Submitted: 12 February, 2024 Accepted: 09 April, 2024 Published: 15 June, 2024 DOI:10.22514/ejgo.2024.053

ORIGINAL RESEARCH

European Journal of Gynaecological Oncology

Knockdown of GDF15 inhibits endometrial cancer cell proliferation and EMT

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Abstract

Endometrial cancer (EC) is a malignant tumor affecting the uterine upper layer. Despite recent advancements, identifying new therapeutic targets remains important for improving patient prognosis. Growth differentiation factor 15 (GDF15) belongs to the Transforming Growth Factor (TGF)-β superfamily and is often upregulated in pathological conditions, including injury and cancers. However, its involvement in EC remains poorly understood. This study aims to elucidate the significance of GDF15 in EC and its potential underlying mechanism. Our results indicate increased GDF15 expression levels in EC tissues, and the knockdown of GDF15 was found to suppress EC cell growth and epithelial-mesenchymal transition (EMT). Moreover, GDF15 depletion inhibited the TGF-β pathway activation. In summary, GDF15 can promote EC cell growth and EMT by modulating the TGF-β/Smad2/Smad3 axis.

Keywords

Endometrial cancer (EC); Growth differentiation factor 15 (GDF15); Growth; EMT; TGF-β/Smad2/Smad3 axis

1. Introduction

Endometrial cancer (EC) is a malignant tumor primarily affecting the upper layer of the uterus, showing a concerning increase in both incidence and associated mortality worldwide [1]. In 2020, epidemiological investigations reported a total of 417,367 cases worldwide [2, 3] and that its incidence is rapidly rising. The 5-year survival rates of EC patients vary significantly based on the stage of diagnosis [4], with patients diagnosed with localized tumors having a survival rate $\geq$95% while those with metastasis beyond the uterus facing a sharp decline in survival, ranging from 69% with local metastasis to only 17% with distant metastasis [5, 6]. Although advancements in targeted therapy for EC have been achieved through extensive research into its pathological mechanisms [7, 8], further improvements in prognosis necessitate the identification and development of novel therapeutic targets.

Growth differentiation factor 15 (GDF15) is a member of the transforming growth factor-beta (TGF-β) superfamily. Normally, GDF15 exhibits weak and stable expression across most tissues. However, its expression significantly increases under pathological conditions such as injury, inflammation, and cancer [9, 10]. Mounting evidence suggests a pivotal role for GDF15 in various cancer-related processes, including tumor growth, motility, and angiogenesis [11–13]. Similarly, recent studies have reported higher expression of GDF15 mRNA and protein in the biopsies of patients with prostate cancer, urothelial cancer, kidney cancer, ovarian cancer, pancreatic cancer and colorectal cancer, and observed to be associated with shortened survival in patients with multiple cancers [11–14]. GDF15 knockdown in glioblastoma has been shown to reduce both cell growth and tumorigenesis [14]. In cervical cancer cells, GDF15 promoted growth by upregulating CyclinD1 and CyclinE1 while downregulating p21 through the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) and mitogen-activated protein kinases (MAPK)/extracellular signal-regulated kinase (ERK) pathways within the ErbB2 complex [15]. Its expression correlated with aggressive gastric cancer, potentially through the promotion of signal transducer and activator of transcription 3 (STAT3) phosphorylation, suggesting the GDF15-STAT3 signaling axis as a promising therapeutic target against gastric cancer [11]. In colorectal cancer, GDF15 may facilitate metastasis by activating epithelial-mesenchymal transition (EMT) [16], and it holds promise as a novel prognostic marker in clinical settings for colorectal cancer [16]. Moreover, inhibition of GDF15 leads to 5-fluorouracil resistance in human colon cancer by modulating epithelial-mesenchymal transformation and apoptosis [17]. Despite these findings, the role of GDF15 in EC remains underexplored, with its underlying mechanism yet to be elucidated.

This study aims to elucidate the role of GDF15 in EC and its underlying mechanism. The results showed that GDF15 is overexpressed in EC and promotes the growth and EMT of EC cells by regulating the TGF-β pathway, indicating that targeting GDF15 could hold promise as a potential therapeutic approach for EC.

2. Materials and methods

2.1 Bioinformatic analysis

The Gene Expression Profiling Interactive Analysis (GEPIA) database was used to analyze GDF15 expression in EC tissues sourced from The Cancer Genome Atlas (TCGA) database.

