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ORIGINAL RESEARCH

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FOXK2 affects the motility of endometrial cancer cells by mediating ZEB1

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Abstract

Endometrial cancer (EC) is a prevalent type of malignancy, highlighting the need for the development of effective therapies and the identification of novel therapeutic targets. FOXK2, a member of the Foxhead box (FOX) family, has been implicated in cancer progression. However, the role of FOXK2 in EC and its underlying mechanisms remain poorly understood. This study investigates the function of FOXK2 in EC. FOXK2 is significantly overexpressed in EC tissues. Knockdown of FOXK2 impedes the proliferation of EC cells and inhibits their motility and epithelial-mesenchymal transition (EMT). Mechanistically, FOXK2 depletion disrupts EC progression by targeting Zinc Finger E-Box Binding Homeobox 1 (ZEB1). In conclusion, FOXK2 regulates EC cell progression through modulation of ZEB1.

Keywords

Foxhead box K2 (FOXK2); Endometrial cancer (EC); Motility; EMT; ZEB1

1. Introduction

Endometrial cancer (EC) is a prevalent type of malignancy and ranks fourth in incidence among cancers affecting women [1]. In China, both the incidence as well as mortality rates of EC are increasing in line with population growth [2]. As one of the most common gynecological cancers, the overall prognosis for EC is relatively favorable; however, recurrence remains a significant issue, particularly for patients with high-risk factors [3]. While surgery is the primary treatment modality, radiotherapy plays a crucial supplementary role [3, 4]. Despite advances in treatment, the management of advanced EC requires further improvement, indicating an urgent need for novel therapeutic approaches and targets.

FOXK2, a member of the Foxhead box (FOX) family, is vital in various cellular processes, including metabolism, and proliferation [5]. Unlike other FOX family members, FOXK2 exhibits context-dependent and tumor-specific functions [6]. In colon cancer models, FOXK2 promotes tumor progression by Disheveled (DVL) and activating the Wnt axis. Conversely, it inhibits the proliferation of estrogen receptor-positive breast cancer cells by interacting with transcriptional co-suppressor complexes [7]. In ovarian cancer, FOXK2 influences tumor progression through the unfolded protein response pathway [8], and in colorectal cancer, it enhances metastasis by upregulating ZEB1 and Epidermal Growth Factor Receptor (EGFR) [9]. Additionally, FOXK2 has been shown to facilitate the proliferation of thyroid papillary cancer cells by downregulating autophagy [10].

ZEB1 is a critical transcription factor involved in EMT by regulating E-cadherin expression. ZEB1 represses E-cadherin expression by binding to E-box sequences in its promoter region [11, 12]. ZEB1 has been implicated in promoting EMT and tumor invasion in epithelial cells [13], and it enhances EC invasion and metastasis by interacting with the Hepatoma-Derived Growth Factor (HDGF) and inducing its transcription [14].

Despite these insights, the role of FOXK2 in EC and its underlying mechanisms remain unclear. This study aims to elucidate the function of FOXK2 in EC and its mechanism of action. FOXK2 regulates the motility of EC cells through the modulation of ZEB1, suggesting that FOXK2 could serve as a target for EC.

2. Materials and methods

2.1 Bioinformatics

Transcriptome and survival data were sourced from The Cancer Genome Atlas (TCGA) database. The expression of FOXK2 in EC were analyzed using TCGA.

2.2 Cell culture and transfection

A human endometrial cell line (hESC), as well as four EC cell lines (Ishikawa, RL95-2, KLE, and AN3_CA) were purchased from American Type Culture Collection (ATCC). Cells were cultured in a complete medium. After 12 hours, Lipofectamine®3000 (Invitrogen, Carlsbad, CA, USA) was used to co-transfect cells with sh-negative control (NC), si-FOXK2, pcDNA3.1-Vector and FOXK2 plasmids.

2.3 Western blotting

Proteins were separated by Sodium Dodecyl Sulfate-Polyacrylamide Gel Electrophoresis (SDS-PAGE) and transferred to Polyvinylidene Fluoride (PVDF) membranes. Membranes were blocked with Tris-Buffered Saline with Tween 20 (TBST) containing 5% milk for 1 hour and then incubated overnight at 4 °C with the following primary antibodies: FOXK2 (Abcam, Cambridge, UK, ab309489; 1:500), E-cadherin (Abcam, Cambridge, UK, ab231303; 1:1000), N-cadherin (Abcam, Cambridge, UK, ab76011; 1:500), Vimentin (Abcam, Cambridge, UK, ab92547; 1:1000), ZEB1 (Abcam, Cambridge, UK, ab203829; 1:1000), and β-actin (Abcam, Cambridge, UK, ab8226; 1:3000). Secondary antibodies were applied for 1 hour, and protein bands were visualized using a chemiluminescence detection system.

