was decreased in GC tissues and several GC cell lines. Lentivirus-mediated downregulation of BTF3 reduced cell proliferation, induced S and G_2/M cell cycle arrest, and increased apoptosis. Knockdown of BTF3 significantly reduced the expression of Forkhead box M1 (FOXM1). Upregulation of FOXM1 significantly inhibited the decrease in cell proliferation due to BTF3 silencing, S and G_2/M cell cycle arrest, and increase in apoptosis. Knockdown of BTF3 decreased Ki-67 and PCNA expression, whereas it increased p27 expression, which was inhibited by upregulation of FOXM1. Knockdown of BTF3 significantly decreased the ability to invade and migrate. Moreover, knockdown of BTF3 increased E-cadherin expression, whereas it decreased N-cadherin and ZEB2 expression, indicating a decrease in epithelial–mesenchymal transition (EMT). Phosphorylation of Janus kinase 2/signal transducer and activator of transcription 3 (JAK2/STAT3) was significantly inhibited by knockdown of BTF3. IL-6-stimulated phosphorylation of STAT3 and JAK2 markedly suppressed inhibition of EMT due to BTF3 silencing. Silencing of BTF3 decreased tumor volume and weight and reduced peritoneal nodules in implanted tumors. Our findings provide a novel understanding of the mechanism of GC and highlight the important role of BTF3/FOXM1 in tumor growth and BTF3/JAK2/STAT3 in EMT and metastasis.

Key words: Basic transcription factor 3 (BTF3); Gastric cancer (GC); Epithelial–mesenchymal transition (EMT); Forkhead box M1 (FOXM1); Janus kinase 2/signal transducers and activators of transcription

INTRODUCTION

Gastric cancer (GC) is the most common epithelial malignancy and the leading cause of cancer-related deaths worldwide, especially in China[1,2]. Despite the rapid progress in the combined treatments including gastrectomy, chemotherapy, and radiotherapy, patients with advanced GC usually have a poor prognosis[3,4]. The molecular mechanism underlying the pathogenesis of GC is still not clear, and a better understanding of the pathogenesis of GC and exploration of novel therapeutic targets are urgently needed.

Basic transcription factor 3 (BTF3), a 27-kDa protein, is encoded by the BTF3 gene in humans[5]. BTF3 is a general RNA polymerase II transcription factor that is evolutionarily conserved in a variety of mammalian cells[6,7]. It was initially discovered that BTF3 was a member of the general transcription machinery and acted as a transcriptional initiation factor via forming a stable complex with RNA polymerases[6]. BTF3 plays a crucial role in the regulation of various biological processes, including early development, cell proliferation, and apoptosis[8,9]. In recent years, the role of BTF3 in the development of tumors was found in a variety of types of cancers. In brain astrocytomas, the level of BTF3 is higher in the highly infiltrating and aggressive form than in the indolent low-grade form[10]. Overexpression of BTF3 has been found in nasopharyngeal carcinoma[11] and pancreatic ductal adenocarcinoma[12], and in liver tumor nodules of aflatoxin

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B1-treated rats[13]. Moreover, BTF3 overexpression is considered to be an early event in colorectal cancer development and could be a useful biomarker in the early stage of colorectal cancer[14]. BTF3 can regulate the transcription of tumor-associated genes in pancreatic cancer cells[12]. BTF3 suppression is involved in kahweol-induced apoptosis in non-small cell lung cancer cells[15]. Recently, BTF3 was found to be overexpressed in GC tissues and cells, and downregulation of BTF3 was shown to inhibit GC cell proliferation[16]. However, the mechanism of the tumor-suppressive role of BTF3 in GC is not completely clear.

We designed experiments to investigate the molecular mechanism underlying the role of BTF3 in GC cell proliferation, invasion, and migration. Here we reported that Forkhead box M1 (FOXM1) was involved in BTF3-exhibited regulation of cell proliferation, apoptosis, and cell cycle progression. Decreased expression of BTF3 decreased epithelial–mesenchymal transition (EMT) through regulating the Janus kinase 2/signal transducer and activator of the transcription 3 (JAK2/STAT3) pathway in GC cells.

MATERIALS AND METHODS

Patients and Ethics Statement

Tumor and adjacent nontumor tissues were obtained from 11 patients in The First Affiliated Hospital of Xinxiang Medical University. These patients did not receive chemoradiotherapy prior to resection. Signed consent forms were obtained from all patients. The tissues samples were stored at −80°C until use. The study was approved by The First Affiliated Hospital of Xinxiang Medical University and complied with the Declaration of Helsinki.

Cell Culture and Transfection

Human gastric epithelial cell line GES-1 and human GC cell lines, including AGS, HGC-27, MKN-28, MGC-803, and SGC-7901 cells, were obtained from the Institute of Biochemistry and Cell Biology at the Chinese Academy of Sciences (Shanghai, P.R. China) and were grown in RPMI-1640 medium with 10% fetal bovine serum (FBS; Gibco, Carlsbad, CA, USA) and 1% penicillin–streptomycin at 37°C with a humidified 5% CO_2 atmosphere. Lentivirus (LV)-expressing shRNA of BTF3 was obtained from Santa Cruz Biotechnology (Santa Cruz, CA, USA). SGC-7901 cells were transfected with LV-shBTF3 or pCMV-BTF3 according to the manufacturer's protocols.