2.2 Cell culture and transfection

The human endometrial epithelial cell line HcerEpic and four types of EC cell lines, namely JEC, KLE, HEC-1-A, and Ishikawa cells, were procured from Jennio (Guangzhou, China) and cultured in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% fatal bovine serum (FBS) at 37 °C in a 5% CO_2 atmosphere. The passage number of these cell lines was less than 10. The cells were transfected with shNC (negative control) or shGDF15 plasmids (Addgene, USA) using Lipofectamine 3000 (L3000015, Thermo, Waltham, MA, USA) for 24 h. The sequences of *GDF15* shRNA were as follows: 5′-AAA AGA CCA ACT GCT GGC AGA ATC TTT GGA TCC AAA GAT TCT GCC AGC AGT TGG TC-3′. A volume of 100 μL of the transfection mixture was slowly added to the 6-well plate, and cells were incubated for 6 h. The transfection efficiency was verified for subsequent experiments.

2.3 CCK-8 assay

EC cells were seeded into 96-well plates and allowed to incubate. Subsequently, cells were cultured with cell counting kit (CCK)-8 solution (C0038, Beyotime, Beijing, China) for 4 h. The optical density at 450 nm (OD450) was then measured.

2.4 Colony formation assay

EC cells were seeded into 24-well plates and maintained for 14 days at 37 °C. Then, the cells were incubated with 0.2% crystal violet solution and imaged using a fluorescence microscope (LSM710, Zeiss, Oberkochen, Germany).

2.5 Cell apoptosis

Apoptosis detection was performed using Annexin V/Propidium iodide (PI) apoptosis detection following the manufacturer's protocol (Sigma Aldrich, USA).

2.6 Immunoblotting

Protein extraction from EC cells was conducted, followed by separation *via* Sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) and transfer to Polyvinylidene Fluoride (PVDF) membranes. The membranes were blocked with 5% Bovine serum albumin (BSA) for 1 h. Primary antibodies targeting GDF15 (1:500, ab206414, Abcam), E-cadherin (1:1000, ab40772, Abcam), N-cadherin (1:1000, ab245117, Abcam), α-Smooth; muscle actin (SMA) (1:300, ab7817, Abcam), Smad2 (1:1000, ab40855, Abcam), Smad3 (1:1000, ab40854, Abcam), p-Smad2 (1:500, ab280888, Abcam), p-Smad3 (1:300, ab63403, Abcam), and β-actin (1:3000, ab8226, Abcam) were incubated with the membranes. Subsequently, secondary antibodies were applied, followed by imaging after chemiluminescence treatment.

2.7 Statistics

GraphPad software (Graphpad, plc., San Diego, CA, USA) was utilized for statistical analysis, and the student's *t*-test was performed. Data are presented as mean ± Standard deviation (SD), and significance was considered at $p < 0.05$.

3. Results

3.1 GDF15 was highly expressed in EC tissues and cells

To elucidate its role in EC progression, we initially examined its expression in human EC tissue samples and cells. Analysis using the GEPIA database revealed abnormal upregulation of GDF15 in human EC tissues (Fig. 1a). Furthermore, immunoblot assays were conducted to assess GDF15 expression levels in HcerEpic and the JEC, KLE, HEC-1-A and Ishikawa cell lines. The results demonstrated elevated expression of GDF15 in EC cells (Fig. 1b, $p < 0.01$), confirming its overexpression in EC.

3.2 Knockdown of GDF15 suppressed the growth of EC cells

Subsequent knockdown of GDF15 was performed to assess its impact on EC cell growth. GDF15 shRNAs were transfected

