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GOLM1 Promotes Epithelial-Mesenchymal Transition by Activating TGFβ1/Smad2 Signaling in Prostate Cancer

Xuke Qin, MD[1,†], Lin Liu, MS[2,†], Yanze Li, MD[1], Hongbo Luo, MD[1,3], Hui Chen, MD[1], and Xiaodong Weng, MD[1]

Abstract

Background: Prostate cancer (PC) is one of the most commonly diagnosed cancer in men worldwide. Epithelial-mesenchymal transition (EMT) is considered to play a crucial role in the development of the metastatic castration-resistant prostate cancer, which causes the majority of the death cases in PC. Golgi membrane protein 1 (GOLM1) is highly expressed in PC and has been identified as a driver factor for EMT in various cancers. However, its biological functions and underlying mechanisms remain ambiguous in PC. **Method:** GOLM1 expression level of PC was detected by Western blot and immunohistochemistry analyses. To investigate GOLM1 functions in cancer cells, we overexpressed and knocked down GOLM1 in different prostate cancer cell lines. Transwell assay and wound healing assay were used to determine the role of GOLM1 in cell EMT, such as migration and invasion abilities. TGF-β1/Smad2 signaling pathway downstream of GOLM1 was detected by Western blot and Transwell assay. **Result:** GOLM1 expression is up-regulated in PC and correlated with a worse prognosis. GOLM1 promotes the abilities of migration and invasion in PC cell lines (DU145 and LNCaP). Furthermore, TGF-β1/Smad2 signaling is positively regulated by GOLM1 to facilitate EMT in PC, whereas this role can be restored by TGF-β1 after GOLM1 knockdown or be abrogated by p-Smad inhibitor SB431542. **Conclusion:** GOLM1 is significantly upregulated in PC and acts as a critical oncogene by promoting PC cell EMT process by activating TGF-β1/Smad2 signaling pathway. Therefore, GOLM1 has the potential to be a biomarker for PC diagnosis and to predict the prognosis of PC patients. It is of great significance to seek effective and specific inhibitor of GOLM1 for PC treatment as well.

Keywords

GOLM1, TGF-β1, epithelial-mesenchymal transition, prostate cancer

Abbreviations

PC, prostate cancer; EMT, epithelial-mesenchymal transition; CRPC, castration-resistant prostate cancer; GOLM1, golgi membrane protein 1; IHC, immunohistochemistry; GEPIA, gene expression profiling interactive analysis; SEM, standard error of mean.

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Introduction

As of 2021, prostate cancer (PC) has become the second most common cancer in men worldwide after lung cancer. And PC is one of the most common cancers in developed regions such as Europe and the United States.[1] There are approximately 1.2 million new cases of PC each year, accounting for 7% of newly diagnosed cancers in men globally. In addition, PC-related deaths exceed 350,000 annually, making it one of the leading causes of cancer-associated death in men.[1–3] Most patients with PC die of the disease because of the primary tumor metastasizing to an organ vital to survival such as the

[1] Renmin Hospital of Wuhan University, Wuhan, Hubei, China
[2] Renmin Hospital, Hubei University of Medicine, Shiyan, Hubei, China
[3] The Second Hospital of Huangshi, Huangshi, Hubei, China

[†] These authors contributed equally to this work.

Corresponding Authors:
Hui Chen, Department of Urology, Renmin Hospital of Wuhan University, Wuhan 430060, Hubei, China.
Email: drchenhuiyx@whu.edu.cn

Xiaodong Weng, Department of Urology, Renmin Hospital of Wuhan University, Wuhan 430060, Hubei, China.
Email: 12942169@qq.com

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lungs or the liver.[4] PC also has the ability of bone metastasis. The standard treatment for metastatic PC is androgen-deprivation therapy (ADT). However, after a period of treatment, PC tends to become castration-resistant and does not respond to ADT.[5] PC cell is able to become invasive, migratory and acquire the ability of metastasis through Epithelial-mesenchymal transition (EMT) process.[6] Therefore, EMT plays a critical role in the development of metastatic castration-resistant PC.[7] And the mechanism of EMT has been considered the key to suppressing PC progression. Although many studies have focused on EMT, the mechanism of how the PC cells undergo EMT is still ambiguous.

Golgi membrane protein 1 (GOLM1, also termed as GP73 or GOLPH2) was first identified in 2000.[8] GOLM1 is a 73 kDa transmembrane glycoprotein, with 401 amino acids, located in cis-Golgi cisternae. And it contains a transmembrane domain at the N-terminal region (13-35aa), 2 α-helixes at the C-terminal region (56– 205 and 206-401aa),[9,10] and a cytoplasmic domain(1-12aa). The cytoplasmic region of GOLM1 interacts with its substrates and involves in their vesicular trafficking.[10–12] It was reported that furin can exclusively cleave GOLM1 at R55 on the intracellular side of the cell surface. And this interaction makes the remaining part(56-401aa) able to be covered by exosomes and secreted into extracellular spaces through exosome-dependent secretion.[13] Therefore, 56–401aa residue of GOLM1 can be extracellularly detected.[14] GOLM1 has been shown to be highly expressed in a variety of cancers, including PC, and related to poor outcomes.[15,16] GOLM1 is now considered to be the driver of EMT in some cancers. Recent literature has identified GOLM1 as a driver of EMT in hepatocellular carcinoma and bladder carcinoma through TGF-β1/Smad2 signaling.[17,18] However, the role of GOLM1 in EMT of PC is still unclear.