2.4 Cell counting kit-8 (CCK-8) assay

EC cells were seeded into 96-well plates at a density of 1000 cells per well and cultured for 2 days. Cells were then incubated with CCK-8 solution (Beyotime, C0038, Beijing, China) for 4 hours. Absorbance at 450 nm was measured.

2.5 Colony formation assay

EC cells were plated in 6-well plates and maintained in media supplemented with 10% Fetal Bovine Serum (FBS) for 14 days at 37 °C. Cells were fixed with Paraformaldehyde (PFA) for 15 minutes, stained with 0.1% crystal violet, and the obtained colonies were photographed.

2.6 Transwell assay

EC cells were seeded into the upper chamber of transwell inserts and allowed to migrate for 24 hours. Cells that invaded through the membrane were fixed and stained with 2% crystal violet, and images were captured to assess cell invasion.

2.7 Wound-healing assay

A scratch was made in the monolayer of EC cells using a 10-μL pipette tip. The cells were washed twice, and images of the wound area were taken at 0 and 24 hours to evaluate wound closure.

2.8 2.8 Statistical analysis

Statistical analyses were performed using GraphPad Prism 5.0 software (GraphPad Software, LLC, San Diego, CA, USA). Data are expressed as mean $\pm$ Standard Deviation (SD). Differences were considered statistically significant at $p < 0.05$.

3. Results

3.1 FOXK2 is highly expressed in EC

To examine the role of FOXK2 in EC, we analyzed its expression levels using data from TCGA. Bioinformatics analysis revealed that FOXK2 exhibited high transcript levels in EC tissues (Fig. 1a). Furthermore, FOXK2 expression was correlated with survival rates in EC patients, suggesting its potential role in disease prognosis (Fig. 1b). Consistent with these findings, Western blot analysis confirmed elevated FOXK2 protein levels in the human endometrial cell line hESC and in four EC cell lines: Ishikawa, RL95-2, KLE and AN3_CA (Fig. 1c).

3.2 Knockdown of FOXK2 blocks EC cell proliferation

To assess the functional role of FOXK2 in EC cell proliferation, we transfected FOXK2 siRNA (si-FOXK2) and FOXK2 overexpression plasmids into the Ishikawa and KLE cell lines. Transfection with si-FOXK2 effectively reduced FOXK2 expression compared to the negative control, while FOXK2 overexpression plasmids increased its expression (Fig. 2a). Cell viability was evaluated using the CCK-8 assay, which showed that FOXK2 knockdown significantly decreased cell viability, as indicated by a reduced Optical Density (OD)450 value. Conversely, FOXK2 overexpression resulted in increased OD450 values (Fig. 2b). Additionally, colony formation assays revealed that FOXK2 depletion reduced the number of colonies formed by Ishikawa and KLE cells, while its overexpression enhanced colony formation (Fig. 2c). These findings suggest that FOXK2 depletion inhibits EC cell proliferation.

3.3 Depletion of FOXK2 restrains EC cell motility

Depletion of FOXK2 resulted in a significant reduction in the migration of Ishikawa and KLE cells, as evidenced by an increased wound width. Conversely, FOXK2 overexpression stimulated cell migration (Fig. 3a). Transwell assays further supported these observations, showing that FOXK2 depletion decreased the number of invasive Ishikawa and KLE cells, while FOXK2 overexpression promoted cell invasion (Fig. 3b). These results indicate that FOXK2 plays a role in modulating EC cell motility.

3.4 FOXK2 ablation suppresses EMT in EC cells

To determine whether FOXK2 influences EMT in EC cells, we conducted Western blot analyses to assess the expression of EMT markers. FOXK2 knockdown resulted in decreased levels of N-cadherin as well as increased levels of E-cadherin, while FOXK2 overexpression led to the opposite effect, indicating that FOXK2 promotes EMT in EC cells (Fig. 4a). Additionally, FOXK2 depletion reduced Vimentin levels in Ishikawa and KLE cells, whereas its overexpression increased Vimentin expression (Fig. 4b). These results further confirm that FOXK2 regulates EMT in EC cells.