Cell Proliferation, Cell Cycle, and Apoptosis Analysis

Cell proliferation was assayed by cell counting kit-8 (CCK-8) (BOSTER Biotechnology, Wuhan, P.R. China). Cell cycle analysis was performed using propidium iodide staining. In brief, cells were fixed in 100% ice-cold ethanol, washed, and incubated in 1 mg/ml propidium iodide with RNase A (200 μg/ml). Cell cycle distribution was analyzed by flow cytometry (BD Biosciences, San Jose, CA, USA). Apoptotic cell death was determined by TUNEL staining using In Situ Cell Death Detection Kit, Fluorescein (Roche, Switzerland) following the manufacturer's protocol. The percentage of apoptotic cells was analyzed by a flow cytometry software (BD).

Cell Invasion and Migration Assays

The Transwell assay was conducted in order to evaluate the invasive potential using 12-well Matrigel-coated Transwell chambers (BD Biosciences, Billerica, MA, USA). Cells were seeded in serum-free medium in the upper chamber. Standard culture medium with 5% FBS was added in the lower wells of the chamber. Cells were incubated at 37°C for 24 h. The cells remaining in the upper chamber were then carefully removed, whereas the cells on the other side of the membrane were fixed, stained with hematoxylin–eosin, and counted. The relative Transwell cell number was shown.

The wound healing assay was performed to evaluate cell migration. Cells were cultured and starved in serum-free medium for 12 h. In the center of the cell monolayer, a 2-mm-wide wound was made using a P-200 pipette tip when the cells reached 90% confluence. Cells were then cultured in a fresh medium containing 1% FBS for 24 h to allow the wound to heal. At the 0- and 24-h time points, the wound closure areas were visualized using phase-contrast microscopy. The relative wound closure area was shown.

Quantitative Real-Time PCR

Total RNA was isolated from tissues and cells using TRIzol reagent (Invitrogen, Carlsbad, CA, USA) according to the manufacturer's protocol. RNA was reverse transcribed to cDNA using One Step PrimeScript cDNA Synthesis Kit (TaKaRa, Dalian, P.R. China). The PCR was performed on an ABI 7500 Fast Real-Time PCR system according to the manufacturer's instructions: initial denaturation was at 95°C for 10 min followed by 30 cycles at 95°C for 1 min, annealing at 53°C for 1 min, extension at 72°C for 1 min, and final extension at 72°C for 5 min. The relative expression level of genes was calculated by the $2^{-\Delta\Delta CT}$ method. β-Actin was used as the internal control.

Western Blot Analysis

Cells were lysed in radioimmunoprecipitation assay (RIPA) lysis reagent (Life Technologies, Carlsbad, CA, USA). Protein lysates were then separated by 10% sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) and transferred to polyvinylidene

fluoride (PVDF) membranes (Millipore, Billerica, MA, USA). After blocking with 5% nonfat dry milk in Tris-buffered saline plus Tween (TBST), the membranes were incubated with primary antibodies [β-actin, 1:1,000 (Abcam); BTF3, 1:1,000; FOXM1, 1:1,000; STAT3, 1:1,000; p-STAT3, 1:1,000; JAK2, 1:1,000; p-JAK2, 1:1,000 (all from Cell Signaling Technology)] and then incubated with HRP-conjugated secondary antibody (Thermo Fisher Scientific, Waltham, MA, USA). Blots were detected using an enhanced chemiluminescence (ECL) detection system (Thermo Fisher Scientific) and captured using Bio-Rad Imaging Systems (Bio-Rad, Hercules, CA, USA).

In Vivo Tumor Xenograft Model

All animal studies were approved by The First Affiliated Hospital of Xinxiang Medical University. SGC-7901 cells transfected with LV-Control or LV-shBTF3 were suspended in 100 ml of a 1:1 mixture of culture medium and growth factor-reduced Matrigel, and then implanted subcutaneously into the forelegs of nude mice at the age of 4–5 weeks. Thirty days after the implantation, tumor volume was calculated using the equation $(L \times W^2)/2$, and tumor weights were measured and recorded in grams. Peritoneal metastasis nodules were counted.

Statistical Analysis

All the results were expressed as the means ± SEM. Statistical analysis was performed using GraphPad Prism software 5.0. The statistical significance of differences between two groups was analyzed with two-sided unpaired Student's *t*-tests. The statistical significance of differences among more than two groups was analyzed by one-way analysis of variance (ANOVA) followed by a Turkey test for multiple comparisons. A value of $p < 0.05$ was considered to be statistically significant.

RESULTS

BTF3 Expression Is Increased in GC Tissues and Cells

We determined the expression of BTF3 in GC tissues and cell lines. The results showed that BTF3 mRNA expression was significantly increased in tumors, compared with adjacent nontumor tissues (Fig. 1A). In addition, BTF3 mRNA expression in GC cell lines was notably higher than in the gastric epithelial cell line GES-1.

Downregulation of FOXM1 Is Involved in BTF3 Silencing-Induced Inhibition of GC Cell Proliferation, Cell Cycle Arrest, and Apoptosis

To explore the possible mechanism of BTF3-exhibited regulation of GC growth, we transfected SGC-7901 cells with LV expression BTF3 shRNA. The efficiency of the knockdown of BTF3 is confirmed in Figure 2A and B. Knockdown of BTF3 resulted in a significant decrease in the expression of FOXM1 (Fig. 2C), an important factor involved in tumor growth. To examine the possible role of the downregulation of FOXM1 in BTF3-exhibited regulation of GC cell proliferation, SGC-7901 cells were transfected with plasmids expressing FOXM1 (Fig. 2D and E). We found that upregulation of FOXM1 significantly inhibited the decrease in cell proliferation resulting from BTF3 silencing (Fig. 3A). In addition, upregulation of FOXM1 increased cell proliferation (Fig. 3A). Knockdown of BTF3 markedly increased the cell population in the S and G_2/M phases (Fig. 3B), resulting in significant cell cycle arrest. The S and G_2/M cell cycle arrest induced by knockdown of BTF3 was blocked

