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Original Article

Erianin inhibits endometrial cancer cell proliferation and migration by modulating glutamine metabolism through the ERK signaling pathway

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Abstract: Objective: To investigate the therapeutic use of erianin, a bioactive compound derived from traditional Chinese medicine, in the treatment of EC and its regulatory effects on glutamine metabolism. Methods: Human Endometrial cancer (EC) cell lines, HEC-1A and Ishikawa, were exposed to erianin, and cellular proliferation and migratory capacity were assessed using the Cell Counting Kit-8 (CCK-8) assay and the Transwell migration assay, respectively. Glutamine metabolism was evaluated by quantifying intracellular glutamine, α-ketoglutaric acid (α-KG), and adenosine triphosphate (ATP). A xenograft tumor model was used to validate the antitumor efficacy of erianin *in vivo*. The changes in extracellular signal-regulated kinase (ERK) signaling were analyzed by western blotting. Results: Erianin treatment significantly inhibited the proliferation and migration of EC cells *in vitro* and suppressed tumor growth *in vivo*. Additionally, erianin downregulated glutamine metabolism, as evidenced by reduced levels of glutamic acid, α-KG, and ATP. Interestingly, activation of the ERK signaling pathway mitigated the antitumor and metabolic inhibitory effects of erianin on EC cells. Conclusion: Erianin inhibits glutamine metabolism and suppresses the growth of EC through the ERK signaling pathway.

Keywords: Endometrial cancer, migration, glutamine metabolism, ERK

Introduction

Erianin, a bioactive dibenzocyclooctadiene lignan derived from *Dendrobium chrysotoxum* (a traditional Chinese medicinal herb), has garnered significant attention in oncological research due to its potent antitumor properties. Structurally characterized by a biphenyl core, this natural compound exhibits diverse pharmacologic activities, including anti-inflammatory, antioxidant, and notably, antitumor effects [1, 2]. Erianin plays a multifaceted role in cancer therapy, demonstrating potent antitumor effects through various mechanisms. Its pharmacologic actions include: (1) inhibition of cancer cell proliferation, (2) induction of cell cycle arrest and apoptosis, (3) suppression of tumor angiogenesis, and (4) modulation of the tumor microenvironment. Evidence from both clinical studies and experimental models has validated erianin's therapeutic efficacy against various malignancies, notably hepatocellular carcinoma, non-small cell lung cancer, breast cancer, and colorectal carcinoma [3-6]. Erianin not only significantly inhibits cancer cell growth but also reduces tumor invasiveness and metastatic potential, positioning it as a promising candidate for targeted cancer therapy [7, 8]. Despite its promising preclinical findings, the clinical translation of erianin is still in the exploratory stage. Further elucidation of its molecular mechanisms and pharmacologic properties is essential to allow clinical use in oncology. Several studies have reported that erianin regulates multiple metabolism-related pathways, including the c-Jun N-terminal kinase (JNK)/stress-activated protein kinase (SAPK) pathway, the phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt)/mechanistic target of rapamycin (mTOR) pathway, and the wingless/integrated

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(Wnt)/β-catenin pathway [6, 9]. However, its effects on glutamine metabolism during cancer progression remain unclear.

Cancer cells undergo metabolic reprogramming to meet their heightened demands for energy, biosynthetic precursors, and redox homeostasis, thereby sustaining rapid proliferation [10, 11]. A key feature of this metabolic shift is dysregulated glucose metabolism, characterized by increased glucose uptake and preferential conversion to lactate - even under aerobic conditions - rather than oxidative phosphorylation in the tricarboxylic acid (TCA) cycle, a phenomenon known as the Warburg effect [12]. However, this glycolytic shift alone is insufficient to fulfill the bioenergetic and biosynthetic needs of highly proliferative cancer cells, necessitating alternative metabolic pathways [13]. A major alternative energy source is amino acids, with glutamine being the most abundant amino acid in mammalian systems. Cancer cells exhibit a pronounced dependence on glutamine compared to other amino acids, upregulating glutamine metabolism to meet the bioenergetic and biosynthetic demands of sustained proliferation [14]. Glutamine metabolism primarily serves to supply carbon for energy production during cell proliferation. The uptake of glutamine into cells is mediated by the alanine-serine-cysteine transporter 2 (ASCT2). Once internalized, glutamine is catabolized to glutamate within the mitochondria through the enzymatic activity of glutaminase (GLS) [15]. Subsequently, glutamate is converted to α-ketoglutarate (α-KG), a reaction predominantly catalyzed by glutamate dehydrogenase 1, thereby feeding into the TCA cycle to support adenosine triphosphate (ATP) generation [16]. Beyond its role in energy production, glutamine also functions as a nitrogen donor, facilitating the biosynthesis of nucleotides and non-essential amino acids. Moreover, glutamate serves as a precursor for glutathione synthesis, a critical antioxidant that maintains cellular redox homeostasis and mitigates oxidative stress [17, 18].

