

ORIGINAL RESEARCH

Knockdown of NUA2 promotes ferroptosis by regulating the mTOR/c-Myc signaling pathway to inhibit endometrial cancer cell progression

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Abstract

Background: Endometrial cancer (EC) represents a major gynecologic malignancy with unknown confirmed causes. Although NUA2 family kinase 2 (NUAK2) is overexpressed and has been shown to promote progression in multiple cancers, its role in regulating ferroptosis in EC remains poorly understood. **Methods:** NUA2 expression was analyzed using the Gene Expression Profiling Interactive Analysis (GEPIA) database. Western blot detection of protein levels of NUA2, key ferroptosis regulators (solute carrier family 7 member 11 (SLC7A11) and Glutathione Peroxidase 4 (GPX4)), and major components of the mechanistic target of rapamycin (mTOR)/MYC Proto-Oncogene (c-Myc) signaling pathway. Intracellular ferrous ion (Fe²⁺) and Reactive Oxygen Species (ROS) levels were quantified to evaluate ferroptosis, small interfering RNA (siRNA)-mediated silencing of NUA2 and pharmacological interventions, including Ferrostatin-1 (Fer-1) and the mTOR activator MHY1485, were performed to determine the underlying mechanisms. **Results:** NUA2 was overexpressed in EC tissues and cell lines. Knockdown of NUA2 significantly inhibited EC cell proliferation and induced ferroptosis, as indicated by elevated Fe²⁺ and ROS levels, together with decreased expression of the ferroptosis-related proteins SLC7A11 and GPX4. Mechanistically, NUA2 knockdown inhibited activation of the mTOR/c-Myc signaling cascade, whereas treatment with the mTOR activator MHY1485 effectively counteracted the ferroptosis induction and proliferation inhibition resulting from NUA2 silencing. **Conclusions:** Our findings demonstrate that NUA2 knockdown promotes ferroptosis and suppresses the malignant progression of EC cells by inhibiting the mTOR/c-Myc signaling pathway. These findings support NUA2 as a promising therapeutic target in EC treatment.

Keywords

NUAK2; Endometrial cancer; Ferroptosis; mTOR/c-Myc pathway; Cell proliferation

1. Introduction

Endometrial carcinoma ranks among the most common malignancies affecting the female reproductive system, and its incidence has been rising steadily in recent years, with an increasing proportion of younger patients being affected. Clinical epidemiological data indicate that despite continued advances in therapeutic strategies, the overall survival rate of patients with EC has not improved substantially [1, 2]. Ferroptosis is an iron-dependent cell death pathway that is fundamentally different from apoptosis and autophagy. This process is vital for maintaining cellular homeostasis through its regulation of iron metabolism, oxidative stress, and amino acid metabolism [3, 4]. Ferroptosis has recently been recognized as a promising therapeutic strategy for various malignancies. Conversely, inhibition of ferroptosis, or anti-ferroptosis, has been identified as a key mechanism underlying the malignant progression of

EC, although its specific molecular targets remain unknown [5].

NUAK family kinase 2 (NUAK2), a member of the Adenosine Monophosphate (AMP)-activated protein kinase family, participates in diverse cellular processes including proliferation, metabolism, and stress responses [6]. NUA2 plays role in cancer formation and progression, particularly in gynecological malignancies. For example, the inhibitory effect of NUA2 silencing on the proliferation, migration, and epithelial-mesenchymal transition of cervical cancer cells has been demonstrated [7]. In breast cancer, NUA2 activates the mechanistic target of rapamycin (mTOR)/c-Myc oncogene (c-Myc) pathway, leading to glucose and glutamine metabolic reprogramming that enhances tumor growth and metastasis [8]. Furthermore, NUA2 loss in lung cancer cells reduces stemness and angiogenesis while promoting cellular senescence through the induction of ferroptosis [9].

The mTOR/c-Myc signaling pathway is crucial for the regulation of cellular metabolism, and its dysregulation is frequently observed in malignant tumors. Recent studies have implicated this pathway in the control of ferroptosis; however, its role in EC remains largely undefined [10, 11]. Accordingly, this study was designed to investigate the function of NUA2 in EC progression and to determine if it regulates ferroptosis via the mTOR/c-Myc signaling pathway.