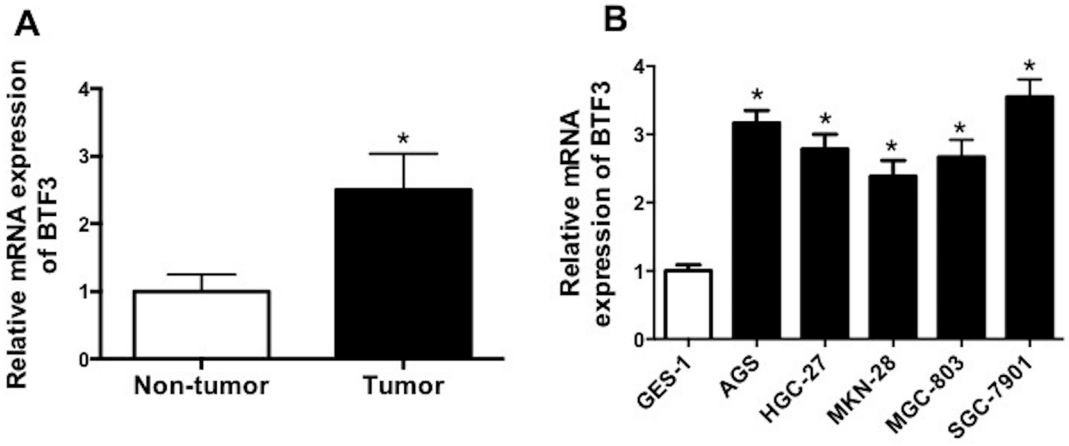

Figure 1. Increased basic transcription factor 3 (BTF3) expression in gastric cancer (GC) tissues and cell lines. (A) mRNA expression of BTF3 in GC tissues and adjacent nontumor tissues. (B) mRNA expression of BTF3 human gastric epithelial cell line GES-1 and human GC cell lines, including AGS, HGC-27, MKN-28, MGC-803, and SGC-7901 cells. *$p < 0.05$ versus control.