In our research, we first searched top 20 genes up-regulated of PC in Gene Expression Profiling Interactive Analysis (GEPIA) database. Among these genes, we found GOLM1 is correlated to worse overall survival. Then we further performed experiments to verify the up-regulation of GOLM1 in PC tissues and cells. In addition, we observed that GOLM1 can promote PC cell invasion and migration. Importantly, TGF-β1 inhibitors can revert this oncogenic function of GOLM1. In conclusion, GOLM1 can facilitate PC progression by activating TGF-β1/Smad2 signaling. Therefore, GOLM1 may act as a novel biomarker for PC diagnosis and prognostic predictors, as well as a potential therapeutic target of PC.

Materials and Methods

Gene Expression and Overall Survival Analysis in GEPIA

The online database GEPIA (http://gepia.cancer-pku.cn/index.html) was used to analyze the mRNA expression level of GOLM1 in pan-cancers and the difference in GOLM1 expression between PC tissues and normal tissues. Moreover, GEPIA was used to conduct Kaplan–Meier analysis of overall survival.

Patients and Clinical Specimens

Twenty-two pairs of PC and adjacent tissues were obtained from patients undergoing urological surgery from 2019 to 2020. All research protocols were approved by the Ethics Committee. Informed consent was obtained from patients before surgery and the collection of relevant clinical data.

Cell Lines and Cell Culture

BPH-1 (ACC143) was purchased from DSMZ (Deutsche Sammlung von Mikroorganismen und Zellkulturen) LNCaP (ATCC CRL-1740), and DU145 (ATCC HTB-81) cells were purchased from the ATCC (American Type Culture Collection). RPMI 1640 medium (Beyotime Biotechnology) with 10% fetal bovine serum (FBS) (GIBCO) was used to culture the cells, at 37 °C with 5% CO_2. Cells were treated with 10 ng/ml TGF-β1 (MedChemExpress) or 2.5 μM SB-431542 (MedChemExpress, China) for 24 h before detecting the protein levels and invasion ability in the rescue experiment.

Immunohistochemical Staining and Assessment

Serial sections with 5 μm were cut from the tissue blocks, deparaffinized by xylene, and hydrated in a series of graded alcohol. Then the sections were incubated with specific antibodies for GOLM1 (rabbit polyclonal, 1:50, affinity), E-cadherin (rabbit polyclonal, 1:100, Proteintech). Finally, sections were stained by using the DAB chromogenic agent (Dako Corp). Negative control experiments were routinely conducted. The slides were scored by 2 experienced pathologists independently in the condition of unawareness of slides source.

Plasmid Construction and Cell Transfection

After vaccination and amplification of single colonies, a small Plasmid Extraction Kit (EM101, TransGen Biotech) was used to extract plasmid. 293 T cells were co-transfected with pLVXGOLM1-ZsGreen-Puro to obtain high titer lentiviral (rLV-GOLM1) containing target gene by Lentiviral packaging kit (R003, Wuhan Viraltherapy Technologies Co. Ltd). A total of 5×10^5 cells/ml cells were transferred to cell plates when cell confluences reached 80% to 90%. And the cells were transfected by rLV-FBXW7 on the basis of MOI = 20 the next day. lentivirus-infected cells were selected using complete medium (DMEM with 10% FBS and 1% penicillin-streptomycin) with 10 mg/ml puromycin after 2 days transfection,

SiRNA was constructed and obtained from Wuhan Viraltherapy Technologies Co. Ltd Lipofectamine RNA iMAX (Invitrogen) was used to transfect SiRNA into cells. At least 48 h later, cells were then harvested for protein extraction.

Table 1. Top 20 Genes up-Regulated in PC.

Gene Symbol	Log_2FC	adj-p
RP11-40C6.2	7.801	1.25E-105
PCA3	5.596	2.30E-70
AMACR	4.686	6.88E-103
MTND4P12	4.418	8.80E-15
RNY3P8	4.18	2.18E-14
DLX1	4.159	1.68E-79
OR51E2	4.115	3.55E-48
PCAT14	4.095	1.48E-46
TP53TG1_2	3.688	2.37E-14
AP003391.1	3.524	7.08E-15
GOLM1	3.286	1.37E-105
HPN	3.225	2.77E-124
GLYATL1	3.223	2.84E-64
RPL7P16	3.154	3.80E-64
ACSM1	3.153	7.02E-48
AC005943.2	2.993	2.95E-31
TRGC1	2.99	2.06E-81
TMEFF2	2.984	3.77E-25
U91328.1	2.947	4.68E-10

Abbreviations: GOLM1, Golgi membrane protein 1; PC, prostate cancer.