The relationship between erianin's antitumor activity and glutamine metabolism remains unclear. In this study, we aimed to investigate the therapeutic effects of erianin on endometrial cancer (EC) and elucidate its modulation of glutamine metabolic pathways.

Materials and methods

Cell culture and treatment

EC cell lines HEC-1A and Ishikawa were obtained from the China Center for Type Culture Collection (Wuhan, China). Both cell lines were maintained in their recommended growth media at 37°C in a humidified 5% CO_2 incubator. For treatment, erianin at varying concentrations, the ERK activator mSIRK (5 μM), and the ERK inhibitor PD98059 (5 μM) were added to the culture medium and incubated for the indicated durations.

Cell proliferation

Cell viability and proliferation were assessed using the CCK-8 assay (Dojindo, Japan). Cells were exposed to different concentrations of erianin for 24 hours, followed by incubation with CCK-8 reagent for 2 hours. Absorbance at 450 nm was recorded using a microplate reader to determine the number of viable cells.

Cell migration

Cell migration was analyzed using Transwell chambers (Corning, USA). Briefly, 5×10^4 cells (Ishikawa or HEC-1A) were suspended in serum-free medium and placed in the upper chamber, while the lower chamber contained complete medium supplemented with progesterone (P4) as a chemoattractant. After 48 hours, migrated cells on the lower membrane surface were fixed with 4% paraformaldehyde, stained with 0.1% crystal violet, and visualized under an inverted microscope (Nikon, Japan). Migration was quantified by counting cells in five randomly selected fields at 100× magnification.

Metabolite analysis

Glutamine metabolism was assessed by measuring intracellular concentrations of glutamine, ATP, and α-KG. Glutamine levels were measured using a Gln Content Assay kit (SBC5305, Solarbio) according to the manufacturer's protocol. ATP concentrations were measured using an ATP Colorimetric Assay kit (BC0305, Sosarbio) and α-KG levels were assessed with an α-KG Content Assay kit (BC5425, Sosarbio) as per the manufacturer's instructions.

Western blot assay

Total proteins were isolated using RIPA lysis buffer (Beyotime, China) containing protease and phosphatase inhibitors. Protein quantification was performed using the BCA method, with 30 μg of protein per sample separated by 10% SDS-PAGE. The resolved proteins were transferred onto nitrocellulose membranes (0.45 μm, Millipore, USA). After blocking with 5% non-fat milk in TBST for 1 hour at room temperature, the membranes were probed overnight at 4°C with primary antibodies from Proteintech (Wuhan, China), including anti-AKT (1:1000), anti-phospho-AKT (1:800), anti-PI3K (1:1000), and anti-β-actin (1:5000) as an internal control. Following TBST washes, the membranes were incubated with HRP-conjugated secondary antibodies (Proteintech; 1:5000) for 1 hour at room temperature. Protein signals were detected using an ECL system (Thermo Fisher Scientific, USA) and analyzed densitometrically with ImageJ (NIH, USA).

Xenograft tumor model

Four-week-old female BALB/c nude mice were used for *in vivo* experiments. The mice were housed at 25°C±2°C with *ad libitum* access to food for one week of acclimatization. In the subcutaneous tumor transplantation model, 1×10^6 Ishikawa cells were inoculated into the dorsal region of the mice (five mice per experimental group). After 7 days, mice in the erianin group were intravenously injected with erianin (10 mg/kg body weight) every 3 days for 3 weeks. Tumor growth was monitored weekly using calipers, and the volume was calculated using the formula: tumor volume = (length × width^2)/2. At the end of the experiment, mice were anesthetized with 4% isoflurane (R510-22-10, RWD) and sacrificed by cervical dislocation. All animal research was approved by the Ethics Committee of Li Huili Hospital Affiliated to Ningbo University (Application number: 13217) and was conducted in accordance with the National Institutes of Health (NIH) Guidelines for the Care and Use of Laboratory Animals.