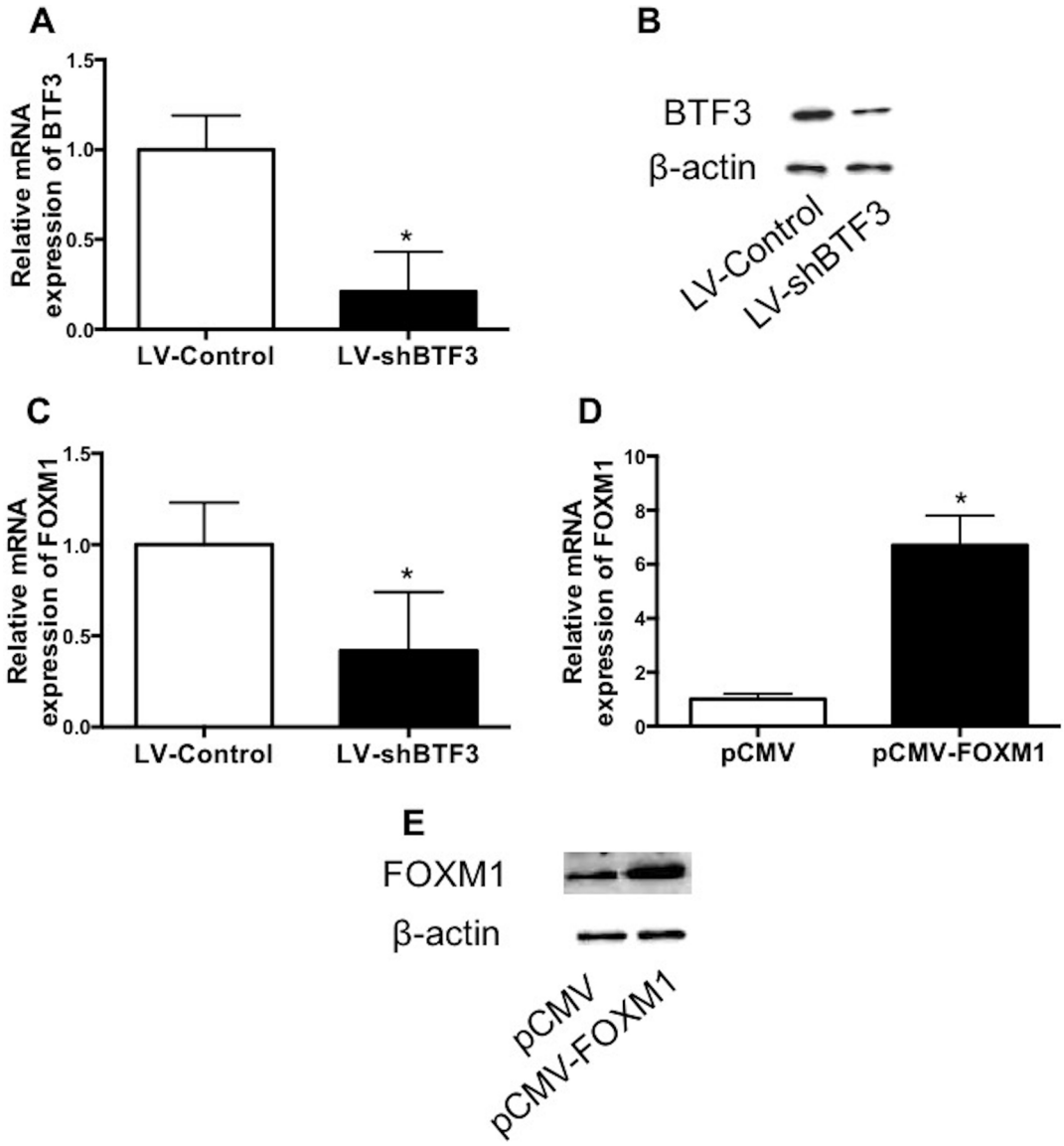

Figure 2. Downregulation of BTF3 decreases Forkhead box M1 (FOXM1) expression in SGC-7901 cells. SGC-7901 cells were transfected with lentivirus (LV)-mediated shRNA of BTF3. (A, B) mRNA and protein expression of BTF3. (C) mRNA expression of FOXM1. SGC-7901 cells were transfected with pCMV or pCMV-FOXM1. (D, E) mRNA and protein expression of FOXM1. $*p < 0.05$ versus control.

by the upregulation of FOXM1 (Fig. 3B). Knockdown of BTF3 resulted in a significant increase in apoptosis, which was suppressed by the upregulation of FOXM1 (Fig. 3C). Upregulation of FOXM1 decreased the percentage of apoptotic cells (Fig. 3C). Furthermore, knockdown of BTF3 decreased Ki-67 and PCNA expression, whereas it increased p27 expression (Fig. 3D–F). These changes in gene expression induced by knockdown of BTF3 were notably suppressed by the upregulation of FOXM1 (Fig. 3D–F). Upregulation of FOXM1 resulted in a significant increase in Ki-67 and PCNA expression and a notable decrease in p27 expression (Fig. 3D–F).

BTF3 Silencing Inhibits Epithelial–Mesenchymal Transition in GC Cells

In the next step, we explored the role of BTF3 in EMT in GC cells. We showed that knockdown of BTF3 significantly decreased the ability to invade and migrate (Fig. 4A and B). Moreover, the mRNA expression of E-cadherin expression was increased by knockdown of BTF3 (Fig. 4C). The mRNA expression of N-cadherin and zinc finger E-box-binding homeobox 2 (ZEB2) was decreased by knockdown of BTF3 (Fig. 4C). These results demonstrated that knockdown of BTF3 decreased EMT in GC cells.