2. Methods

2.1 Cell culture

Human endometrial epithelial cells (hEECs) and EC cell lines (HEC-1A, Ishikawa) were purchased from the American Type Culture Collection (ATCC, Manassas, USA) and cultured in Dulbecco's Modified Eagle Medium/Nutrient Mixture F-12 (DMEM/F12) medium enriched with 10% fetal bovine serum and 1% penicillin-streptomycin (100 U/mL each), and incubated them at 37 °C in a humidified incubator with 5% CO₂. The cell lines were authenticated using short tandem repeat sequence analysis, and no mycoplasma contamination was detected.

2.2 Transfection

The siRNAs used in this study were synthesized by RiboBio (Guangzhou, China). EC cells were transfected using Lipofectamine 3000 (L3000001, Invitrogen, Carlsbad, MA, USA) and treated with Ferostat-1 (Fer-1, 20 μM) or MHY1485 (10 μM). The final siRNA concentration was 50 nM, and 2 μL of Lipofectamine 3000 reagent was used per 12-well plate. The target sequences of *NUAK2* siRNA were as follows: si-*NUAK2*, 5'-GCATGACCATAAGATCCTA-3'; small interfering RNA negative control (si-NC), 5'-GCGTTCTTAACCTTTGAACC-3'. The control group referred to cells that were not transfected and served as the experimental baseline, while the nonspecific control (si-NC) group consisted of cells transfected with scrambled non-targeting siRNA sequences.

2.3 Cell counting kit-8 (CCK-8)

Cell viability was assessed using the CCK-8 assay. Briefly, EC cells (3×10^3 cells/well) in 96-well plates were cultured for 24, 48, and 72 hours. Then, 10% CCK-8 reagent (C0037, Beyotime, Shanghai, China) was added directly to the wells, followed by a 2-hour incubation. The absorbance was measured at 450 nm.

2.4 5-ethynyl-2'-deoxyuridine (EdU) proliferation assay

EC cells were fixed for 15 minutes with 4% paraformaldehyde and subsequently stained using an EdU assay kit (C0071S, Beyotime, Shanghai, China). Cells were seeded and cultured for 24 hours prior to testing. Each well received 250 μL of 10 μM EdU reagent and was incubated for 2 hours to label proliferating cells. The fixed cells (4% paraformaldehyde, 15 minutes) were first permeabilized with 0.3% Triton X-100 for 15 minutes. They were then treated with the click reaction

mixture and incubated for 30 minutes at room temperature in the dark.

2.5 Detection of Fe²⁺ levels

We seeded 6-well plates with EC cells at 1×10^6 cells per well. After rinsing twice with Phosphate-Buffered Saline (PBS), the cells were lysed and centrifuged, and the Fe²⁺ levels were determined using a ferrous ion detection kit (S0116, Beyotime, Shanghai, China).

2.6 Detection of reactive oxygen species (ROS)

EC cells were seeded in 6-well plates at a density of 5×10^5 cells per well. After exposure to 10 μM Carboxy-2',7'-Dichlorodihydrofluorescein diacetate (H₂DCFDA, D399, Thermo, Waltham, MA, USA; 30 minutes, 37 °C, dark), the cells were washed twice with PBS, then trypsinized, collected, and resuspended. The fluorescence intensity of intracellular ROS was then measured using flow cytometry.

2.7 Western blot

Total protein was harvested using Radioimmunoprecipitation Assay Buffer (RIPA) lysis buffer, and concentrations were determined via the Bicinchoninic Acid Assay (BCA) method (P0009, Beyotime, Shanghai, China). After electrophoretic separation on 12% Sodium Dodecyl Sulfate-Polyacrylamide Gel Electrophoresis (SDS-PAGE) gels (Beyotime), proteins were transferred to Polyvinylidene fluoride (PVDF) membranes (Thermo). Membranes were blocked for 1 hour at room temperature in 5% non-fat milk before an overnight incubation with primary antibodies at 4 °C. *NUAK2* (1:1000, Abcam, ab322265, Cambridge, UK), Solute Carrier Family 7 (SLC7A11, 1:1000, Abcam, ab307601, Cambridge, UK), Glutathione Peroxidase 4 (GPX4, 1:1000, Abcam, ab125066, Cambridge, UK), phosphorylated mTOR (p-mTOR, 1:1000, Abcam, ab109268, Cambridge, UK), mTOR (1:1000, Abcam, ab134903, Cambridge, UK), c-Myc (1:1000, Abcam, ab185656, Cambridge, UK), and Glyceraldehyde-3-Phosphate Dehydrogenase (GAPDH, 1:1000, Abcam, ab9485, Cambridge, UK). On the following day, the membranes were incubated for 2 hours with an Horseradish Peroxidase (HRP)-conjugated secondary antibody (1:5000, Abcam, ab205719, Cambridge, UK). Protein bands were visualized with an Enhanced Chemiluminescence (ECL) Western blotting detection kit (32106, Thermo, Waltham, MA, USA). The relative expression levels of the target proteins were normalized to GAPDH.