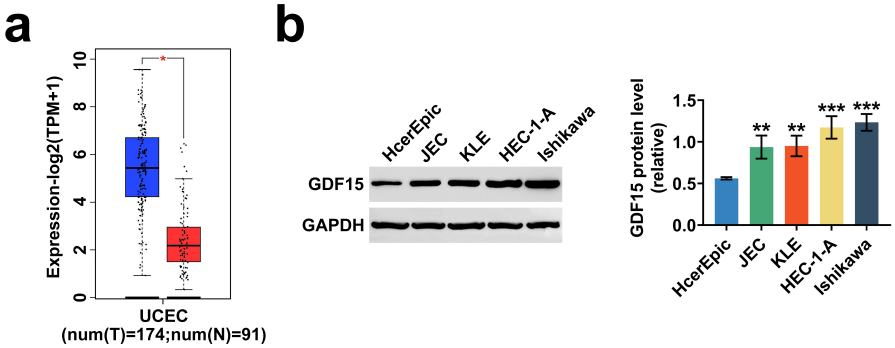


FIGURE 1. Overexpression of GDF15 in EC. (a) Analysis of the GEPIA database showing the transcripts per million (TPM) value of GDF15 in 174 UCEC tissues and 91 normal tissues. *$p < 0.05$. (b) Immunoblot assays revealing the expression of GDF15 in HcerEpic, JEC, KLE, HEC-1-A, and Ishikawa cells. **$p < 0.01$, ***$p < 0.001$, *vs.* HcerEpic. GAPDH, glyceraldehyde-3-phosphate dehydrogenase; GDF15, Growth differentiation factor 15; EC, endometrial cancer.

into HEC-1-A and Ishikawa cells to deplete GDF15 expression at the cellular level. Immunoblot assays confirmed the effective downexpression of GDF15 in both cell lines post-transfection (Fig. 2a, $p < 0.01$). Following this, CCK-8 assays revealed a significant decrease in cell survival rates in HEC-1-A and Ishikawa cells upon GDF15 depletion, as evidenced by reduced OD450 values (Fig. 2b, $p < 0.001$). Additionally, colony formation assays demonstrated a decrease in colony numbers upon GDF15 knockdown in both cell lines, indicative of suppressed cell growth (Fig. 2c, $p < 0.001$). Moreover, FCM assays revealed enhanced apoptosis of HEC-1-A and Ishikawa cells upon GDF15 depletion (Fig. 2d, $p < 0.001$). Overall, these findings suggest that GDF15 depletion inhibits the growth of EC cells.

3.3 Depletion of GDF15 suppressed the EMT in EC cells

Next, we investigated the influence of GDF15 on the EMT process in EC cells. Immunoblot assays revealed that depletion of GDF15 led to suppression of N-cadherin and α-SMA expression, along with upregulation of E-cadherin expression, three key EMT markers, in both HEC-1-A and Ishikawa cells (Fig. 3, $p < 0.05$). These results indicate that GDF15 depletion restrains the EMT process in EC cells.

3.4 GDF15 activated the TGF-β pathway in EC cells

Moreover, we elucidated the mechanism underlying the suppression of EC progression by GDF15 depletion. Given the pivotal role of the TGF-β pathway in EC, we investigated the effects of GDF15 on this pathway in HEC-1-A and Ishikawa cells. Immunoblot analysis was conducted to assess the expression and phosphorylation levels of Smad2 and Smad3, two key regulators of the TGF-β pathway, in EC cells. Remarkably, the phosphorylation levels of both Smad2 and Smad3 were found to be reduced in these EC cells, indicating suppression of the TGF-β pathway (Fig. 4, $p < 0.05$). Thus, the knockdown of GDF15 resulted in the suppression of the TGF-β pathway in EC cells.

4. Discussion

EC originates from the endometrium, the inner lining of the uterus, and ranks among the most prevalent gynecological cancers [5]. While it predominantly affects postmenopausal women, it can also occur in younger individuals. Common symptoms include abnormal vaginal bleeding, pelvic pain, and urinary difficulties [1]. Diagnosis typically involves pelvic examinations, ultrasound, and endometrial biopsy. Treatment options, such as surgery, radiotherapy, chemotherapy, and hormone therapy, are tailored to the cancer stage and patient's overall health [4, 7]. Timely detection and intervention are critical for improving cure rates [4, 7]. Targeted therapy for EC focuses on specific genetic mutations or aberrant protein expression in tumor cells [7, 8]. Treatment decisions hinge upon the tumor's molecular profile, often requiring genetic testing to devise an optimal treatment strategy, which may involve combinations of chemotherapy, radiotherapy, or surgery [7, 8]. Despite advancements, there remains a need for more effective targets for EC. Intriguingly, our findings demonstrate elevated expression of GDF15 in human EC and its involvement in mediating EC cell growth and EMT. In this study, we propose that GDF15 could be a promising therapeutic target for EC.