Transwell Assay

Transwell inserts (8.0 μm) were precoated with 20 μg Matrigel (Corning, USA). 5×10^5 cells were resuspended in serum-free medium and seeded onto precoatedtranswell insert. The culture dishes were added RPMI-1640 containing 10% FBS. After 24 h of culture (5%CO_2, 37 °C), Invaded cells were fixed and stained by crystal violet（Beyotime Biotechnology, China）.The results were photographed and quantified under microscope (Olympus).

Wound Healing Assay

Cells were cultured in serum-free medium for 24 h. And a cell-free wound line was created using a sterile 200-mL pipette tip. The width of the wound was observed and photographed under microscope (Olympus) at 0 h and 24 h after the scratch. The results were analyzed using Image J.

Western Blot Analyses

The expression levels of GOLM1, E-cadherin, Vimentin, TGF-β1, Smad2, p-Smad2, and GADPH were detected by Western

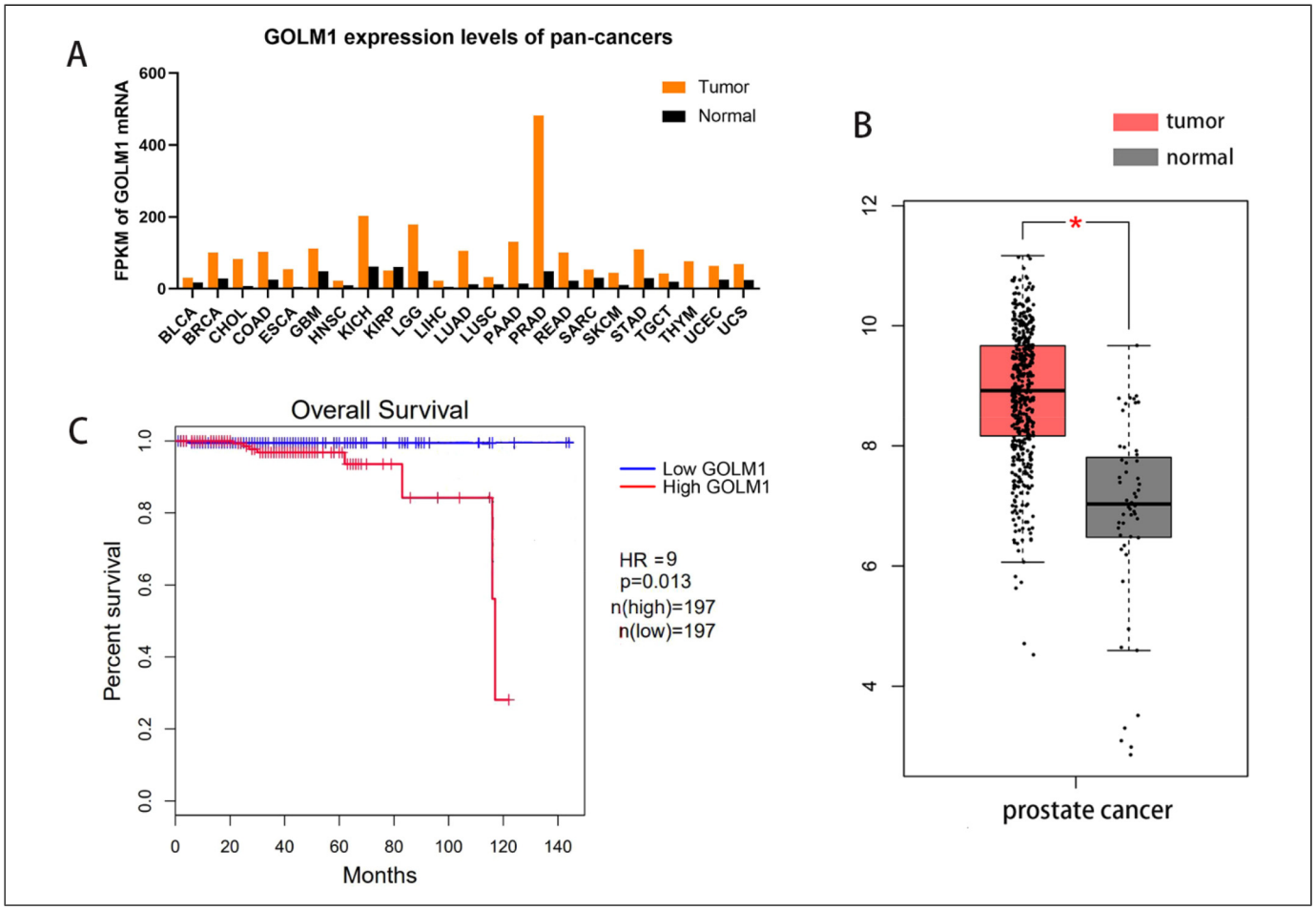

Figure 1. The results of expression and survival analysis of GOLM1 in GEPIA database. (A) GOLM1 mRNA level of tumor tissues and normal tissues in pan-cancers. (B) The expression of GOLM1 mRNA in PC tissues and normal tissues. *$P < .05$. (C) Kaplan–Meier analysis of overall survival of PC patients after surgical treatment. Abbreviations: GOLM1, golgi membrane protein 1; PC, prostate cancer; GEPIA, Gene Expression Profiling Interactive Analysis.