2.8 Statistical analysis

All data are presented as mean ± Standard Deviation (SD). Statistical analyses were performed using GraphPad Prism version 9.0 (GraphPad Software, Boston, MA, USA). Differences between groups were evaluated by one-way Analysis of Variance (ANOVA). A *p*-value < 0.05 was considered statistically significant.

3. Results

3.1 NIAK2 is substantially expressed in endometrial carcinoma

Analysis using the GEPIA database revealed that NIAK2 expression was considerably higher in EC tissues than in normal endometrial tissues (Fig. 1A). Western blot analysis further demonstrated that NIAK2 was highly expressed in the EC cell lines HEC-1A and Ishikawa (Fig. 1B). Our study thus posits NIAK2 as a significant contributor to EC progression, supporting its further investigation as a viable therapeutic target.

3.2 Knockdown of NIAK2 inhibits the growth of EC cells

siRNA technology was employed to reduce NIAK2 expression (Fig. 2A), and it was observed that this markedly decreased cell survival and proliferation. Cell viability measurements (Optical Density (OD)₄₅₀) showed that the viability of NIAK2-knockdown cells was significantly lower after 72 hours compared with the non-specific control group (si-NC) (Fig. 2B). EdU staining further confirmed this finding, revealing that cells with NIAK2 knockdown exhibited

significantly reduced proliferation compared with the si-NC group (Fig. 2C). These findings demonstrate that NIAK2 contributes to the malignant progression of EC cells, and that its suppression effectively curbs oncogenic growth, thereby underpins its potential as a therapeutic target.

3.3 Knockdown of NIAK2 promotes ferroptosis in EC cells

We further observed that NIAK2 knockdown markedly increased Fe²⁺ levels in HEC-1A and Ishikawa EC cells (Fig. 3A). ROS staining experiments demonstrated that NIAK2 knockdown also elevated intracellular ROS production (Fig. 3B). In addition, NIAK2 silencing reduced the expression of SLC7A11 and GPX4 proteins (Fig. 3C), which are associated with cellular antioxidant defense and ferroptosis regulation. Cell viability assays (Fig. 3D) showed that NIAK2 knockdown decreased cell viability, and this reduction could be partially reversed by the ferroptosis inhibitor Fer-1. These results suggest that NIAK2 knockdown suppresses EC cell proliferation by activating the ferroptosis pathway.