Statistical analysis

The statistical analysis was performed using GraphPad Prism 10 (GraphPad Software, Inc.), with the data presented as mean ± SD. Differences between groups were analyzed using a two-tailed t-test (for two groups) or one-way ANOVA with Bonferroni correction (for multiple comparisons). GraphPad 9.0 (USA) was used for analysis. A *p*-value of less than 0.05 was considered significant.

Results

Erianin inhibits EC cell proliferation and migration by modulating glutamine metabolism

To investigate the antitumor effects of erianin, we first evaluated its effect on EC cell viability and migration. Assays showed that erianin treatment significantly inhibited the proliferation of EC cells in a dose-dependent manner (**Figure 1A**). Consistent with these findings, Transwell migration assays revealed that erianin markedly reduced the migratory capacity of EC cells (**Figure 1B**).

Next, we examined whether these antitumor effects were linked to alterations in glutamine metabolism. Interestingly, erianin treatment led to a significant accumulation of intracellular glutamine (**Figure 1C**), accompanied by decreased levels of its downstream metabolites, including glutamic acid (**Figure 1D**), α-ketoglutarate (α-KG; **Figure 1E**), and ATP (**Figure 1F**). Moreover, the addition of glutamine to rescue metabolism significantly elevated the proliferation of cancer cells suppressed by erianin (**Figure 1G**) and restored the levels of α-KG (**Figure 1H**) and ATP (**Figure 1I**). These results collectively suggest that erianin exerts its antiproliferative and anti-migratory effects, at least in part, through the regulation of glutamine metabolism in EC cells.

Erianin suppresses tumor growth and modulates glutamine metabolism in vivo

To validate our *in vitro* findings, we established a xenograft mouse model. Erianin treatment notably inhibited tumor growth and reduced tumor size (**Figure 2A-C**). In line with the *in vitro* results, erianin increased intratumoral glutamine levels (**Figure 2D**) while decreasing glutamic acid (**Figure 2E**) and α-KG (**Figure 2F**) concentrations.

Erianin regulates glutamine metabolism in endometrial carcinoma through ERK signaling pathway

To explore the molecular mechanism by which erianin regulates glutamine metabolism in EC