blotting. First, equal amounts of proteins were loaded onto 10% SDS-PAGE gels for separation and then transferred to polyvinylidene fluoride membrane (Bio-Rad). Second, the membranes were blocked with 5% nonfat milk for 2 h and then were incubated with primary antibodies, and placed on shaker, at 4 °C overnight. Indicated primary antibodies in this study were polyclonal rabbit antibodies against GOLM1 (1:1000 dilution; Affinity), E-cadherin (1:5000 dilution; Proteintech), Vimentin (1:1000 dilution; Proteintech), TGF-β1 (1:1000 dilution; Abclonal), Smad2 (1:1000 diluton; Affinity), p-Smad2 (1:1000) and GADPH (1:1000 dilution; Affinity). Third, the membranes were incubated with HRP-conjugated anti-rabbit secondary antibodies (1:600 dilution; Beyotime Biotechnology) after washing with TBST buffer. Finally, the protein levels were detected by using an enhanced chemiluminescence system (ECL Kit, Pierce Biotechnology) and captured on light-sensitive Xrayfilm (Carestream). The optical densities of bands were analyzed by ImageJ software.

Statistical Analysis

Statistical analysis was conducted with SPSS software, version 25.0 (SPSS). All results are expressed as the mean ± standard error of mean (SEM). One-way analysis of variance and Tukey's multiple comparisons tests were used for statistical analyses. $P < 0.05$ was considered statistically significant.

Results

GOLM1 is up-Regulated in PC and Correlated With Poor Prognosis

In order to investigate the potential molecular mechanisms of PC progression, we searched for the top 20 upregulated genes of PC in the GEPIA database (Table 1). Among these genes, GOLM1 attracted our attention because it has high expression in various cancers and involves in the EMT process.[19] Then we sought GOLM1 in GEPIA database and found it is up-regulated in various types of cancers (Figure 1A). In addition, the expression level of GOLM1 is significantly up-regulated in PC tissues contrast with adjacent normal tissues (Figure 1B). And the Kaplan–Meier analysis showed that higher GOLM1 expression is correlated with poor overall survival of patients (Figure 1C). These results indicated that GOLM1 may be a risk factor to promote the progression of PC.