GDF15, a cytokine within the TGF-β superfamily, is intricately involved in inflammation, cell growth, apoptosis, and metabolism regulation [9, 11]. It holds promise as a biomarker for various diseases, including cancer, cardiovascular diseases, and metabolic disorders, with heightened levels often indicating a poor prognosis, particularly in colorectal, pancreatic, and prostate cancers [10, 13, 15, 16]. Moreover, GDF15 plays a crucial role in appetite suppression, thereby holding implications for the treatment of obesity and metabolic syndrome [18–20]. Its multifaceted involvement in both physiological and pathological processes renders it a subject of considerable ongoing research interest [18–20]. Through a series of *in vitro* assays such as CCK-8, flow cytometry (FCM), and immunoblotting, our data confirm its significant role in EC. Herein, we demonstrated that GDF15 contributes to cell growth as well as EMT of EC cells. However, further studies are warranted to elucidate the precise underlying mechanism.

The TGF-β pathway plays a pivotal role in various biological processes, encompassing cell proliferation, differentiation, migration, and apoptosis [21]. Importantly, it can also maintain tissue homeostasis [21] and suppress tumor formation by activating downstream signaling pathways upon binding to its receptors, with Smad2 and Smad3 being central proteins in this cascade [22]. However, dysregulation of the TGF-β signaling pathway often occurs in EC, potentially facilitating tumor development and progression [23, 24]. This dysregulation may result from reduced expression of TGF-β receptors or mutations in downstream signaling components, leading to loss of normal suppression of cell proliferation and induction of apoptosis [23, 24]. Furthermore, TGF-β signaling can indirectly support tumor growth and metastasis within the tumor microenvironment by promoting processes such as angiogenesis, immune suppression, and extracellular matrix (ECM) remodeling [25]. Researchers are actively investigating therapeutic strategies targeting the TGF-β pathway, including the use of TGF-β inhibitors to counteract its tumor-promoting effects [26]. However, careful consideration of potential side effects is essential due to the crucial role of TGF-β in normal physiological processes. A deeper understanding of the TGF-β pathway's involvement in EC holds promise for the development of novel treatment strategies aimed at improving patient outcomes. Significantly, our data confirm that GDF15 may mediate the TGF-β pathway and further contribute to the progression of EC.

There are several limitations that should be acknowledged. Firstly, our experiments were conducted *in vitro* using EC cell lines, which, while commonly employed models for EC research, may not fully recapitulate the complex physiology of human EC progression. Therefore, the findings may not be directly translatable to the clinical setting. Additionally, while multiple drugs have the potential to exert anti-tumor effects as inhibitors of GDF15, further validation of GDF15 as a potential target for EC is required *in vivo*.