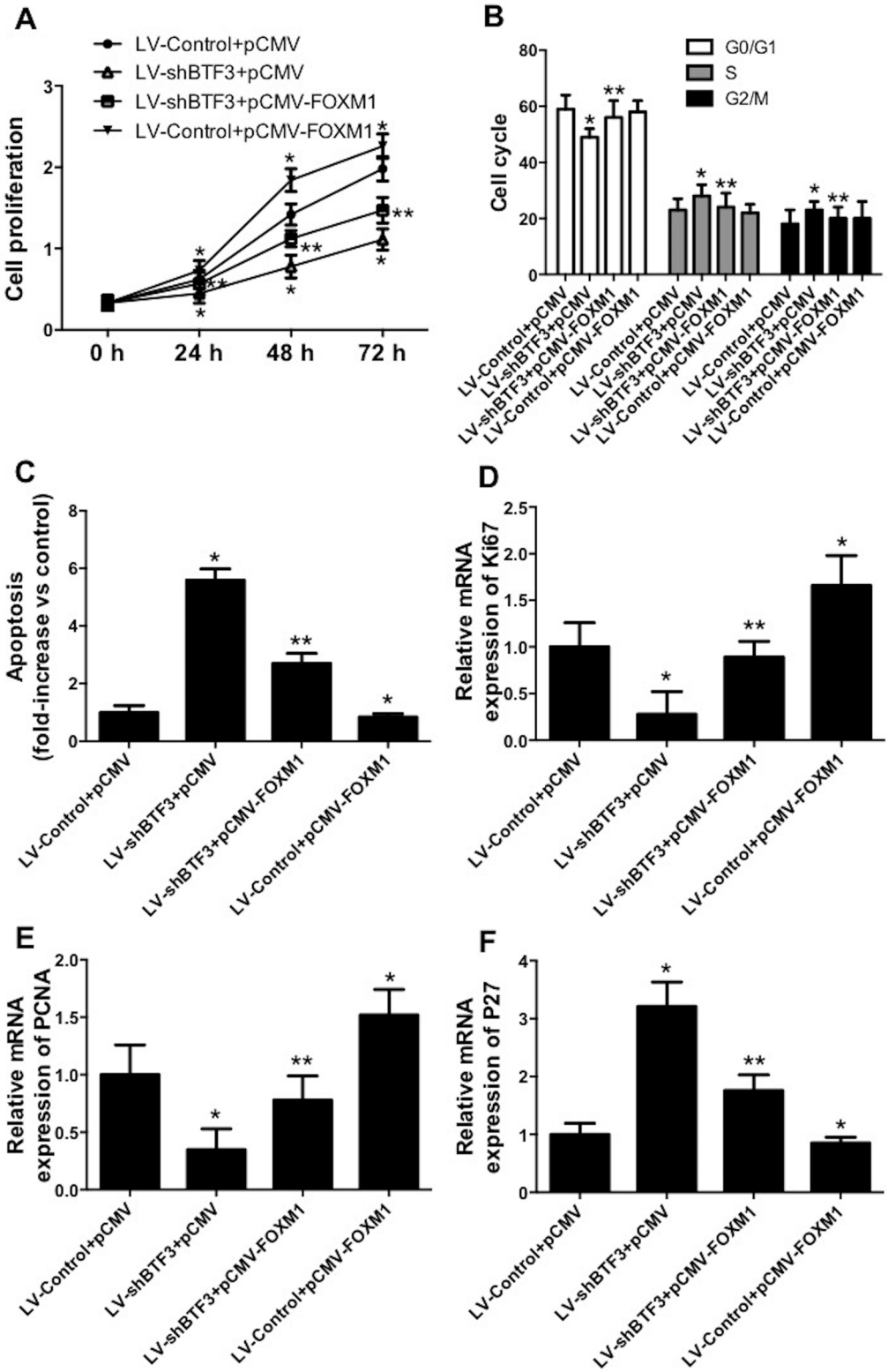

Figure 3. Upregulation of FOXM1 inhibits BTF3 silencing-induced suppression of cell proliferation, cell cycle arrest, and apoptosis. SGC-7901 cells were transfected with LV-mediated shRNA of BTF3 to stably knock down BTF3. The cells were then transfected with pCMV or pCMV-FOXM1 for 24–72 h. (A) Cell proliferation was measured using a cell counting kit-8 (CCK-8). (B) Cell cycle distribution of cells was analyzed by flow cytometry. (C) Apoptotic cell death was detected by TUNEL staining. (D–F) mRNA expression of Ki-67, PCNA, and p27. *$p<0.05$ versus control. **$p<0.05$ versus LV-shBTF3.

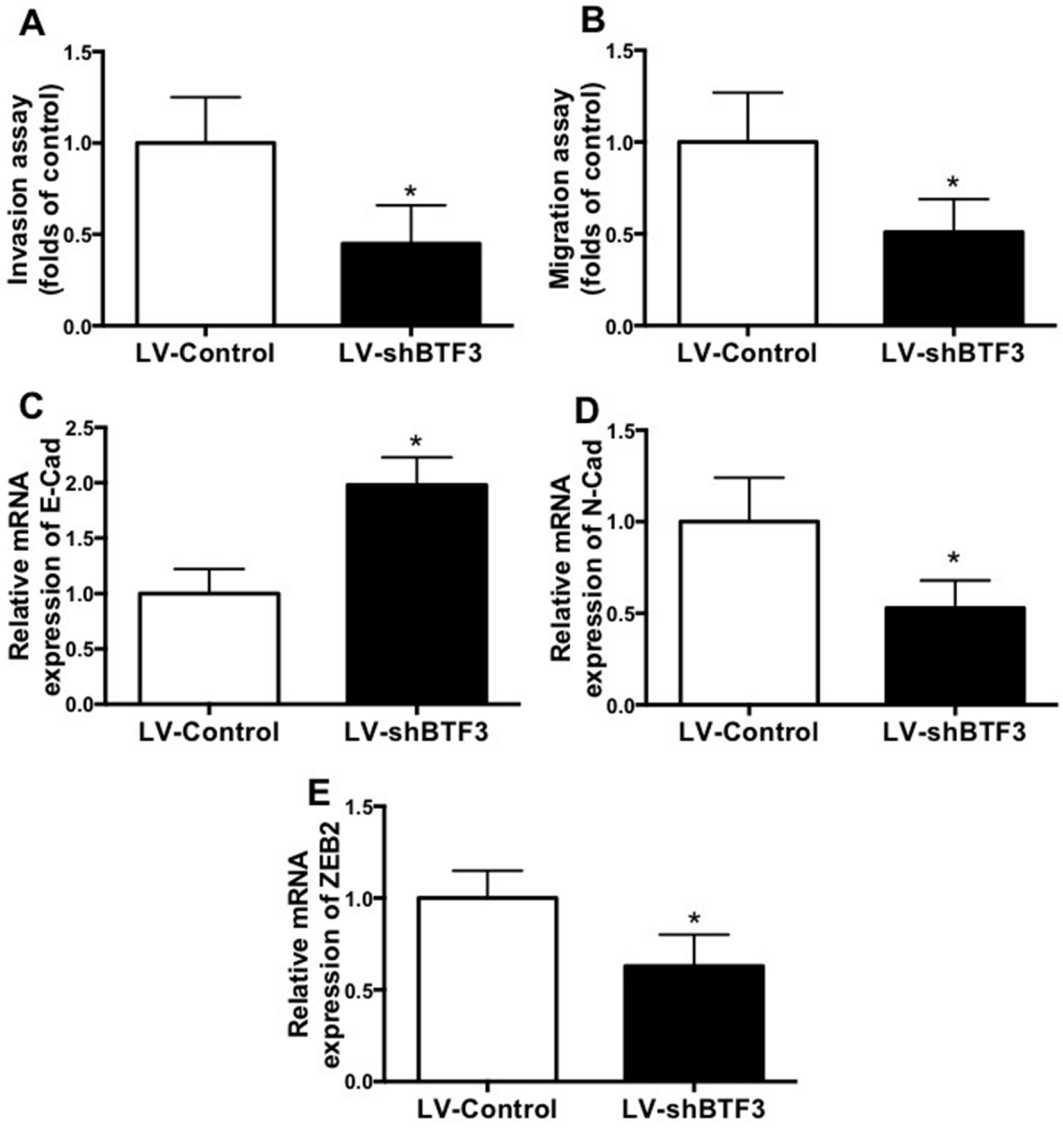

Figure 4. Downregulation of BTF3 decreases epithelial–mesenchymal transition (EMT) transition in SGC-7901 cells. SGC-7901 cells were transfected with LV-mediated shRNA of BTF3. (A) Invasion ability determined by Transwell assay. Relative invasion is shown. (B) Migration ability determined by wound healing assay. Relative migration is shown. (C–E) mRNA expression of E-cadherin, N-cadherin, and ZEB2. $*p < 0.05$ versus control.