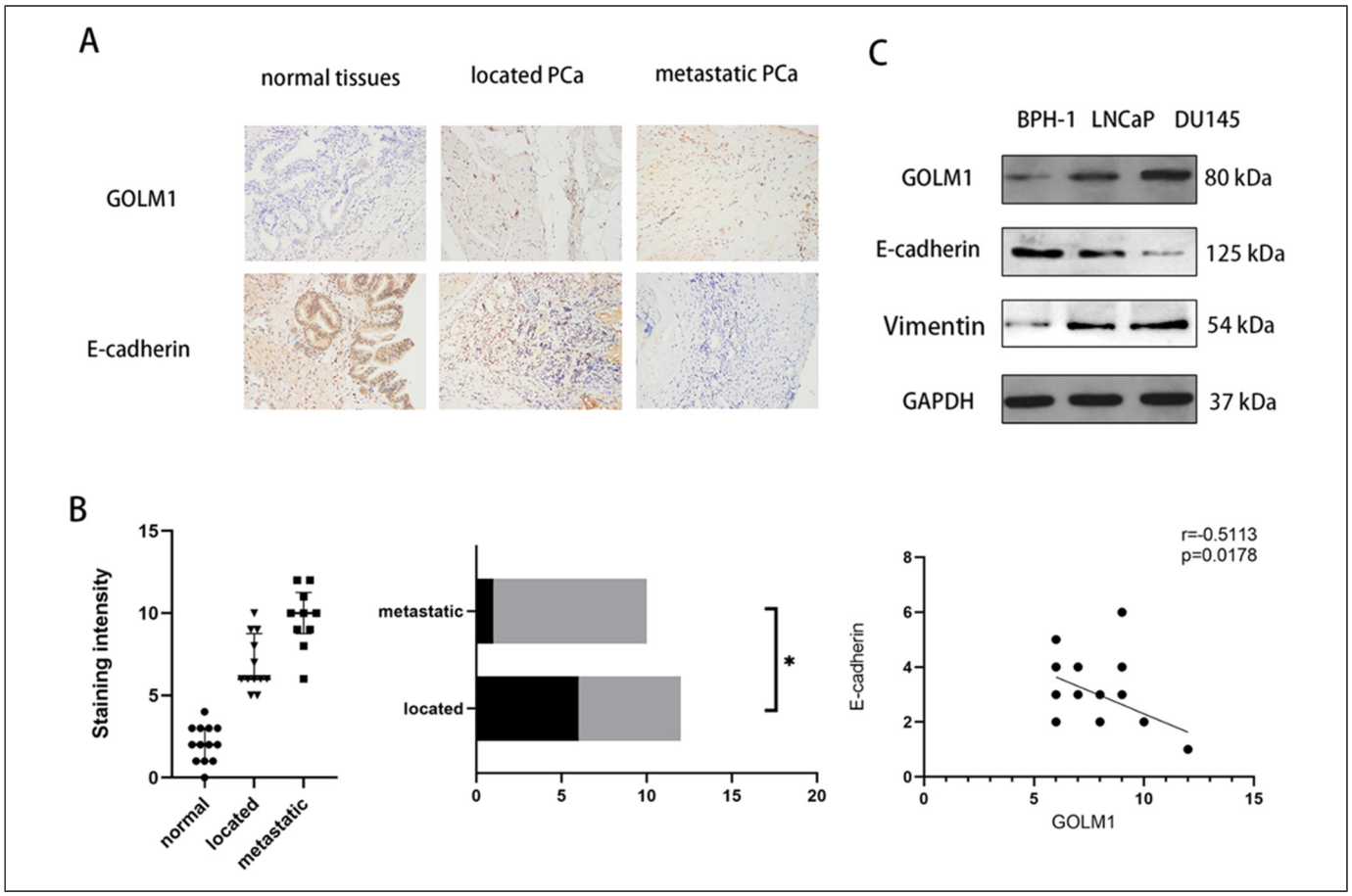

Figure 2. Expression levels of GOLM1 and E-cadherin in PC tissues and cells. (A) Representative images of IHC staining taken at 20×. (B) Statistics analysis of IHC results. (C) Expression levels of GOLM1, E-cadherin and Vimentin in PC cell lines. *$P < 0.05$. Abbreviations: IHC, immunohistochemistry; GOLM1, golgi membrane protein 1; PC, prostate cancer.

GOLM1 Expression is up-Related in PC Tissues and PC Cell Lines, While E-Cadherin is Down-Regulated

We evaluated the relationship among expression levels of GOLM1, E-cadherin in PC samples. We used immunohistochemistry (IHC) to quantitively analyze their expression in 13 adjacent normal specimens, 12 located specimens, and 10 metastatic specimens. IHC staining showed that GOLM1 was significantly up-regulated in PC, while E-cadherin was down-regulated (Figure 2A). Additionally, GOLM1 expression in metastatic tissues is higher than nonmetastatic cases and was negatively correlated with the expression of E-cadherin (Figure 2B). And the Western Blot results of PC cell lines were consistent with IHC (Figure 2C).

GOLM1 Promotes the Migration and Invasion Abilities of PC Cells

To determine whether GOLM1 contributes to the invasion and migration abilities of PC, we examined the effect of GOLM1 overexpression or knockdown on PC cells. Firstly, we used SiRNA to silence GOLM1 expression in DU145 cells and used a plasmid vector to overexpress GOLM1 in LNCaP cells. Then transwell invasion assays and scratch wound-healing assays were conducted to detect the invasion and migration abilities of PC cells. The results showed that GOLM1 knockdown decreased the invasion and migration abilities of DU145 cells compared to the control groups (Figure 3A, B). In opposite, GOLM1 overexpression promoted the invasion