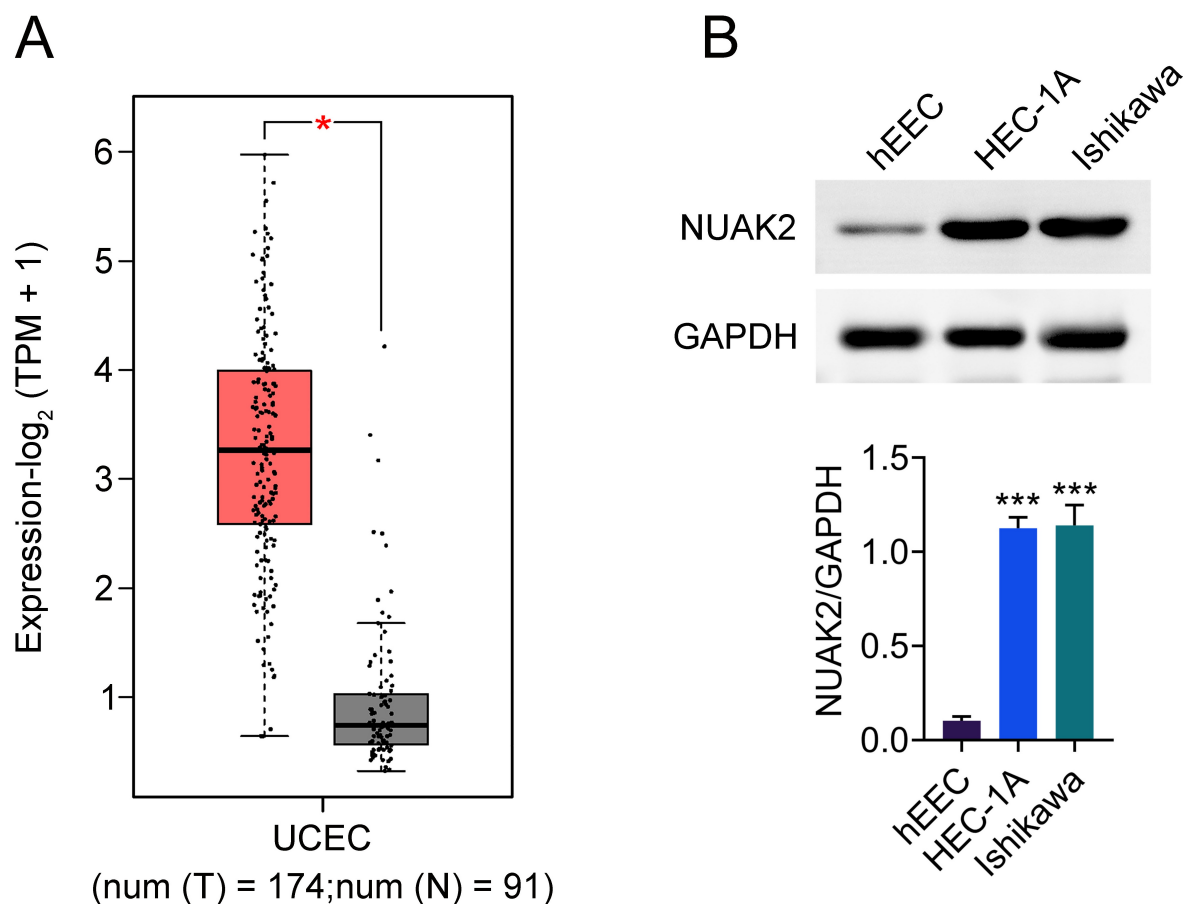


FIGURE 1. NIAK2 is highly expressed in endometrial cancer. (A) The GEPIA website was used to analyze the expression differences of NIAK2 between EC tissues and normal tissues. * $p < 0.05$. (B) Western blotting was used to detect the expression of NIAK2 in normal human endometrial epithelial cells (hEEC) and human endometrial cancer cell lines (HEC-1A and Ishikawa). Values are presented as mean $\pm$ SD. *** $p < 0.001$ vs. hEEC group. $n = 3$. NIAK2: NIAK family kinase 2; GAPDH: Glyceraldehyde-3-Phosphate Dehydrogenase; UCEC: Uterine Corpus Endometrial Carcinoma; TPM: Transcripts Per Million; num (T): number of tumor samples; num (N): number of normal samples.