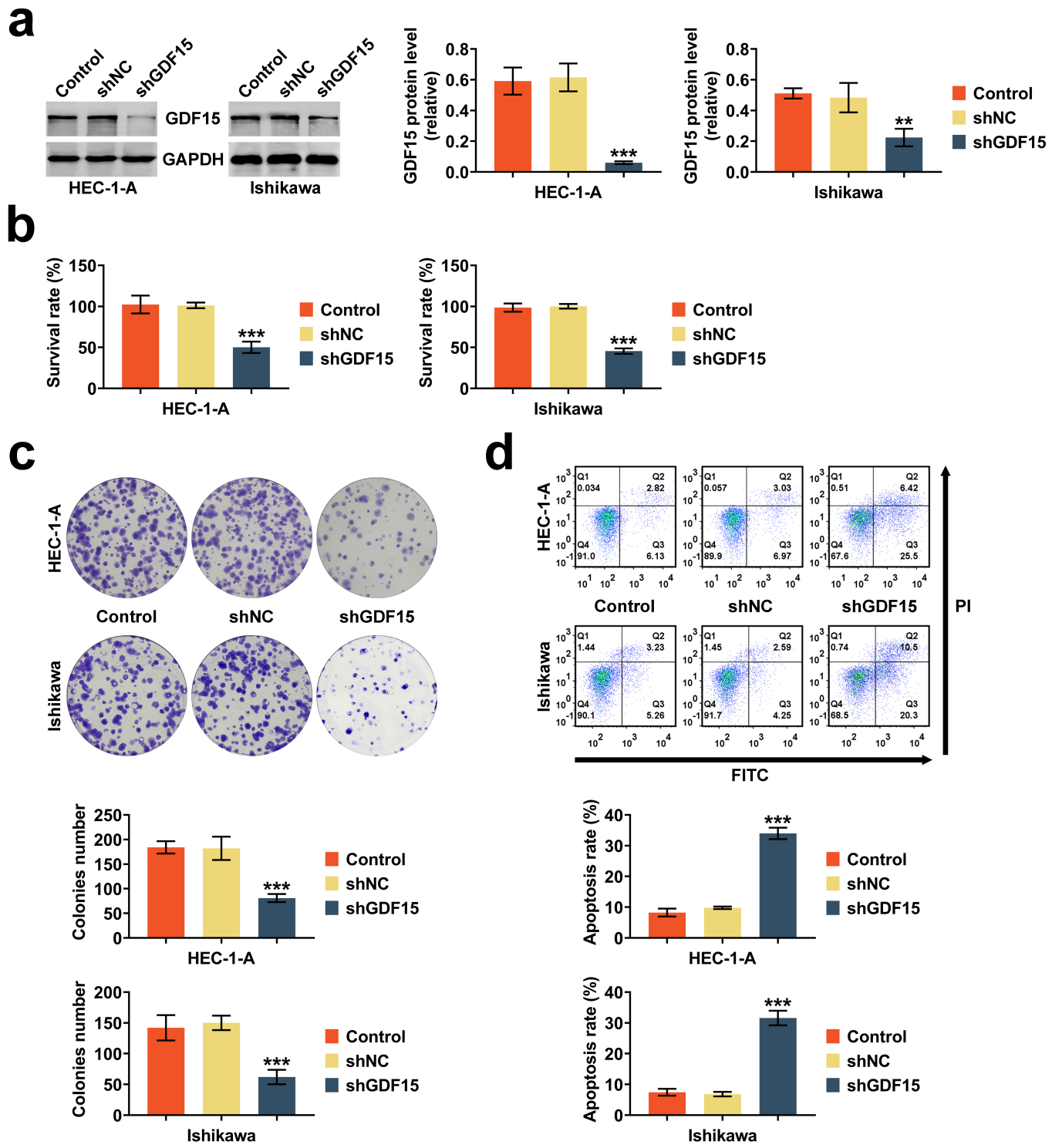
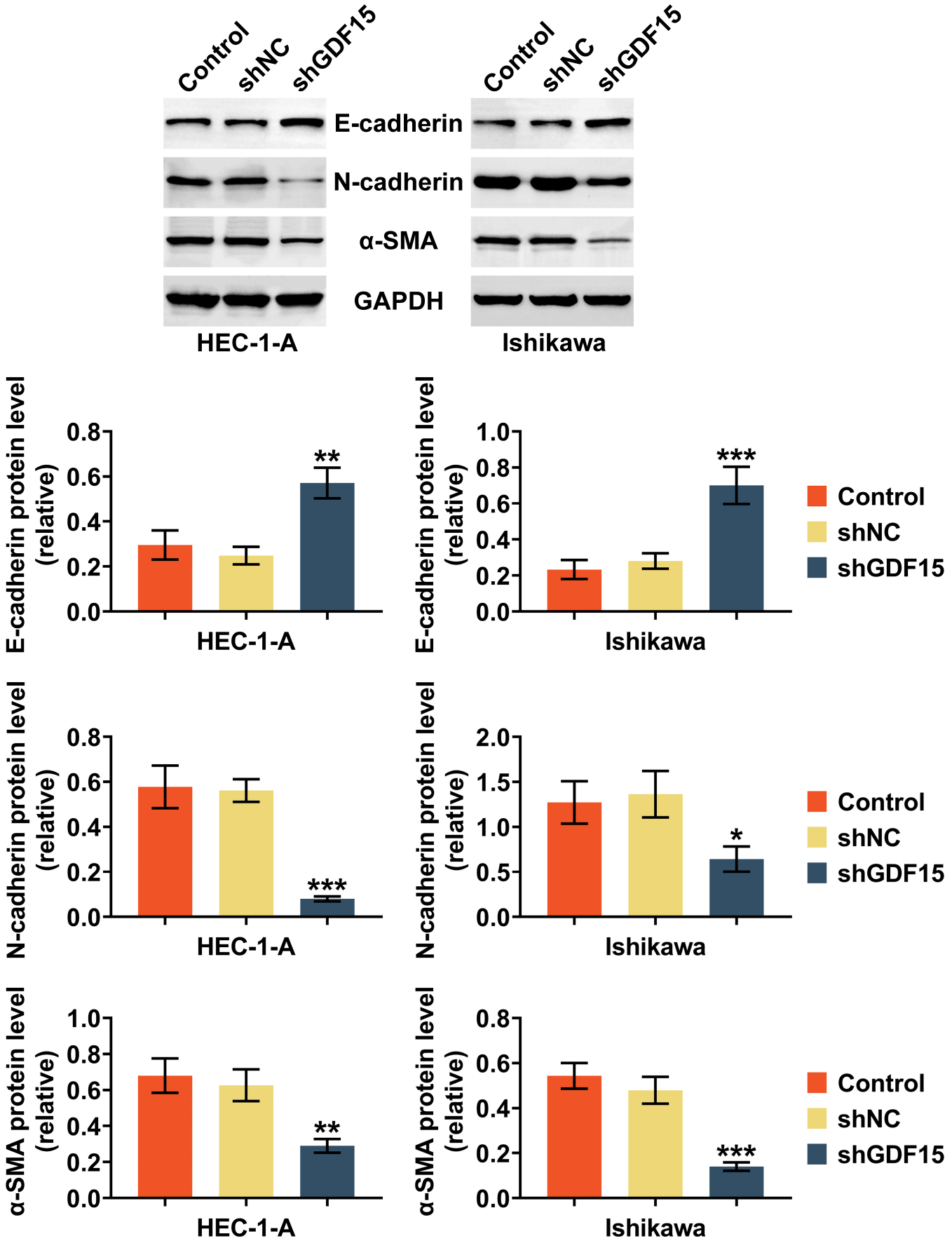