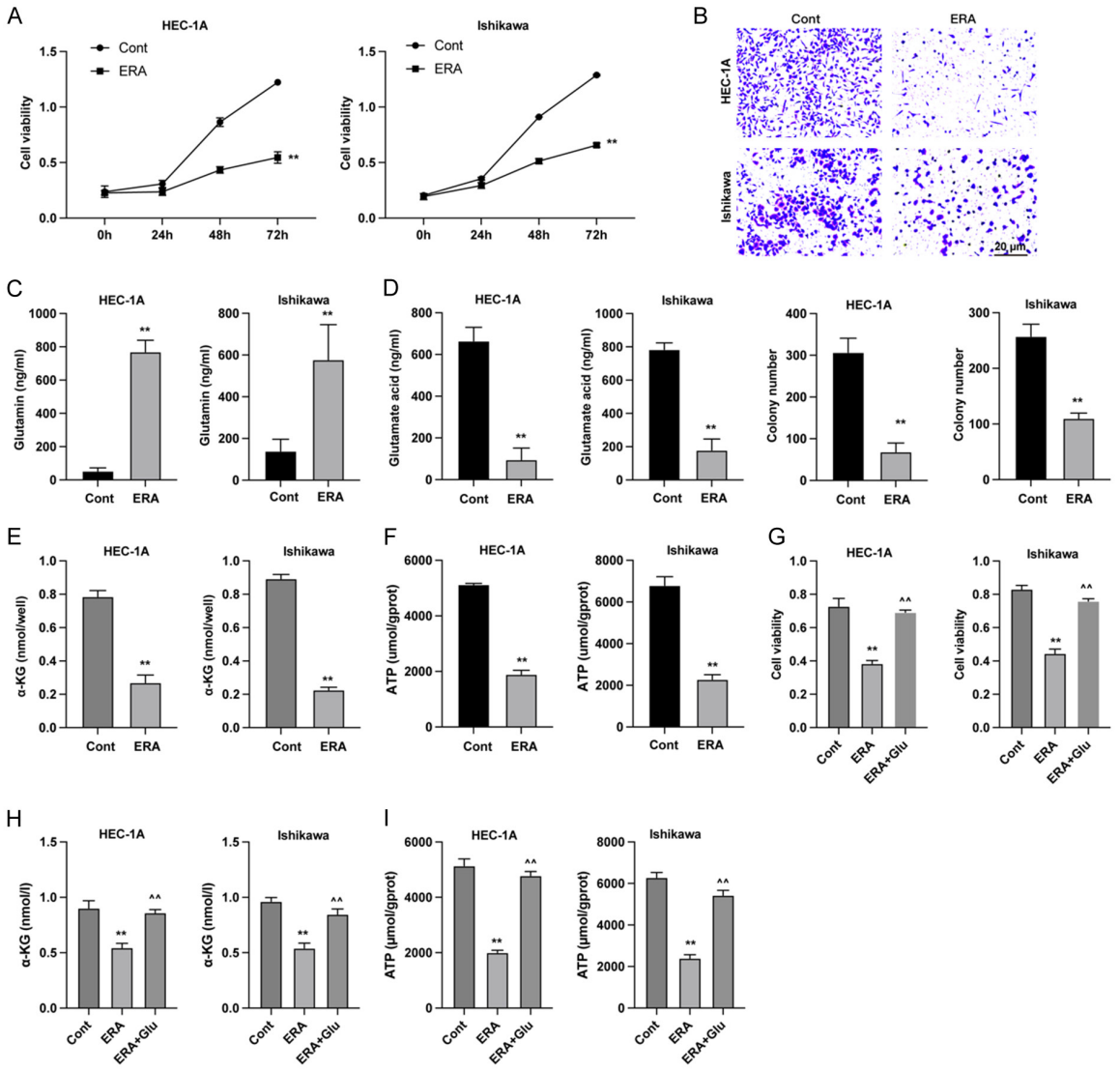

Figure 1. Effects of erianin on glutamine metabolism and endometrial cancer cell proliferation and migration. A. Cell viability was detected by Cell counting kit 8 (CCK-8). B. Cell migration was measured by Transwell assay. Scale bar =20 μm, 100× Magnification. C-F. The intracellular levels of glutamine, glutamic acid, ketoglutaric acid (α-KG), and adenosine triphosphate (ATP). G. Cell viability was detected by CCK-8 after treatment with erianin and glutamine. H, I. The intracellular levels of α-KG and ATP after treatment with erianin and glutamine. ***P*<0.05 vs cont, ^^*P*<0.05 vs ERA. Cont, control. ERA, erianin. Glu, glutamine.

cells, we investigated the involvement of the PI3K/AKT signaling pathway after treatment with either an ERK activator (mSIRK) or erianin. We observed that mSIRK treatment significantly enhanced phosphorylation of both PI3K and AKT, while co-treatment with erianin effectively attenuated this activation (**Figure 3A**). Consistent with these findings, metabolic profiling showed that ERK activation increased intracellular levels of glutamic acid (**Figure 3B**), α-KG (**Figure 3C**), and ATP (**Figure 3D**), all of which were significantly reduced by erianin co-treatment.

Erianin inhibits EC cell proliferation and migration by targeting ERK signaling pathway

Subsequently, CCK-8 assay results indicated that mSIRK-induced ERK activation promoted EC cell growth, while erianin treatment effectively counteracted this proliferative advantage (**Figure 4A**). Similarly, Transwell migration assays demonstrated that erianin significantly suppressed the enhanced migratory capacity induced by ERK activation (**Figure 4B**). At the molecular level, immunoblotting analysis revealed that ERK activation upregulated the mes-