3.5 FOXK2 depletion inhibited EC by targeting ZEB1

To investigate the mechanism by which FOXK2 affects EC, we overexpressed ZEB1 in FOXK2-depleted EC cells using a ZEB1 overexpression plasmid. Western blot analysis revealed that FOXK2 depletion led to decreased ZEB1 levels in Ishikawa and KLE cells, while ZEB1 overexpression increased

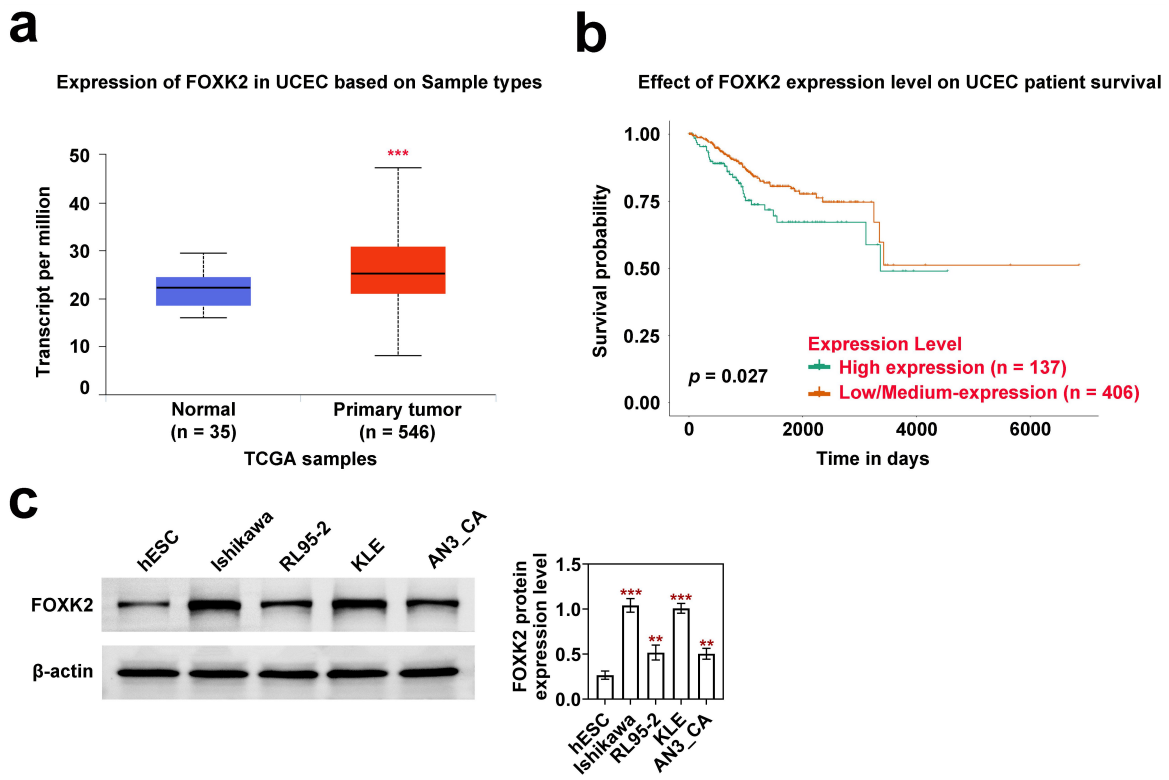

FIGURE 1. FOXK2 Expression in Endometrial Cancer (EC) Tissues and Cell Lines. (a) Analysis of FOXK2 transcript levels in EC tissues (n = 546) and normal tissues (n = 35) from The Cancer Genome Atlas (TCGA) database, presented as transcripts per million (TPM). (b) Correlation between FOXK2 expression levels (high: n = 137; low: n = 406) and patient survival in EC, based on TCGA data ($p = 0.027$). (c) Immunoblot analysis of FOXK2 expression in the indicated EC cell lines. Error bars represent standard deviation (SD). $^{**}p < 0.01$, $^{***}p < 0.001$. FOXK2: Foxhead box K2; hESC: human endometrial cell line; UCEC: Uterine Corpus Endometrial Carcinoma.