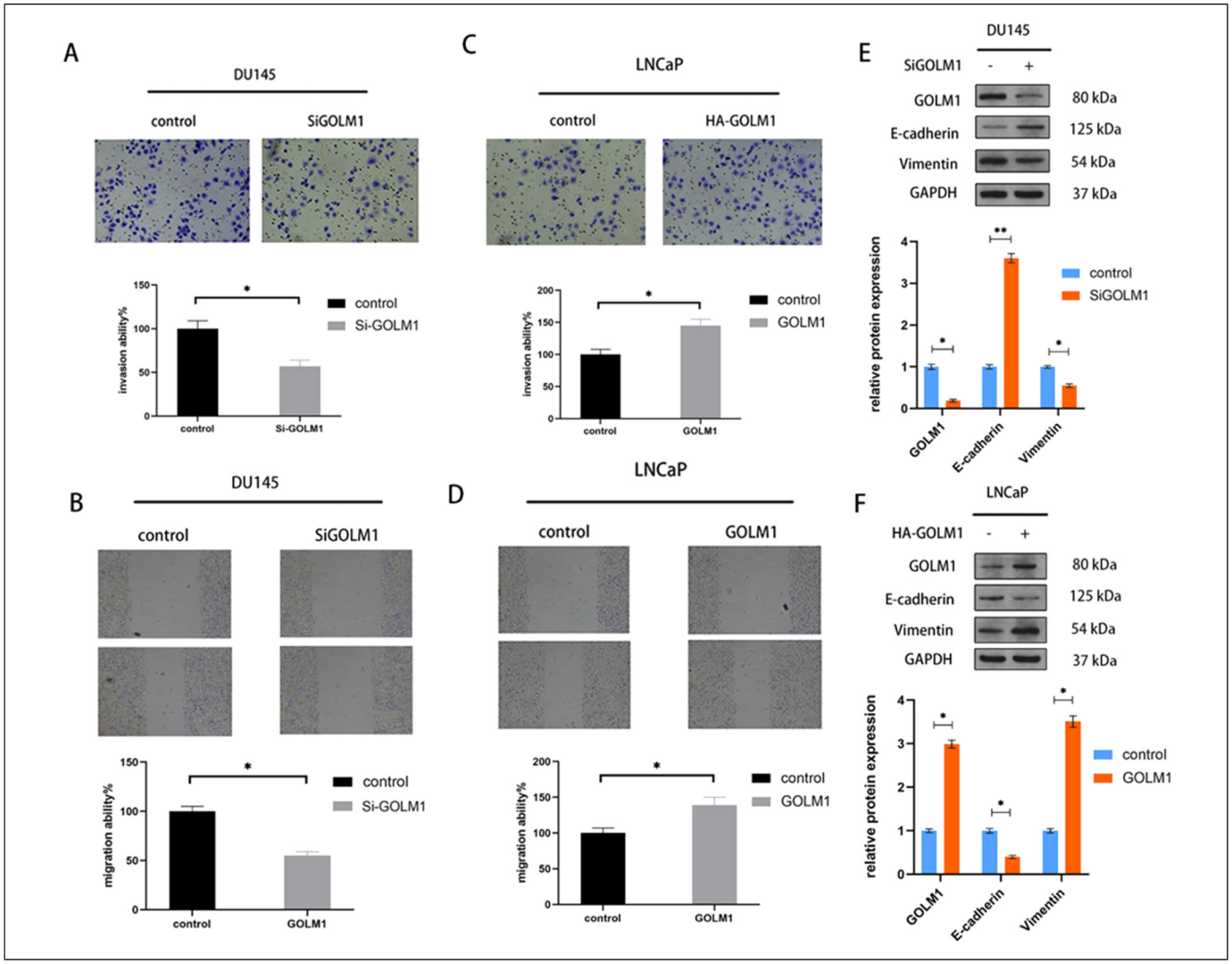

Figure 3. GOLM1 promotes the migration and invasion abilities of PC cells. (A) Transwell assay of DU145 cell after GOLM1 knockdown. (B) Scratch wound-healing assay of DU145 cell after GOLM1 knockdown. (C) Transwell assay of LNCaP cell after GOLM1 overexpression. (D) Scratch wound-healing assay of LNCaP cell after GOLM1 overexpression. (E, F) Relative expression levels of GOLM1, E-cadherin, Vimentin in LNCaP and DU145 cells. Values are expressed as the mean ± SEM. $^{*}P < .05$, $^{**}P < .01$, normalized by GADPH, relative to the control group, n = 3. Abbreviations: GOLM1, golgi membrane protein 1; PC, prostate cancer; SEM, standard error of mean.

and migration of LNCaP cells (Figure 3C, D). In addition, we examined the expression of the EMT markers E-cadherin and Vimentin. GOLM1 knockdown increased the level of E-cadherin and decreased the level of Vimentin in DU145 cells (Figure 3E). Meanwhile, GOLM1 overexpression down-regulated E-cadherin and up-regulated Vimentin in LNCaP cells. (Figure 3F). These results indicated that GOLM1 promotes the invasion and metastasis of PC cells.

GOLM1 Modulates EMT in PC Cells Though TGF-β1/Smad2 Signaling

According to recent literature, TGF-β1 is able to down-regulate E-cadherin and up-regulate Vimentin in PC cells, thus inducing PC EMT. And GOLM1 has been confirmed to play a key role in TGF-β1 induced EMT and cell invasion in Hepatocellular carcinoma and bladder carcinoma.[17,18] Consequently, we intended to investigate whether GOLM1 promoted EMT and invasion in PC via TGF-β1 mediation. Firstly, the knockdown of GOLM1 decreased Smad2 and p-Smad2 levels in DU145 cells (Figure 4A), whereas the overexpression of GOLM1 increased Smad2 and p-Smad2 levels in LNCaP cells (Figure 4B). These results suggested that GOLM1 can regulate the TGF-β1/Smad2 signaling pathway. Next, we conducted a rescue experiment to verify whether GOLM1 promotes PC cell metastasis by regulating TGF-β1/Smad2 signaling. Then, we treated LNCaP-GOLM1 cells with p-Smad2 inhibitor SB431542 but treated DU145-SiGOLM1 cells with 10 ng/ml TGF-β1 for 24 h. In the Transwell assay, with the treatment of TGF-β1, the number of cells invading through the Matrigel was significantly