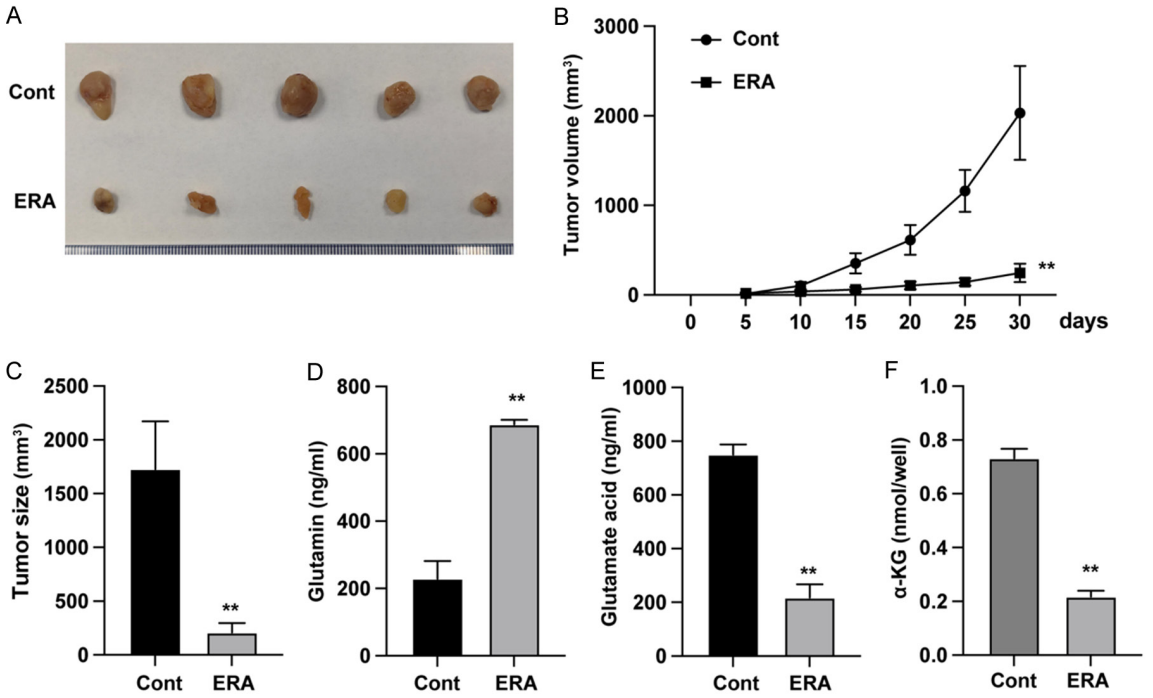

Figure 2. Erianin modulates glutamine metabolism and growth of endometrial carcinoma *in vivo*. Xenograft tumor model was established by using Ishikawa cells. A-C. Tumor growth curve and tumor size. D-F. The levels of glutamine, glutamic acid, and α-KG in tumor tissues. $^{**}P<0.05$. Cont, control. ERA, erianin. α-KG, alpha-Ketoglutarate.

enchymal markers N-cadherin and vimentin, while downregulating the epithelial marker E-cadherin - an effect that was completely reversed by erianin co-treatment (**Figure 4C**). Furthermore, administration of the ERK inhibitor PD98059 further enhanced the inhibitory effects of erianin on cell proliferation (**Figure 5A**) and glutamine metabolism (**Figure 5B**, **5C**). These data suggest that erianin regulates EC cell proliferation and metabolism by the ERK signaling pathway.

Discussion

Endometrial carcinoma (EC) is recognized as one of the leading invasive gynecologic malignancies worldwide. A clinically significant subset of EC cases occurs in women under 40 years of age. With delayed childbearing becoming increasingly common in modern societies, approximately 70% of younger EC patients express strong desires for fertility preservation [19]. This highlights the urgent need to develop therapeutic strategies that effectively address both oncological control and fertility preservation. Our experimental results demonstrate that erianin significantly inhibits EC cell growth both *in vitro* and *in vivo* through its regulatory effects on glutamine metabolism.

Cancer is characterized by profound metabolic heterogeneity, with neoplastic cells frequently diverting TCA cycle intermediates for biosynthetic processes, including protein, lipid, and nucleic acid synthesis. Depletion of TCA cycle metabolites compromises mitochondrial functionality, prompting tumor cells to activate compensatory metabolic pathways to maintain homeostasis [20, 21]. Glutamine serves as a critical anaplerotic substrate, being converted to α-KG to replenish the tricarboxylic acid (TCA) cycle, thereby sustaining cellular energetics. Additionally, glutamine provides essential nitrogen and carbon moieties for purine and pyrimidine biosynthesis, as well as for hexosamine pathway activity. The marked glutamine dependence of malignant cells facilitates the restoration of TCA cycle intermediates, which is essential for energy production, biomolecule synthesis, and the preservation of redox balance. Emerging evidence indicates that glutamine metabolism significantly promotes EC cell survival and proliferation [22]. Following cellular uptake through specific transporters, gluta-