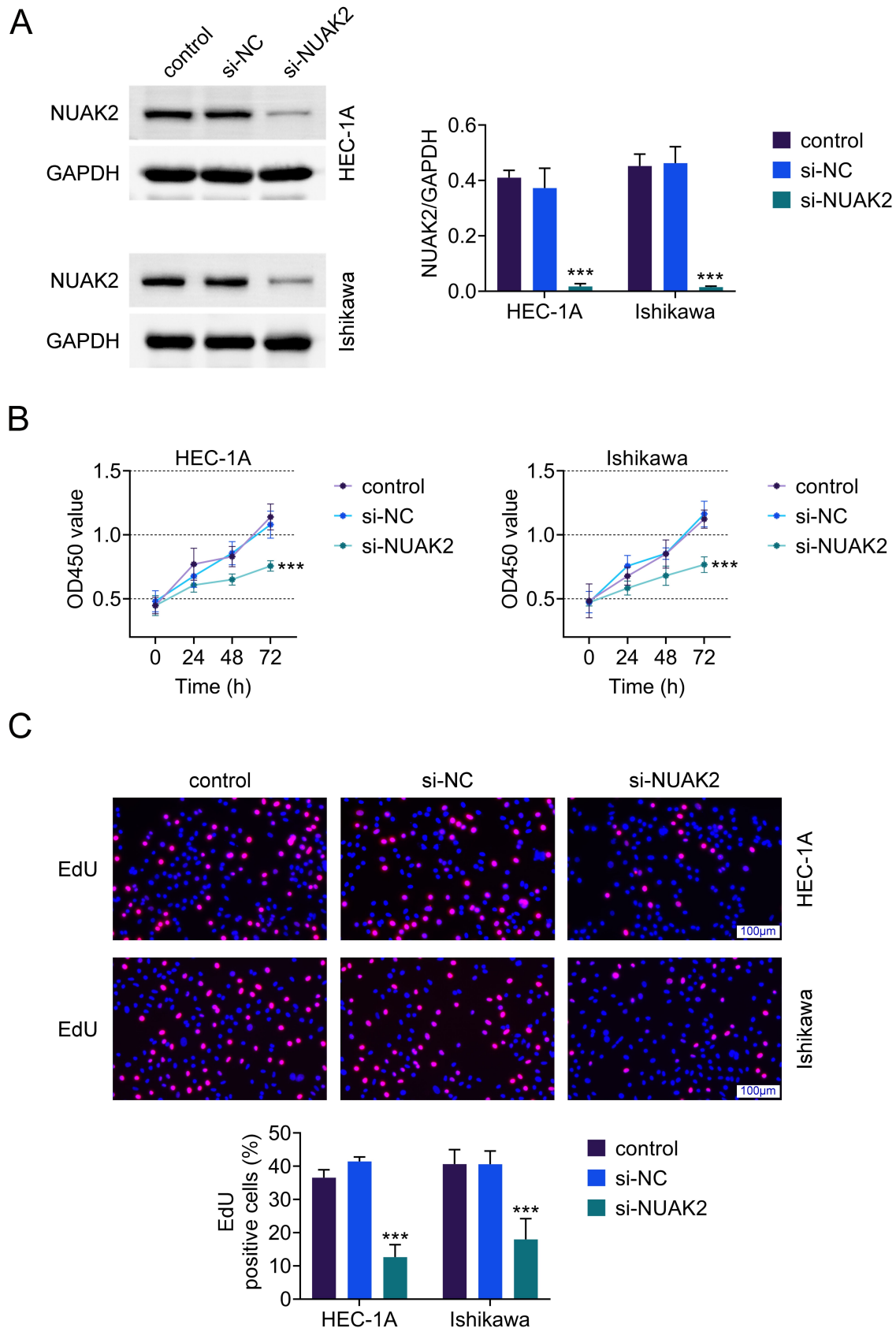


FIGURE 2. Knockdown of NUA2 inhibits the growth of endometrial cancer cells. (A) Western blotting analysis of NUA2 expression. (B) CCK-8 assay for cell viability. (C) EdU staining for cell proliferation. Blue staining represents the nuclei of all cells, and pink staining represents proliferating cells undergoing DNA replication. Values are presented as mean $\pm$ SD. *** p < 0.001 vs. si-NC group. n = 3. NUA2: NUA family kinase 2; GAPDH: Glyceraldehyde-3-Phosphate Dehydrogenase; EdU: 5-ethynyl-2'-deoxyuridine; OD: Optical Density; si-NC: small interfering RNA negative control; HEC-1A: human endometrial cancer cell lines.