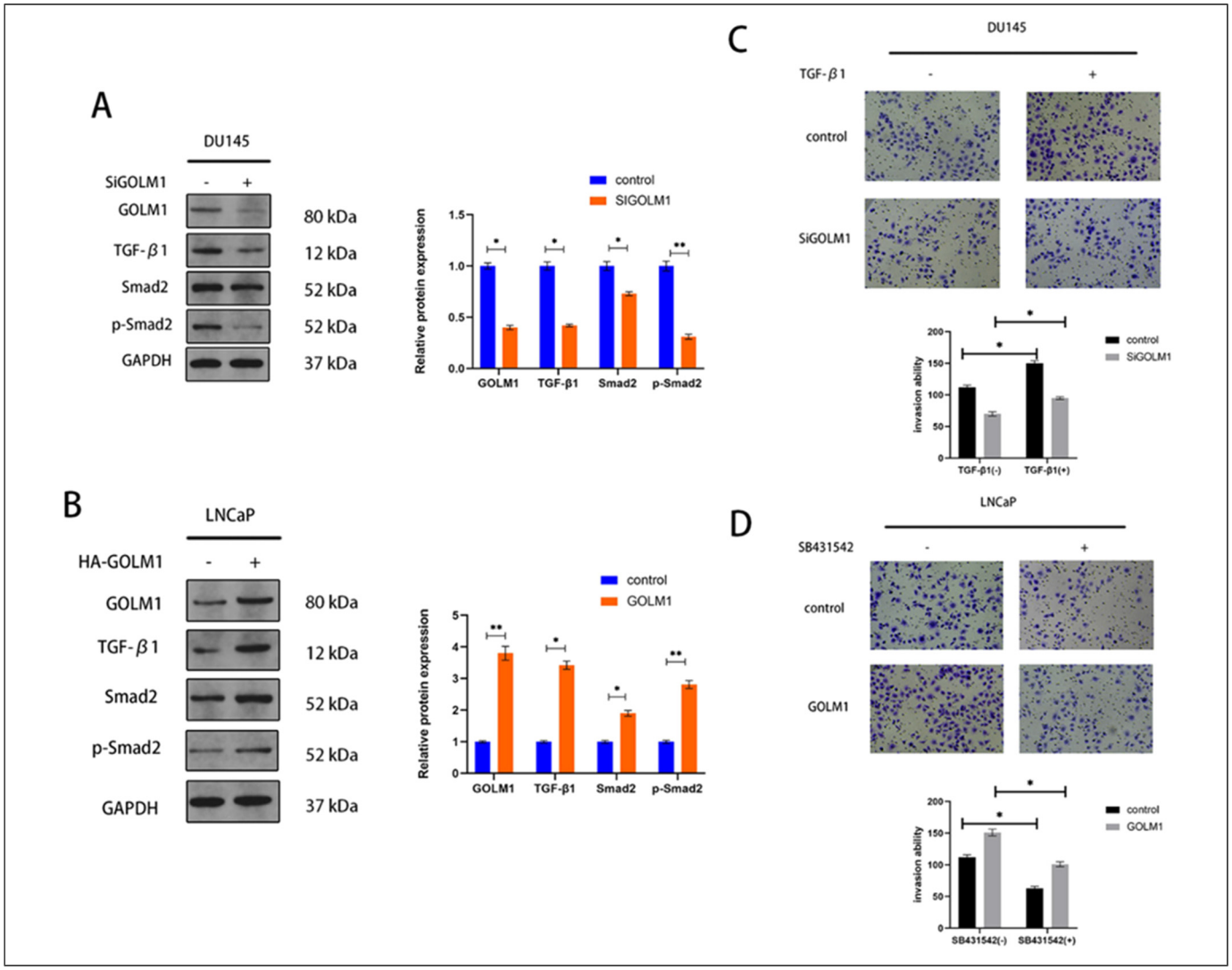

Figure 4. GOLM1 can regulate TGF-β1/Smad2 signaling in PC. (A) Silencing GOLM1 down-regulated TGF-β1, Smad2, p-Smad2 in PC cells. (B) GOLM1 overexpression up-regulated TGF-β1, Smad2, p-Smad2 in PC cells. (C) TGF-β1 treatment promoted cell invasion of PC and reverse the effects of GOLM1 knockdown. (D) SB431542 treatment supressed cell invasion of PC and reverse the effects of GOLM1 overexpression. Values are expressed as the mean ± SEM. *P < 0.05, **P < 0.01, normalized by GADPH, relative to the control group, n = 3. Abbreviations: GOLM1, golgi membrane protein 1; PC, prostate cancer; SEM, standard error of mean.

increased in DU145-SiGOLM1 cells (Figure 4C). Consistently, SB431542 also decreased the invasion abilities of LNCaP cells with GOLM1 overexpression (Figure 4D). Collectively, the results revealed that GOLM1 plays a key role in EMT of PC by regulating TGF-β1/Smads signaling.