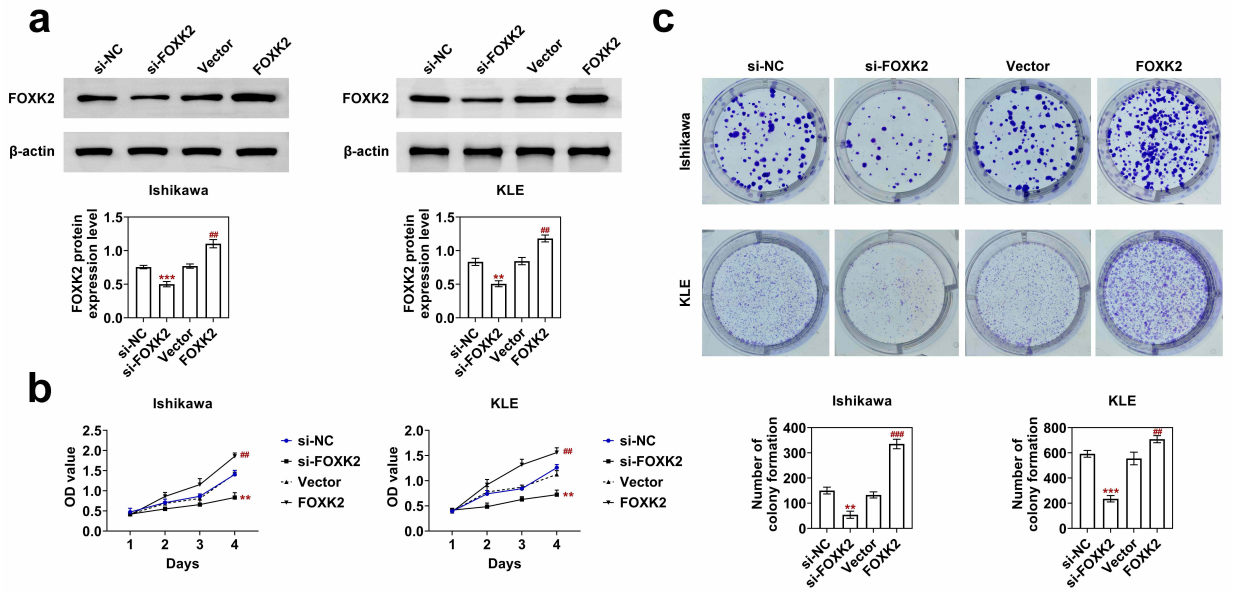

FIGURE 2. Knockdown of FOXK2 blocks EC cell proliferation. (a) Immunoblot analysis showing FOXK2 expression in Ishikawa and KLE cells following the indicated transfections. (b) CCK-8 assay demonstrating the effect of FOXK2 knockdown or overexpression on cell viability in Ishikawa and KLE cells, with optical density (OD) measured at 450 nm over 4 days. (c) Colony formation assays evaluating the impact of FOXK2 depletion or overexpression on colony formation in Ishikawa and KLE cells. Colony numbers were quantified. Error bars represent SD. $^{**}p < 0.01$, $^{***}p < 0.001$, si-FOXK2 *vs.* Si-NC, $^{\#\#}p < 0.01$, $^{\#\#\#}p < 0.001$, FOXK2 *vs.* control. NC: negative control; FOXK2: Foxhead box K2.