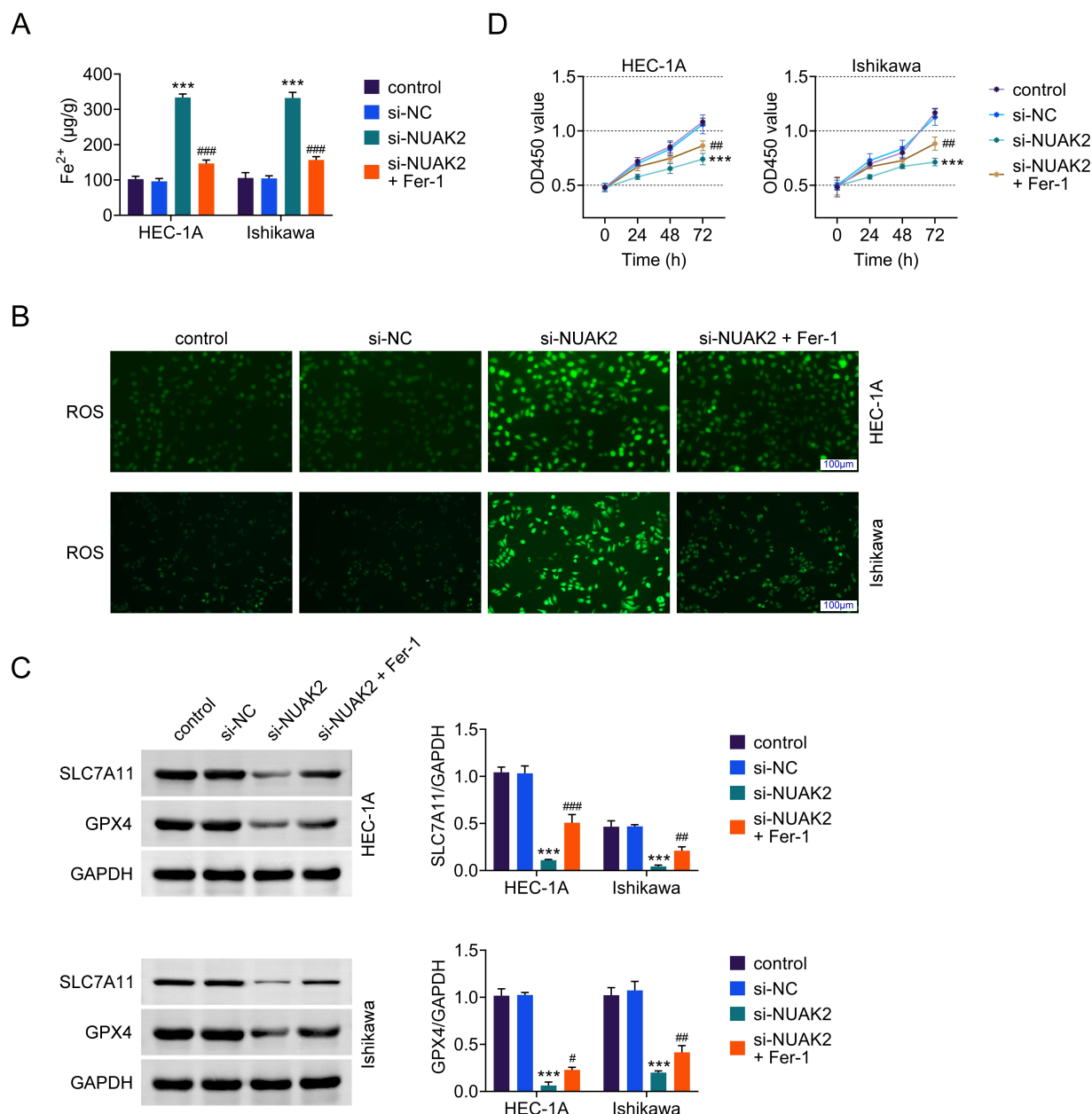


FIGURE 3. Knockdown of NUA2 promotes ferroptosis in endometrial cancer cells. (A) Detection of Fe²⁺ levels using a commercial assay kit. (B) Detection of ROS fluorescence intensity using a DCFH-DA probe. (C) Western blotting analysis of SLC7A11 and GPX4 protein expression. (D) CCK-8 assay for cell viability. Values are presented as mean ± SD. ****p* < 0.001 vs. si-NC group; #*p* < 0.05, ###*p* < 0.01, ####*p* < 0.001 vs. si-NUAK2 group. *n* = 3. NUA2: NUA family kinase 2; GAPDH: Glyceraldehyde-3-Phosphate Dehydrogenase; Fer-1: Ferrostatin-1; SLC7A11: Solute Carrier Family 7; GPX4: Glutathione Peroxidase 4; ROS: Reactive oxygen species; Fe²⁺: ferrous ion; OD: Optical Density; si-NC: small interfering RNA negative control; HEC-1A: human endometrial cancer cell lines.

3.4 Knockdown of NUA2 promotes ferroptosis through the mTOR/c-Myc signaling pathway, thereby inhibiting the growth of EC cells

Western blot analysis showed that the protein expression levels of p-mTOR and c-Myc were significantly decreased in the si-NUAK2 group compared with the si-NC group, while the total mTOR protein level remained unchanged among the groups (Fig. 4A). Furthermore, the effect of NUA2 knockdown on cell proliferation and ferroptosis was reversed by the mTOR activator MHY1485 (Fig. 4B–D). These results suggest that

NUAK2 knockdown can inhibit the mTOR/c-Myc signaling pathway, promoting ferroptosis and thereby suppressing the malignant progression of endometrial cancer cells.