Discussion

GOLM1 is detectable in extracellular spaces due to exosome-dependent secretion and has the potential to be a serum biomarker for the diagnosis of cancers.[13,14] GOLM1 was found to be up-regulated in tissues and urine of PC patients.[20] However, its function in PC remains ambiguous. In our study, we found GOLM1 was up-regulated in PC tissues and associated with a lower overall survival rate according to GEPIA database. Then we verified the expression level of GOLM1 in PC tissues and cell lines. Additionally, GOLM1 was negatively correlated with the EMT biomarker E-cadherin. Therefore, we supposed that GOLM1 can facilitate EMT process in PC. Consistent with our hypothesis, GOLM1 can promote the invasion and migration abilities of PC cells through activating TGF-β1/Smads signaling.

GOLM1 is a glycosylated protein, residing on cis-Golgi cisternae, which mainly functions in posttranslational modification and sorting of proteins, which are widely associated with mitosis, apoptosis, migration, and invasion.[21] GOLM1 is highly expressed in various cancers and is a secretory protein. Hence, it is detectable in the serum of cancer patients and has been regarded as a potential biomarker for cancer diagnosis, such as hepatocellular carcinoma. In recent years, it has been found that GOLM1 is an important factor in promoting epithelial–mesenchymal-transformation in cancer cells and leading to cancer metastasis.[19] It was reported that GOLM1 can promote cell invasion and migration in hepatocellular carcinoma[22] and oesophageal cancer.[23] The latest studies revealed that GOLM1 promotes hepatocellular carcinoma and bladder cancer invasion and metastasis by activating TGF-β1/Smad signaling. However, the role and mechanism of GOLM1 in PC are unclear.

TGF-β is considered to play crucial roles in multiple cellular biological processes as a multifunctional regulator. It is involved in cell proliferation, differentiation and bone remodeling etc.[24] interestingly, TGF-β has a paradoxical role in PC: TGF-β inhibits cell proliferation and promotes apoptosis as a tumor suppressor in the early stage, while it facilitates invasion and metastasis in late-stage.[25] In advanced PC, TGF-β is shown to be up-regulated, resulting in increased cell invasion and metastasis.[26] It plays a role in EMT by downregulating epithelial markers such as E-cadherin and upregulating interstitial markers such as vimentin.[7,25,27] TGF-β signaling contains Smad and non-Smad pathways.[25] In the Smad pathway, TGF-β binds to its receptor(TGF-β type II receptor, TβRII), leading to the activation of TβRI. Then activated TβRI recruits and phosphorylates Smad2 and Smad3, thus permitting them to form complexes with Smad4 to translocate into the nucleus to regulate target genes.[28] It is reported that c-Jun, one of the target genes of Smad protein complexes, can bind to snail promoters to initiate the migration and invasion of PC cells.[29] And non-Smad pathways include MAPK, mTOR, RAS, c-Src, PI3 K/Akt, etc[25] In our research, we have confirmed that GOLM1 is a regulator of TGF-β1.

In summary, we demonstrated that GOLM1 is highly expressed in PC and plays a key role in PC. GOLM1 is correlated with poor outcomes for patients. And, GOLM1 is able to promote EMT through activating TGF-β1/Smad2 signaling pathway in PC. Therefore, GOLM1 has the potential to become a novel biomarker for PC diagnosis and risk classification, as well as the target for the treatment of advanced PC. However, there are still many limitations in our research. We did not explore the mechanism of interaction between GOLM1 and TGF-β1, so it is still unclear how GOLM1 acts on TGF-β1. Furthermore, it is interesting that GOLM1 can be secreted into extracellular spaces by the exosome, but the function of exosomal GOLM1 is not verified in this study. And in subsequent studies, in vivo experiments should be conducted.

Conclusion

Our research demonstrated that GOLM1 is up-regulated in PC and can promote the EMT process by activating TGF-β1/Smad2 signaling pathway, thus playing oncogenic functions.

Author Information

Xuke Qin: Doctor of Medicine; Lin Liu: Master of Medicine, attending doctor; Yanze Li: Doctor of Medicine; Hongbo Luo: Doctor of Medicine, chief physician; Hui Chen: Doctor of Medicine, Deputy chief physician; Xiaodong Weng: Doctor of Medicine, Deputy chief physician

Declaration of Conflicting Interests

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Ethical Approval

This study was approved by the Institutional Ethics Committee of Renmin Hospital of Wuhan University and strictly followed the guidelines of the Institutional Ethics Committee.

Informed Consent

Informed consent was requested as anonymous specimens and was obtained from all participants in this study.

ORCID iD

Xuke Qin https://orcid.org/0000-0001-9273-3081

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