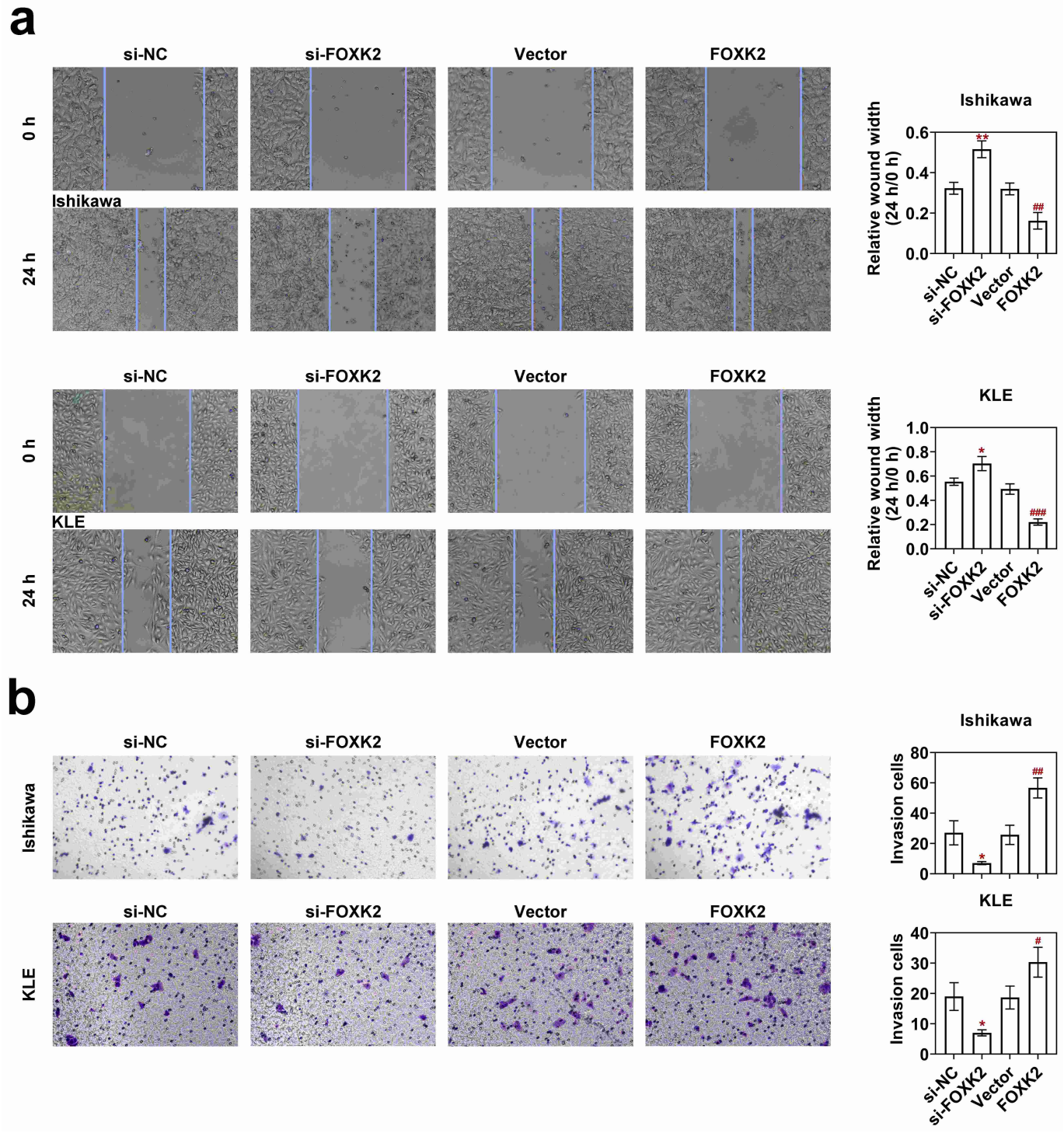

FIGURE 3. Depletion of FOXK2 restrains EC cell motility. (a) Wound healing assays illustrating the effect of FOXK2 depletion or overexpression on the migration of Ishikawa and KLE cells, with wound width measured at 0 and 24 hours. (b) Transwell assays assessing the effect of FOXK2 depletion or overexpression on cell invasion in Ishikawa and KLE cells. The number of invasive cells was quantified. Error bars represent SD. $^{*}p < 0.05$, $^{**}p < 0.01$, si-FOXK2 *vs*. si-NC, $^{\#}p < 0.05$, $^{\#\#}p < 0.01$, $^{\#\#\#}p < 0.001$, FOXK2 *vs*. control. NC: negative control; FOXK2: Foxhead box K2.

its expression (Fig. 5a). CCK-8 assays demonstrated that FOXK2 depletion inhibited cell viability, but ZEB1 overexpression reversed this effect (Fig. 5b). Similarly, transwell assays showed that ZEB1 overexpression counteracted the reduction in cell invasion caused by FOXK2 depletion (Fig. 5c). Wound-healing assays further confirmed that ZEB1 overexpression rescued the migration of EC cells impaired by FOXK2 depletion (Fig. 5d). Additionally, ZEB1 overexpression restored EMT marker levels, as evidenced by the recovery of N-cadherin, E-cadherin, and Vimentin expression (Fig. 5e,f). Collectively, these findings indicate that FOXK2 regulates EC cell growth and migration by modulating ZEB1 expression.