Downregulation of JAK2/STAT3 Signaling Is Involved in BTF3 Silencing-Induced Inhibition of EMT in GC Cells

To examine the mechanism of BTF3 silencing in inducing inhibition of EMT, we determined the JAK2/STAT3 signaling pathway. Phosphorylation of JAK2 and STAT3 was significantly inhibited by knockdown of BTF3, suggesting a possible role for JAK2/STAT3 signaling in BTF3-exhibited regulation of EMT (Fig. 5). SGC-7901 cells were then incubated with IL-6 to activate JAK2/STAT3 (Fig. 6A–C). Activation of JAK2/STAT3 significantly suppressed BTF3 knockdown-induced inhibition of invasion and migration (Fig. 6D and E). In addition, IL-6 treatment significantly suppressed the BTF3 knockdown-induced increase in E-cadherin and decrease in N-cadherin and ZEB2 expression (Fig. 6F–H). These results suggested that downregulation of JAK2/STAT3 signaling is involved in BTF3 silencing-induced inhibition of EMT in GC cells.

Downregulation of BTF3 Decreases Implanted Tumor Growth and Metastasis in Nude Mice Xenografts

To test whether BTF3 regulates tumor growth and metastasis in vivo, we subcutaneously xenografted SGC-7901 cells into nude mice. Thirty days after implantation,

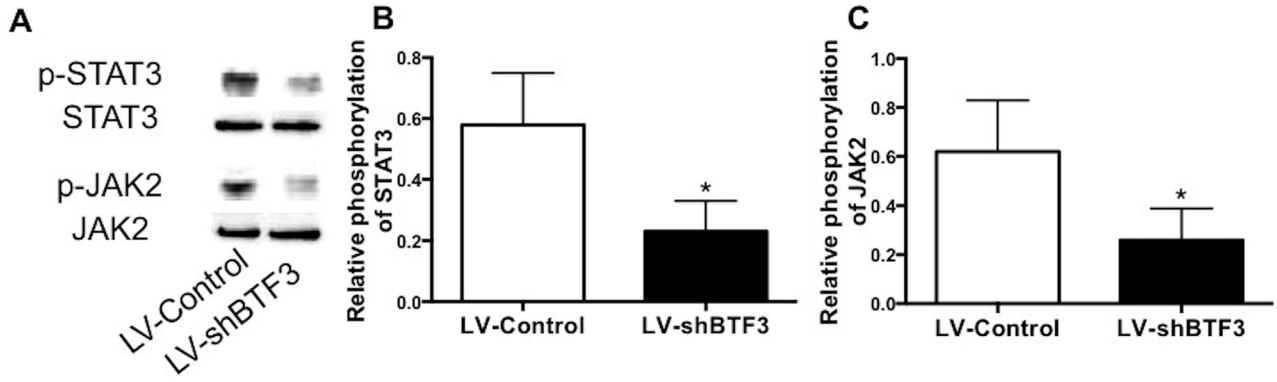

Figure 5. Downregulation of BTF3 decreases Janus kinase 2/signal transducer and activator of transcription 3 (JAK2/STAT3) signaling in SGC-7901 cells. SGC-7901 cells were transfected with LV-mediated shRNA of BTF3. (A) Protein phosphorylation of JAK2 and STAT3. Representative blots are shown. (B, C) Statistical results of protein phosphorylation. $*p<0.05$ versus control.

tumor volumes were calculated, tumors were weighed, and peritoneal nodules were counted. The results showed that downregulation of BTF3 significantly decreased tumor volume and weights in implanted tumors and reduced the number of peritoneal nodules (Fig. 7A–C). Moreover, downregulation of BTF3 markedly decreased the protein expression of FOXM1 and the phosphorylation of JAK2 and STAT3 in implanted tumors (Fig. 7D–F). These results demonstrated that downregulation of BTF3 decreases implanted tumor growth and metastasis in nude mice in vivo.

DISCUSSION

Although much literature has reported that BTF3 is an important regulator of cell proliferation, apoptosis, and tumor development, the exact role of BTF3 in GC is not clear. Recently, an article reported that BTF3 expression was decreased in GC tissues and cells and siBTF3 reduced cell proliferation and induced apoptosis in GC cells. In the current study, we examined the mechanism of BTF3-exhibited regulation of GC cell proliferation and tested the role of BTF3 in the regulation of EMT and metastasis.

We confirmed that BTF3 expression was decreased in GC tissues and several GC cell lines. LV-mediated downregulation of BTF3 reduced cell proliferation, induced S and G_2/M cell cycle arrest, and increased in apoptosis. Downregulation of BTF3 also inhibited tumor growth in implanted tumors in vivo. Knockdown of BTF3 resulted in a decrease in Ki-67 and PCNA and an increase in p27, which are important regulators of proliferation, cell cycle progression, and apoptosis[17,18]. We found that knockdown of BTF3 resulted in significant suppression of FOXM1 expression. FOXM1 is a member of the FOX family, which plays an important role in cell fate decisions. In vertebrates, FOXM1 is an essential transcription factor for tissue development and differentiation[19]. FOXM1 activates cell proliferation through binding to sequence-specific motifs on DNA (C/TAAACA). A number of studies have shown that FOXM1 expression is significantly increased in a variety of human cancers such as GC, acute lymphoblastic leukemia, esophageal and breast cancers, hepatocellular carcinoma, and colorectal cancer[20–25]. Overexpression of FOXM1 is correlated with the poor prognosis of patients with malignant tumors such as GC[25–27]. FOXM1 plays an oncogenic role through regulation of cell cycle progression and proliferation[28]. In our study, we found that upregulation of FOXM1 suppressed BTF3 silencing-induced inhibition of GC cell proliferation, cell cycle arrest, and apoptosis, suggesting that the downregulation of FOXM1 is involved in BTF3 silencing-induced inhibition of GC cell proliferation, cell cycle arrest, and apoptosis.