4. Discussion

This study used systematic *in vitro* experiments to elucidate the pro-oncogenic role of NUA2 in EC and its underlying molecular mechanisms. The findings demonstrated that NUA2 is markedly overexpressed in both EC tissues and cell lines, suggesting its potential function as an oncogene in EC. Further

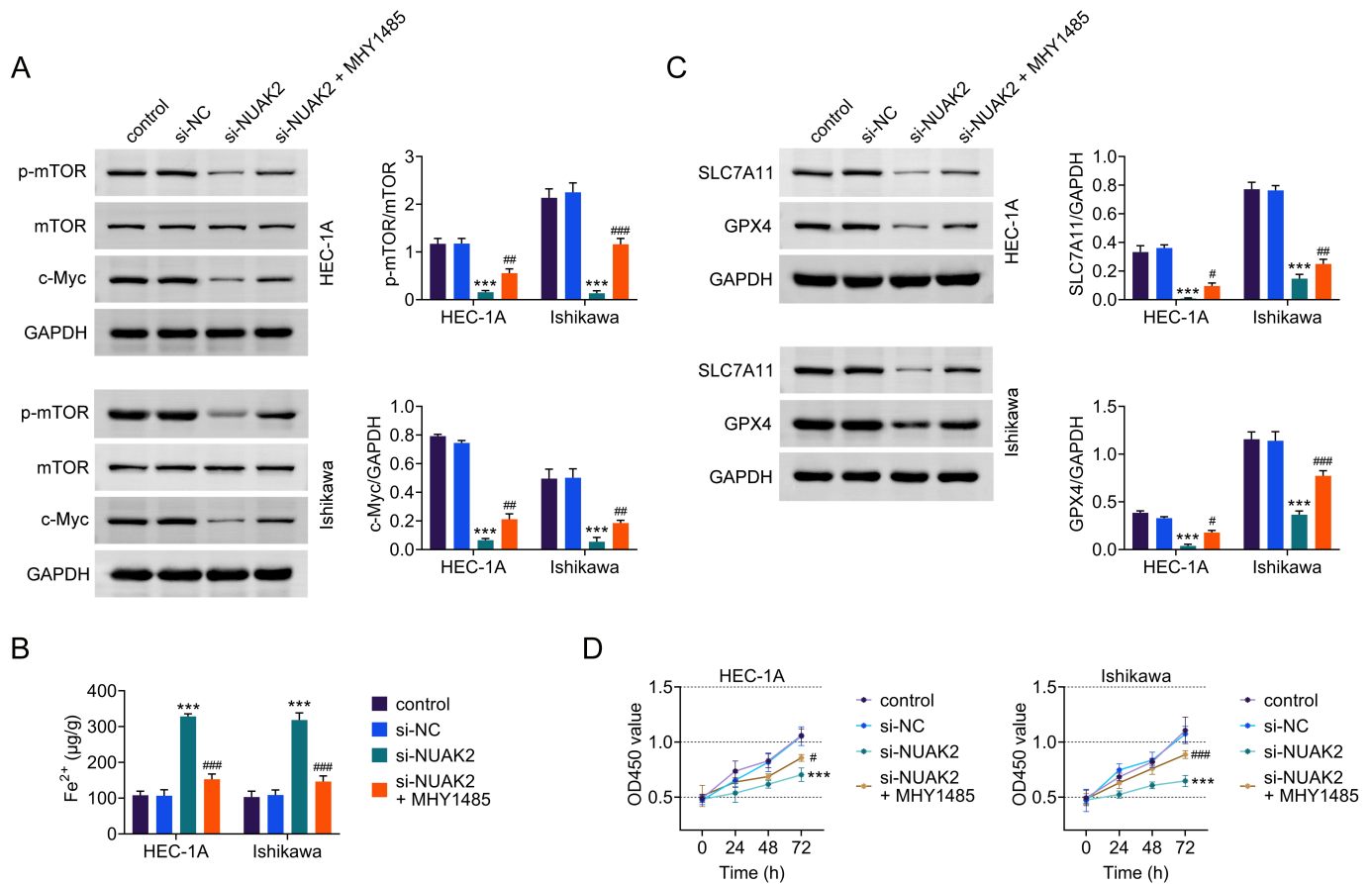


FIGURE 4. Knockdown of NUA2 promotes ferroptosis through the mTOR/c-Myc signaling pathway, thereby inhibiting the growth of endometrial cancer cells. (A) Western blotting analysis of mTOR, p-mTOR, and c-Myc expression. (B) Detection of Fe²⁺ levels using a commercial assay kit. (C) Western blotting analysis of SLC7A11 and GPX4 expression. (D) CCK-8 assay for cell viability. Values are presented as mean ± SD. ****p* < 0.001 vs. si-NC group; #*p* < 0.05, ###*p* < 0.01, ####*p* < 0.001 vs. si-NUAK2 group. *n* = 3. NUA2: NUA family kinase 2; GAPDH: Glyceraldehyde-3-Phosphate Dehydrogenase; SLC7A11: Solute Carrier Family 7; GPX4: Glutathione Peroxidase 4; mTOR: mechanistic target of rapamycin; p-mTOR: phosphorylated mTOR; c-Myc: c-Myelocytomatosis oncogene; Fe²⁺: ferrous ion; OD: Optical Density; si-NC: small interfering RNA negative control; HEC-1A: human endometrial cancer cell lines.

functional analyses revealed that NUA2 knockdown significantly inhibited EC cell proliferation and induced ferroptosis, a process largely dependent on the regulation of the mTOR/c-Myc signaling pathway.