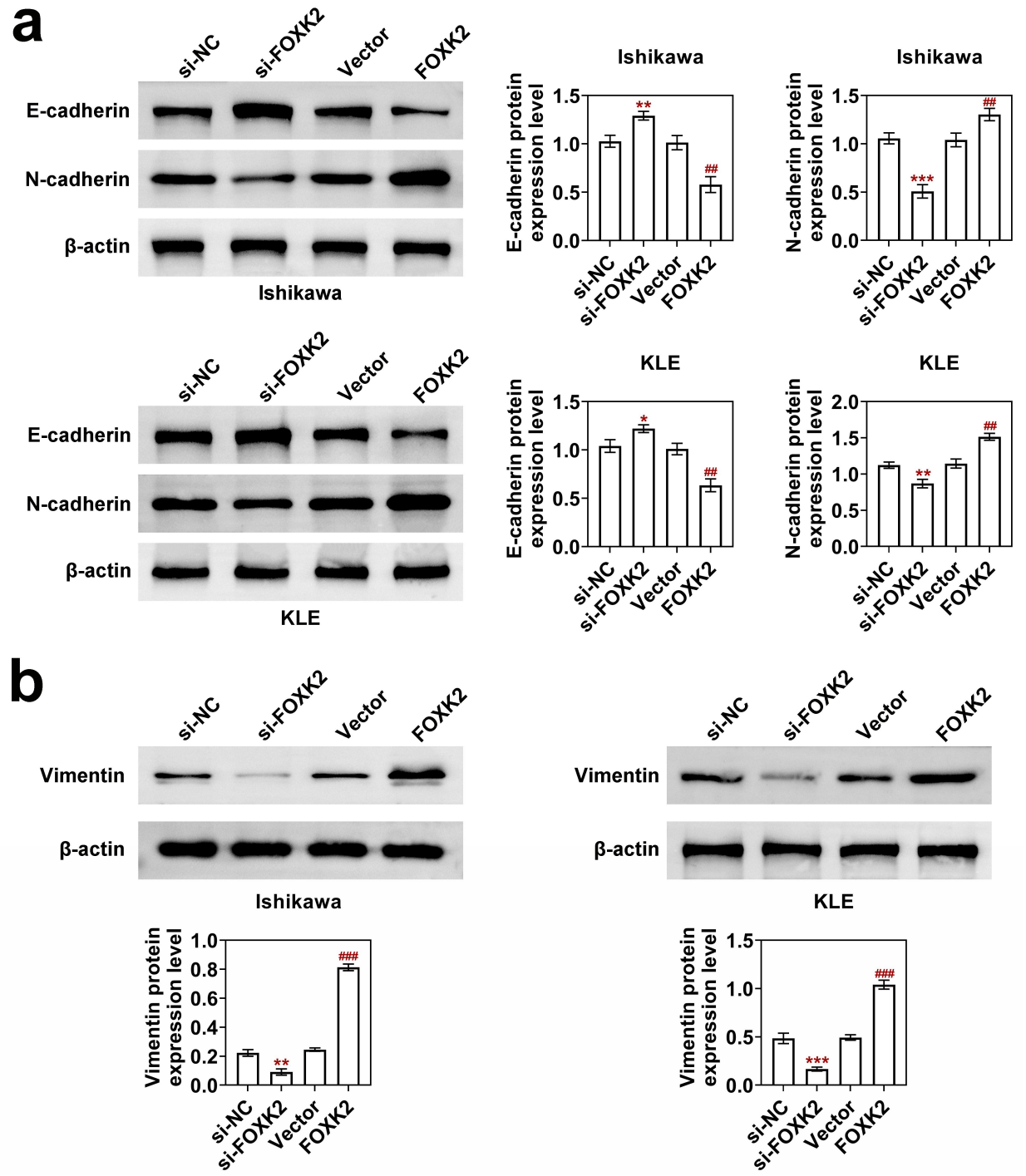

FIGURE 4. FOXK2 ablation suppresses EMT in EC cells. (a) Immunoblot analysis of E-cadherin and N-cadherin expression in Ishikawa and KLE cells following the indicated transfections. (b) Immunoblot analysis of Vimentin expression in Ishikawa and KLE cells following the indicated transfections. Error bars represent SD. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, si-FOXK2 *vs*. Si-NC, $^{\#\#}p < 0.01$, $^{\#\#\#}p < 0.001$, FOXK2 *vs*. control. NC: negative control; FOXK2: Foxhead box K2.

4. Discussion

EC is a prevalent gynecological malignancy and ranks among the top three major cancers affecting women [15, 16]. It is the most common malignancy of the gynecological and reproductive tracts and significantly impacts patients' quality of life and overall health [15, 16]. While surgery remains the primary treatment for EC, additional therapeutic measures, such as chemotherapy and hormone therapy, are often required based on disease progression [16]. Enhancing the efficacy of treatment for endometrial carcinoma is therefore of paramount importance [16–18]. Recent advancements in targeted therapies for EC have demonstrated promising results, with various new drugs and targets undergoing preclinical and clinical evaluation [19]. However, the identification and development of novel, effective therapeutic targets are essential for further improving patient outcomes. Our findings indicate that FOXK2 is highly expressed in endometrial carcinoma, and its elevated expression correlates with poor patient prognosis,