FIGURE 2. Knockdown of GDF15 suppressed the growth of EC cells. (a) Immunoblot assays showing the expression of GDF15 in HEC-1-A and Ishikawa cells upon the transfection of shNC or shGDF15 plasmids for 24 h. (b) CCK-8 assays revealing the growth of HEC-1-A and Ishikawa cells upon the transfection of shNC or shGDF15 plasmids for 24 h. (c) Colony formation assays showing the growth of HEC-1-A and Ishikawa cells upon the transfection of shNC or shGDF15 plasmids for 24 h. The colony numbers were counted. (d) FCM assays showing the apoptosis degree of HEC-1-A and Ishikawa cells upon transfection of shNC or shGDF15 plasmids for 24 h. The percentage of apoptosis cells was measured. $^{**}p < 0.01$, $^{***}p < 0.001$, shGDF15 *vs.* shNC. NC, negative control; EC, endometrial cancer; GDF15, Growth differentiation factor 15; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; PI, Propidium iodide; FITC, Fluorescein Isothiocyanate.



F I G U R E 3. Depletion of GDF15 suppressed the EMT in EC cells. Immunoblot assays showing the expression of E-cadherin, N-cadherin, and α-SMA in HEC-1-A and Ishikawa cells upon transfection of shNC or shGDF15 plasmids for 24 h. The relative expression levels of these proteins were quantified. $*p < 0.05$, $**p < 0.01$, $***p < 0.001$, shGDF15 *vs.* shNC. NC, negative control; GDF15, Growth differentiation factor 15; SMA, Smooth muscle actin.