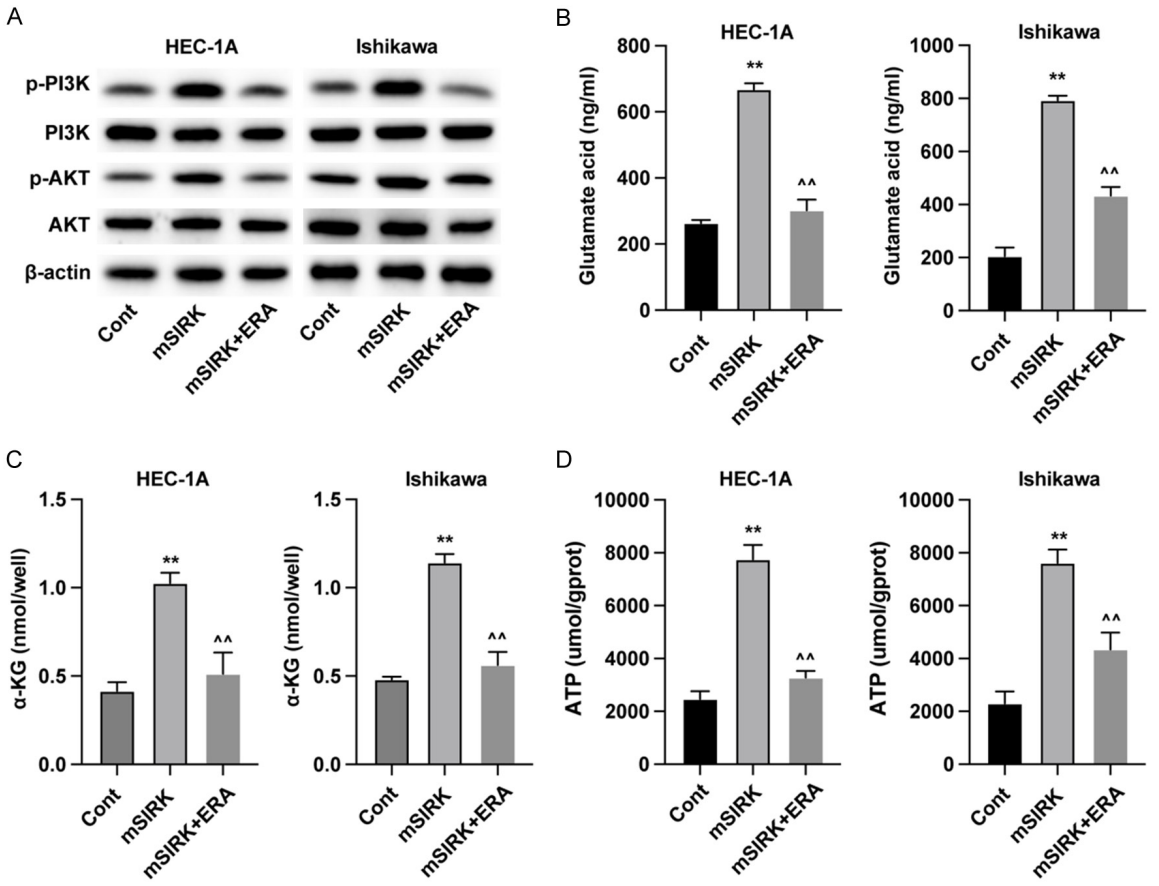

Figure 3. Erianin regulates glutamine metabolism in endometrial carcinoma through extracellular signal-regulated kinases (ERK) signaling pathway. A. Protein levels of total and phosphorylated AKT and PI3K. B-D. Levels of glutamic acid, α-KG and ATP in EC cancer cells. $^{**}P<0.05$ vs cont, $^{\wedge\wedge}P<0.05$ vs mSIRK. Cont, control. ERA, erianin. mSIRK, G-Protein βγ Binding Peptide. α-KG, alpha-Ketoglutarate.

mine undergoes deamidation by GLS to yield glutamate and ammonia, with subsequent conversion of glutamate to α-KG through GDH-mediated deamination, thereby entering the TCA cycle [23]. Notably, the ERK signaling pathway plays a pivotal role in glutamine metabolism, which is central to cellular energy homeostasis and biosynthesis. ERK, a component of the MAPK cascade, modulates the expression of enzymes involved in glutamine use, such as glutaminase, thereby regulating its conversion to glutamate and entry into the TCA cycle [24]. This regulation is critical for modulating cellular respiration and sustaining the anabolic requirements of highly proliferative cells, particularly malignancies. Furthermore, the ERK pathway intersects with glutamine metabolism by modulating the activity of transcription factors that govern genes involved in glutamine synthesis, transport, and utilization [25, 26]. Specifically, ERK activation has been shown to enhance glutaminolysis and glutamate production, supporting anabolic metabolism and redox balance necessary for epithelial-mesenchymal transition (EMT) and cancer cell invasiveness. Previous studies have demonstrated that erianin modulates multiple oncogenic signaling cascades, including MAPK, PI3K/Akt, and JNK, leading to the suppression of cancer cell proliferation and survival [27-29]. For example, erianin induces apoptosis and cell cycle arrest through the ERK pathway in human nasopharyngeal carcinoma [27]. Moreover, several studies have highlighted the involvement of the ERK signaling pathway in cancer cell glutamine metabolism [25, 30]. Consistent with the well-documented role of ERK in glutamine metabolism, our mechanistic study revealed that erianin suppressed ERK signaling, which resulted in a decrease in glutamate levels. This