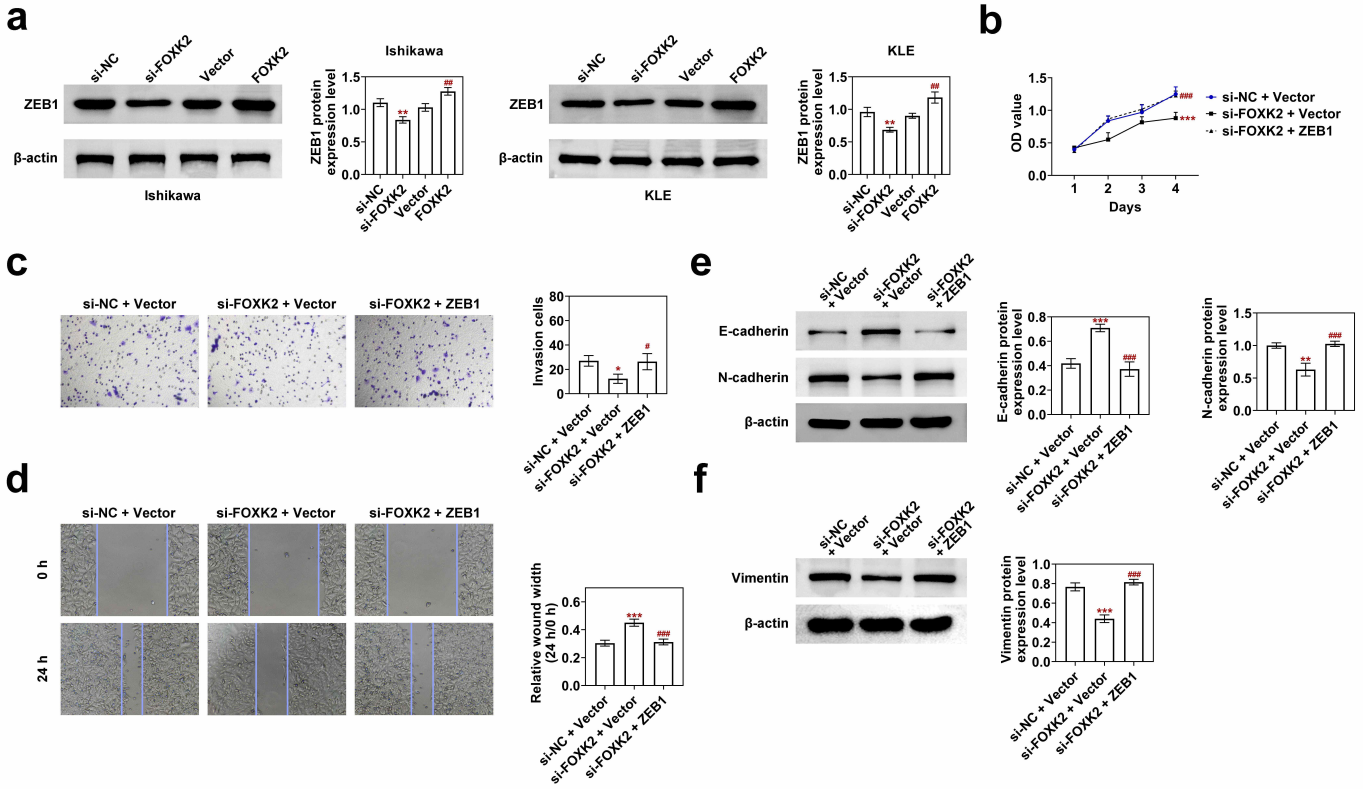

FIGURE 5. FOXK2 depletion inhibits EC by targeting ZEB1. (a) Immunoblot analysis of ZEB1 expression in Ishikawa and KLE cells following the indicated transfections. (b) CCK-8 assays showing the effect of FOXK2 depletion and ZEB1 overexpression on cell viability in Ishikawa and KLE cells. (c) Transwell assays demonstrating the effect of FOXK2 depletion and ZEB1 overexpression on cell invasion in Ishikawa and KLE cells. (d) Wound healing assays illustrating the effect of FOXK2 depletion and ZEB1 overexpression on cell migration in Ishikawa and KLE cells. (e) Immunoblot analysis of E-cadherin and N-cadherin expression in Ishikawa and KLE cells following the indicated transfections. (f) Immunoblot analysis of Vimentin expression in Ishikawa and KLE cells following the indicated transfections. Error bars represent SD. $*p < 0.05$, $**p < 0.01$, $***p < 0.001$, si-FOXK2 *vs.* si-NC, $^{\#}p < 0.05$, $^{\#\#}p < 0.01$, $^{\#\#\#}p < 0.001$, FOXK2 *vs.* control. NC: negative control; FOXK2: Foxhead box K2; ZEB1: Zinc Finger E-Box Binding Homeobox 1.

suggesting that FOXK2 could serve as a valuable therapeutic target for EC.