EMT is a well-characterized embryological process that plays a critical role in tumor metastasis. EMT-regulated invasion and migration are required for metastasis. EMT is characterized by losing epithelial markers (e.g., E-cadherin) and acquiring mesenchymal markers (e.g., N-cadherin, ZEB2)[29]. We showed that silencing BTF3 induced a significant decrease in cell invasion and migration, an increase in E-cadherin expression, and a decrease in N-cadherin and ZEB2 expression. Silencing BTF3 also decreased peritoneal nodules in vivo. These results demonstrated that silencing BTF3 decreased EMT in GC cells. The IL-6/JAK2/STAT3 signaling pathway plays an important role in EMT. IL-6 binds to its receptor on the cell surface and activates STAT3 with the phosphorylation of Tyr705 via the JAK signaling pathway[30]. In our study, we found that downregulation of BTF3 resulted in a significant decrease in phosphorylation of STAT3 and JAK2 in vitro and in vivo. Moreover, IL-6-stimulated phosphorylation of STAT3 and JAK2 markedly suppressed BTF3 silencing-induced inhibition of EMT. The findings demonstrate that downregulation of JAK2/STAT3 signaling is involved

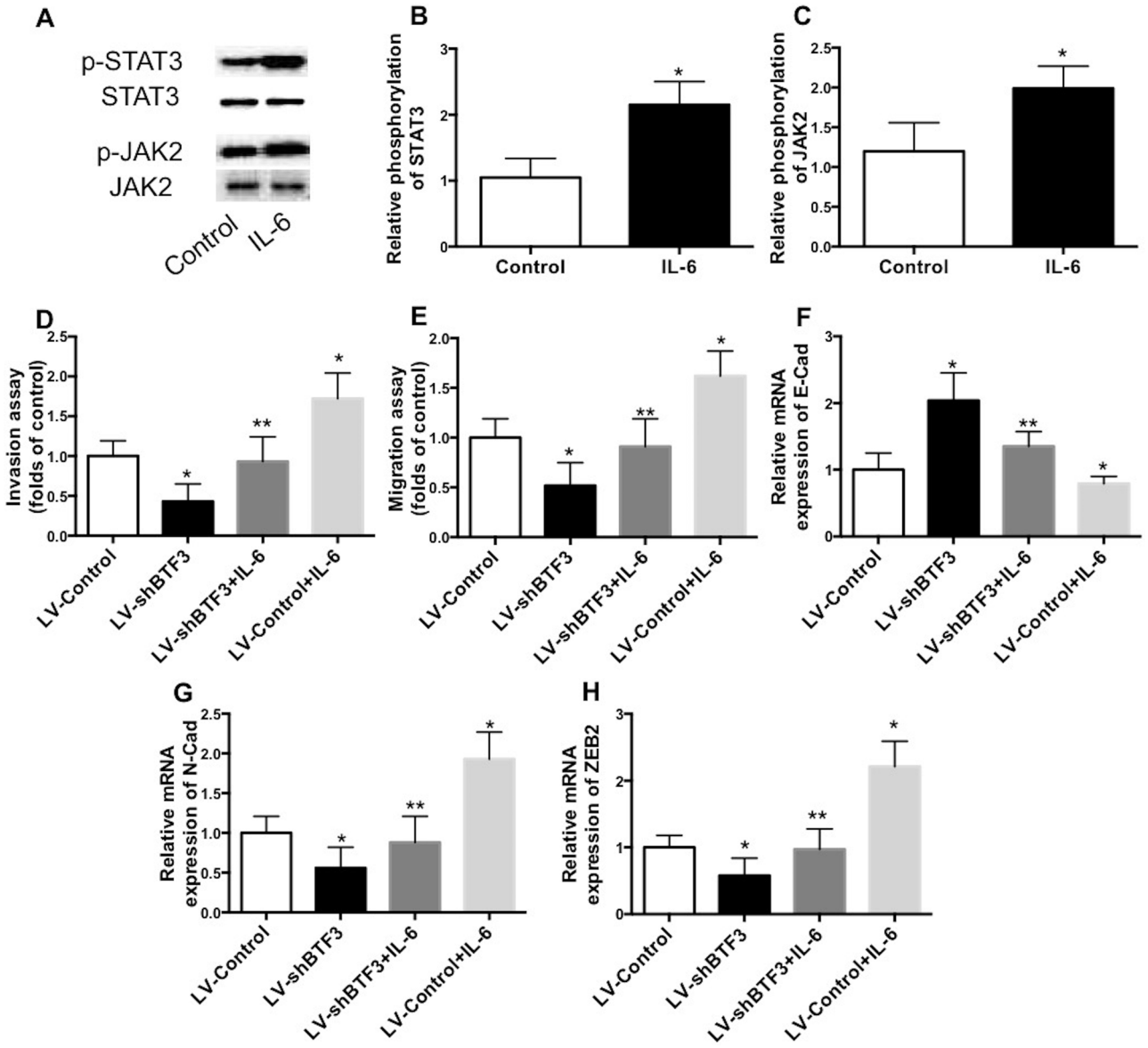

Figure 6. Activation of JAK2/STAT3 signaling inhibits BTF3 silencing-induced suppression of EMT transition. SGC-7901 cells were incubated with 10 ng/ml IL-6 for 24 h. (A) Protein phosphorylation of JAK2 and STAT3. Representative blots are shown. (B, C) Statistical results of protein phosphorylation. SGC-7901 cells were transfected with LV-mediated shRNA of BTF3 to stably knock down BTF3. The cells were then incubated with 10 ng/ml IL-6 for 24 h. (D) Invasion ability determined by Transwell assay. Relative invasion is shown. (E) Migration ability determined by wound healing assay. Relative migration is shown. (F–H) mRNA expression of E-cadherin, N-cadherin, and ZEB2. *$p<0.05$ versus control. **$p<0.05$ versus LV-shBTF3.