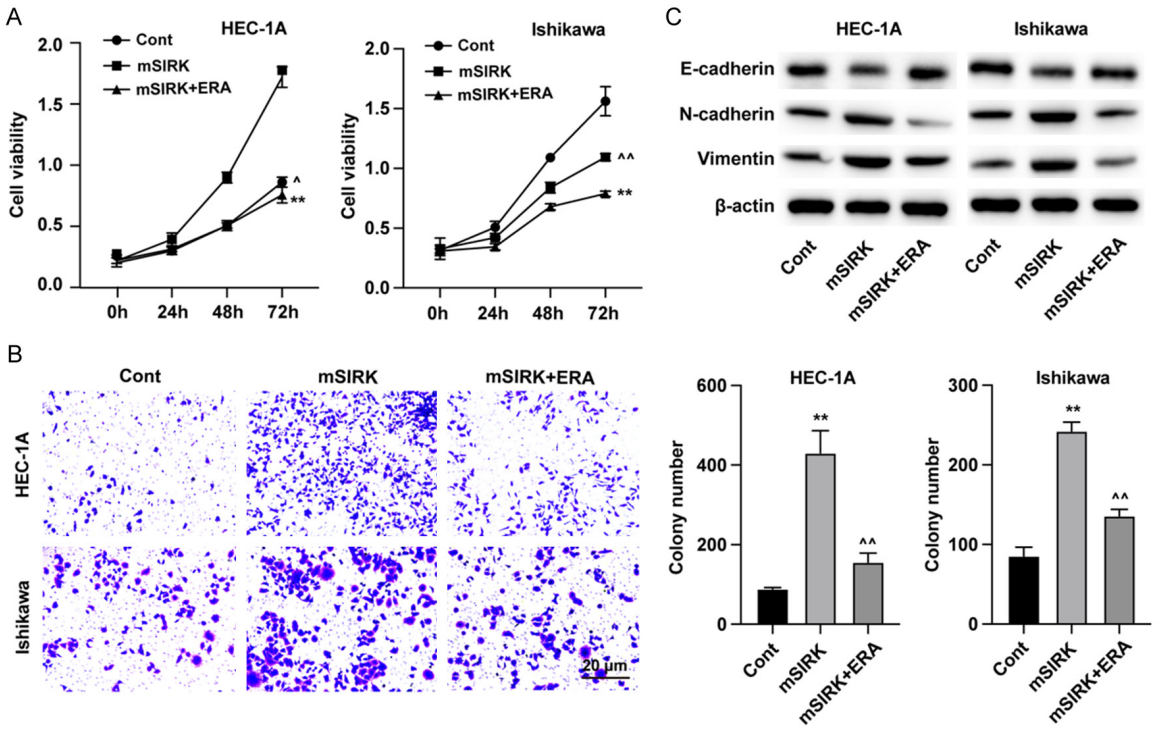

Figure 4. Erianin represses proliferation and migration of endometrial cancer cells through ERK signaling pathway. A. Cell viability was detected by CCK-8. B. Cell migration was measured by Transwell assay. Scale bar =20 μm, 100× Magnification. C. The expression of migration biomarkers was measured by western blotting assay. ***P*<0.05 vs cont, ^^*P*<0.05 vs mSIRK. Cont, control. ERA, erianin. mSIRK, G-Protein βγ Binding Peptide.