We employed a range of *in vitro* assays, to investigate the role of FOXK2 in EC. We observed that FOXK2 knockdown inhibited cell proliferation, motility, and EMT in EC cells. These results indicate that FOXK2 promotes the progression of EC *in vitro*. FOXK2, a member of the FOX family critical in various biological processes [5]. Abnormal FOXK2 function has been associated with several human conditions, including intellectual disability, West syndrome, Andy-Walker deformity, and syndactyly [5]. Recent research highlights FOXK2's involvement in the development of malignant tumors [6, 20]. For instance, FOXK2 has been reported to inhibit the proliferation and invasion of breast cancer cells [21].

FOXK2 functions as a transcriptional suppressor and has been identified to interact with multiple transcriptional repressor complexes *in vivo* [22]. FOXK2 recruits these complexes to inhibit the expression of several oncogenes, such as Enhancer of Zeste Homolog 2 (EZH2), and disrupt key signaling pathways, including Vascular Endothelial Growth Factor (VEGF), Hypoxia-Inducible Factor 1-beta (HIF1β) and Heat Shock Protein 90 Alpha Family Class A Member 1 (HSP90AA1) [23]. Our study extends this knowledge by demonstrating that FOXK2 affects the progression of EC through the regulation of ZEB1. However, the precise mechanisms underlying this interaction require further investigation. Consistent with our findings, other research has shown that FOXK2 promotes human colorectal cancer metastasis by upregulating ZEB1 [24]. ZEB1 is a transcription factor that enhances metastasis and stem cell characteristics [24]. ZEB1 regulates gene expression by binding to the E-box motifs in target gene promoters, playing a crucial role in promoting EMT and tumor metastasis [24]. ZEB1 is aberrantly expressed in several human cancers, including colorectal, breast, endometrial, prostate and gastric cancers [23, 24]. Our results suggest that FOXK2 modulates EC progression by targeting ZEB1. However, further research is needed to elucidate the downstream proteins and pathways involved in this regulatory process.

Tumor heterogeneity and the complexity of regulatory mechanisms can lead to divergent roles for the same protein across different cancer types. For example, while FOXK2 has been reported to inhibit ovarian cancer proliferation by downregulating EMT, our study suggests that FOXK2 promotes EC progression by enhancing EMT. This discrepancy may be attributed to the context-dependent

roles of FOXK2 as a transcription factor, where it regulates the expression of different downstream targets in various tumor environments.

Our data demonstrate that FOXK2 upregulates ZEB1 expression in EC cells, as evidenced by Immunoblot assays. This upregulation may contribute to EC by promoting EMT. However, our study does not confirm whether FOXK2 influences ZEB1 transcription directly at the molecular level. As a transcription factor, FOXK2 may regulate the proliferation and motility of EC cells through its effect on ZEB1 transcription. Future investigations using transcriptome sequencing and Chromatin Immunoprecipitation followed by Sequencing (ChIP-seq) could provide deeper insights into the transcriptional regulation of ZEB1 by FOXK2. Additionally, exploring the effects of recombinant FOXK2 protein and its interactions with key regulatory signals in EC cells may further elucidate the underlying mechanisms.

It is important to note that our study primarily addressed the effects of FOXK2 on tumor cell proliferation and migration *in vitro*. There remains a significant gap between these findings and *in vivo* studies, which will be essential for understanding the full impact of FOXK2 on EC progression and its potential as a therapeutic target.

5. Conclusions

In summary, our findings reveal that FOXK2 is highly expressed in EC and correlates with poor patient prognosis. The knockdown of FOXK2 inhibits progression of EC cells, likely through its regulation of ZEB1 expression. Further research is needed to confirm these mechanisms and explore the applications of targeting FOXK2 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

GY—designed the study and carried them out. GY, DY, FQG and XH—supervised the data collection, analyzed the data, interpreted the data. GY and XH—prepare the manuscript for publication and reviewed the draft of the manuscript. 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.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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