in BTF3 silencing-induced inhibition of EMT in GC cells. However, the total protein expression of JAK2 and STAT3 was not changed by knockdown of BTF3. Since BTF3 is a transcription factor, BTF3 may influence the phosphorylation of JAK2 and STAT3 through a mediator. Further studies are needed to explore the mechanism underlying BTF3-exhibited regulation of JAK2/STAT3 signaling.

In summary, we found that silencing of BTF3 resulted in a decrease in GC tumor growth through downregulation of FOXM1 and reduced EMT and metastasis via JAK2/STAT3 signaling. Our findings provide a novel understanding of the mechanism of GC and highlight the important role of BTF3/FOXM1 in the regulation of tumor growth and BTF3/JAK2/STAT3 in the regulation of EMT and metastasis.

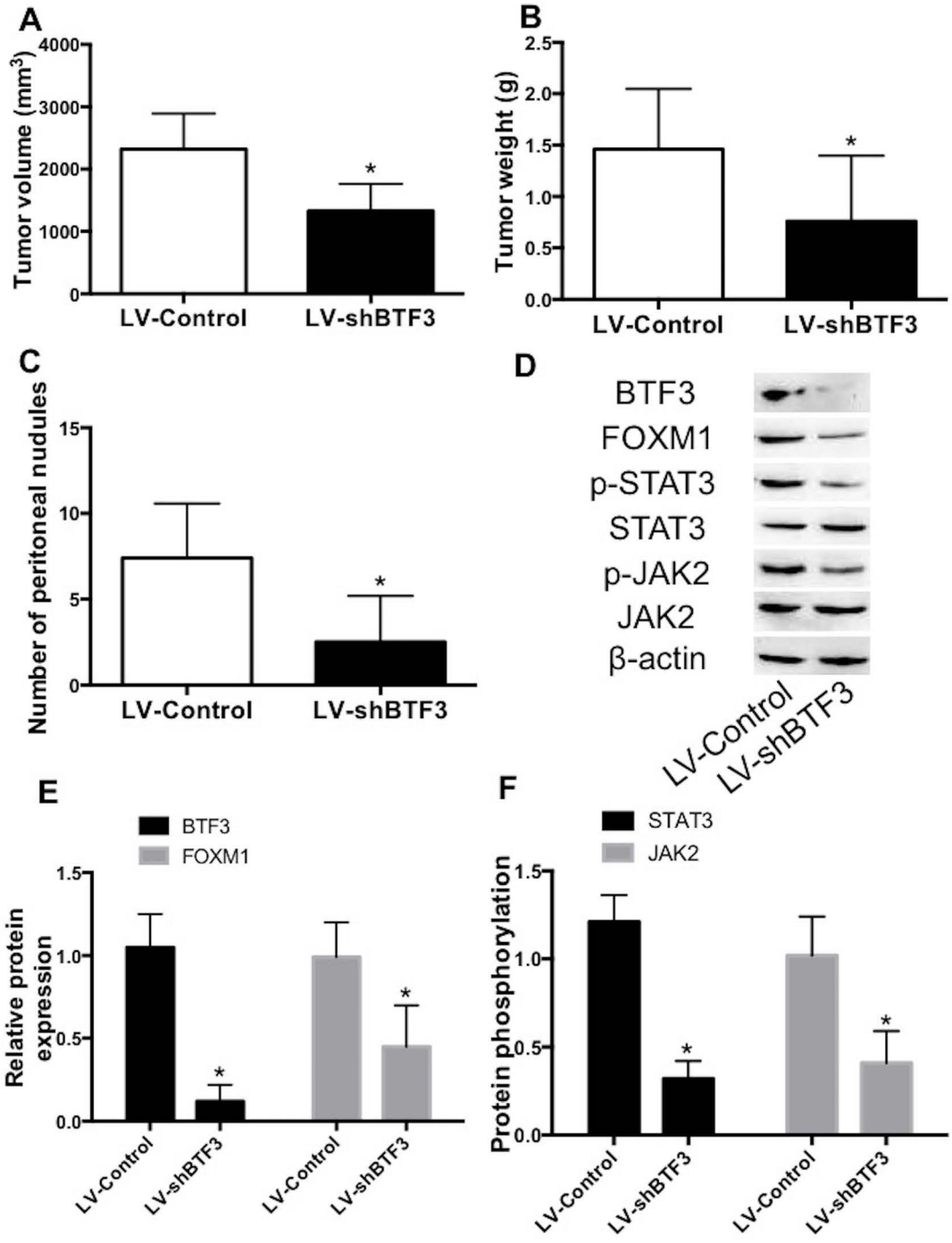

Figure 7. Downregulation of BTF3 decreases tumor growth and metastasis in nude mice xenografts. Nude mice were implanted with cells transfected with LV-Control or LV-shBTF3. Thirty days after the implantation, (A) tumor volumes were measured, (B) tumor weights were measured, and (C) peritoneal nodules were counted. (D) Protein expression of BTF3, FOXM1, STAT3, phosphorylated (p)-STAT3, JAK2, and p-JAK2 in tumors was examined. (E, F) Relative protein expression is shown. *$p<0.05$ versus control.

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