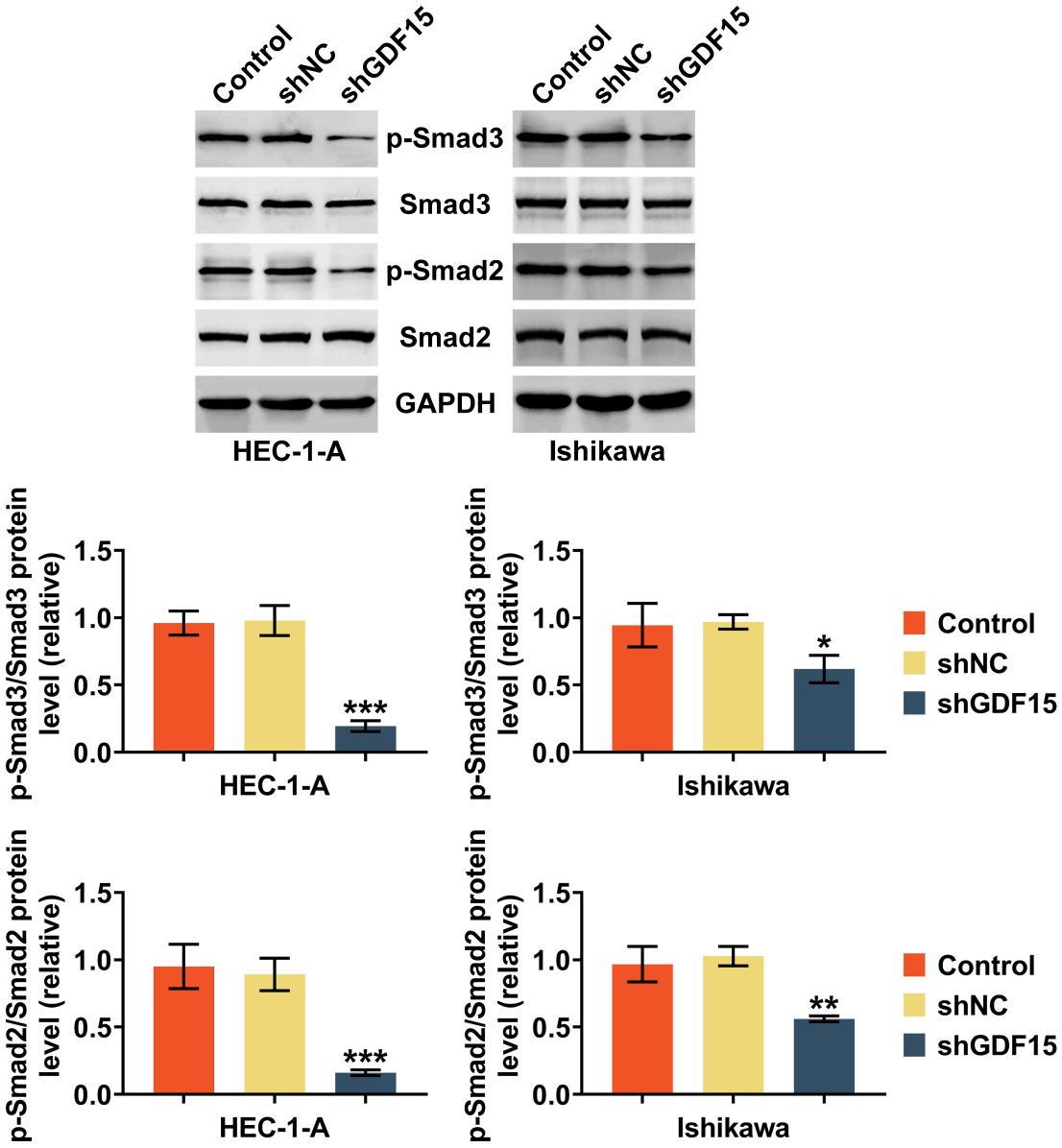


FIGURE 4. GDF15 activated the TGF-β pathway in EC cells. Immunoblot assays showing the expression and phosphorylation levels of Smad2 and Smad3 in HEC-1-A and Ishikawa cells upon transfection of shNC or shGDF15 plasmids for 24 h. The relative phosphorylation levels of these proteins were quantified. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, shGDF15 *vs.* shNC. NC, negative control; GDF15, Growth differentiation factor 15; GAPDH, glyceraldehyde-3-phosphate dehydrogenase.

5. Conclusions

In summary, our study highlights the high expression of GDF15 in human EC and its contribution to the growth and EMT of EC cells *via* targeting the TGF-β pathway. These findings suggest that GDF15 could serve as a promising drug target for the treatment of EC. However, further research, particularly *in vivo* studies, is warranted to validate these findings and explore the therapeutic potential of targeting GDF15 in EC.

AVAILABILITY OF DATA AND MATERIALS

The authors declare that all data supporting the findings of this study are available within the paper and any raw data can be obtained from the corresponding author upon request.

AUTHOR CONTRIBUTIONS

LTY—designed the study and carried them out; prepared the manuscript for publication and reviewed the draft of the manuscript. LTY, JS and KDC—supervised the data collection, analyzed the data, interpreted the data. All authors have read and approved the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This article does not contain any studies with human participants or animals performed by any of the authors.

ACKNOWLEDGMENT

Not applicable.

FUNDING

This research received no external funding.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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How to cite this article: Litao Yu, Jing Shi, Kedan Cao. Knockdown of GDF15 inhibits endometrial cancer cell proliferation and EMT. European Journal of Gynaecological Oncology. 2024; 45(3): 95-101. doi: 10.22514/ejgo.2024.053.