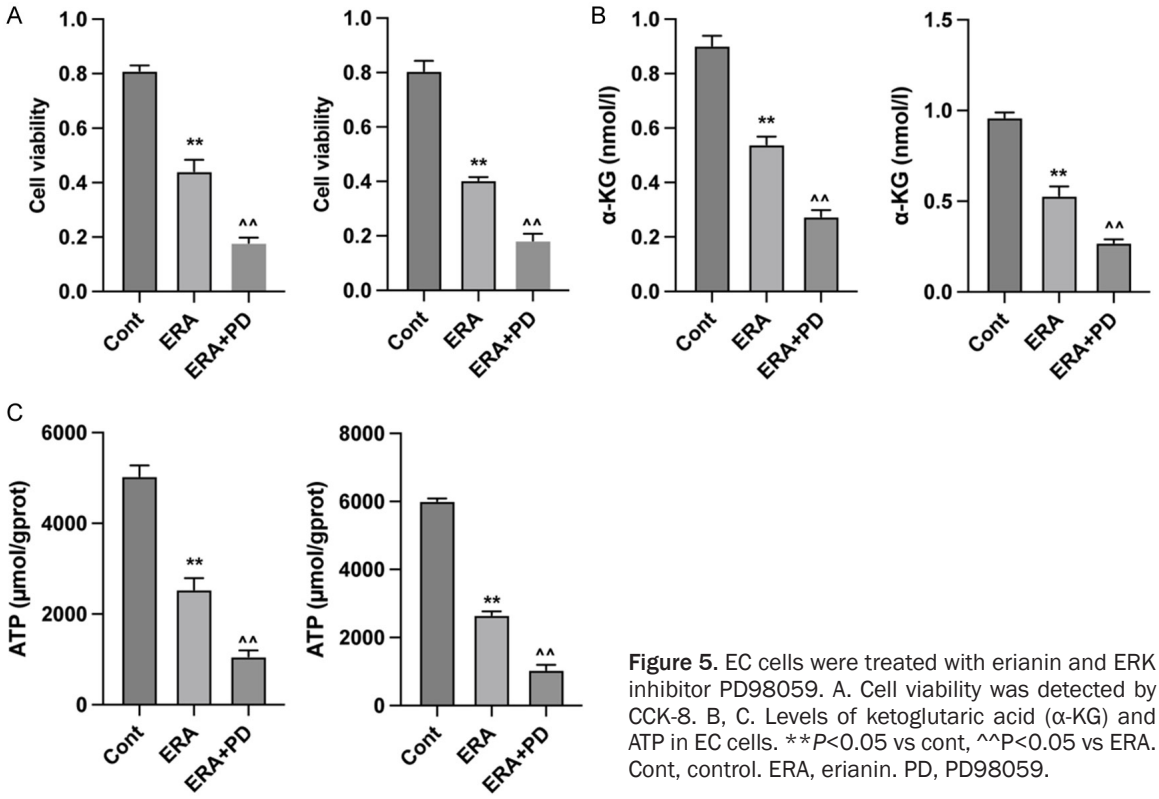

Figure 5. EC cells were treated with erianin and ERK inhibitor PD98059. A. Cell viability was detected by CCK-8. B, C. Levels of ketoglutaric acid (α-KG) and ATP in EC cells. ***P*<0.05 vs cont, ^^P<0.05 vs ERA. Cont, control. ERA, erianin. PD, PD98059.

reduction in glutamate may impair downstream pathways such as the TCA cycle and glutathione synthesis, thereby reducing the bioenergetic and biosynthetic support required for EMT. Consequently, markers of EMT (e.g., increased E-cadherin, decreased N-cadherin/vimentin) were reversed. Therefore, we suggest that erianin inhibits EMT, at least in part, through modulation of glutamine/glutamate metabolism through suppression of ERK signaling. This provides a mechanistic link among ERK, glutamate metabolism, and EMT, contributing to the overall antitumor effect of erianin. However, the direct interaction between erianin and critical regulators of the ERK pathway requires validation through further experiments, such as molecular docking analysis and mass spectrometry. Further studies are necessary to explore any other molecular mechanisms involved in the anti-tumor effects of erianin in EC.

In this study, we identified that erianin suppresses EC cell proliferation and metabolic reprogramming by inhibiting ERK signaling.

While ERK signaling was confirmed as a key mediator, other pathways may also contribute to erianin's effects on EC cells. This study did not fully explore these pathways, and further investigation is needed to clarify erianin's mechanisms of action. Additionally, glutamine metabolism is highly complex, and focusing solely on the ERK-glutamine metabolism axis may have oversimplified the metabolic landscape. Factors such as tumor microenvironment glutamine availability and hypoxia-induced changes in glutamine utilization, which could affect our observations, were not fully addressed and require further study.

Our findings suggest erianin is a promising candidate for inhibiting EC cell proliferation. Future research could develop targeted therapies that modulate glutamine metabolism through ERK signaling, offering more precise and effective treatments for endometrial cancer patients.

Conclusion

Erianin exerted potent antitumor effects by suppressing both proliferation and metabolic reprogramming in EC cells, with the ERK signaling pathway playing a critical mechanistic role in this process. These findings provide compelling preclinical evidence supporting the therapeutic potential of erianin as a novel targeted agent for cancer treatment, particularly in malignancies dependent on glutamine metabolism. Further investigation is warranted to elucidate fully the molecular underpinnings of erianin's anticancer activity and explore its translational applications.

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Disclosure of conflict of interest

None.

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