Through analysis of the GEPIA database and validation by Western blot, our results confirmed that NUA2 expression was dramatically elevated in EC, approximately 3.5-fold higher than in normal endometrial tissues, which aligns with findings from Chen *et al.* [12], who reported NUA2 overexpression in breast cancer, and Tang *et al.* [13], who demonstrated that NUA2 promotes tumor progression in gastric cancer by regulating cell proliferation. Together, these findings indicate that NUA2 may function as a cross-cancer promoter, exerting a significant role in the progression of multiple malignancies.

This study found that knocking down NUA2 markedly reduced the proliferation of EC cells, as demonstrated by CCK-8 and EdU assays (showing an inhibition efficiency of approximately 50%), indicating that NUA2 plays an important role in maintaining the malignant phenotype of EC cells. The underlying mechanism may involve the regulation

of the cell cycle or the suppression of apoptotic pathways. Future research could explore whether NUA2 regulates cell proliferation by influencing proteins such as Cyclin D1 or p21.

Importantly, this study demonstrated for the first time that NUA2 knockdown induces ferroptosis in EC cells. This finding is consistent with the results of Tanu *et al.* [14], who reported that NUA2 silencing decreases GPX4 expression and induces ferroptosis in breast cancer cells. As an iron-dependent cell death process driven by excessive lipid peroxidation, ferroptosis has emerged as a significant contributor to multiple cancer hallmarks, from oncogenesis to therapeutic resistance [15]. NUA2 knockdown significantly increased intracellular Fe²⁺ and ROS levels (approximately three-fold), while reducing the expression of SLC7A11 and GPX4 (approximately 10%), both of which are key negative regulators of ferroptosis. Moreover, treatment with the ferroptosis inhibitor Fer-1 partially reversed the cell death phenotype caused by NUA2 knockdown, further indicating that ferroptosis plays a central role in this process.

At the molecular level, this study suggests that NUA2 may modulate ferroptosis through regulation of the mTOR/c-

Myc signaling pathway. Our experimental results showed that following NUA2 knockdown, the expression levels of p-mTOR and c-Myc proteins decreased by approximately 10%, whereas administration of the mTOR agonist MHY1485 partially restored c-Myc expression and alleviated ferroptosis. This observation is in line with previous reports demonstrating the ability of the mTOR/c-Myc pathway to regulate cell metabolism and cell death [8, 16, 17]. Specifically, c-Myc functions as a master regulatory factor that can directly bind to promoter regions or indirectly regulate the expression of key ferroptosis-related genes such as SLC7A11, a principal component of the cystine/glutamate antiporter system [18]. Therefore, NUA2 may act as an upstream regulatory factor that modulates ferroptosis through mTOR/c-Myc-mediated signaling, thereby revealing the association between NUA2 expression and cell death in EC.

NUA2 has been shown to significantly promote tumor development in various cancers, and inhibiting its expression or activity can effectively suppress malignant progression. This suggests that therapeutic strategies targeting NUA2 may have broad applicability and could be employed to combat multiple types of cancer. In particular, the development of small-molecule inhibitors against NUA2 may represent an effective therapeutic approach. Such inhibitors could suppress the kinase activity of NUA2, thereby blocking its tumor-promoting effects in cancer cells. The findings of this study, together with those of Li *et al.* [7], demonstrate that NUA2 plays an important role in promoting cancer in gynecological malignancies, thus providing a theoretical foundation for therapeutic strategies aimed at targeting NUA2. In endometrial and cervical cancers, inhibition of NUA2 expression or activity may effectively suppress tumor cell proliferation and growth, offering new potential treatment options for affected patients.

However, this study has certain limitations. These include the absence of *in vivo* validation, the lack of correlation analysis with clinical specimens, and the specific molecular mechanisms by which NUA2 regulates the mTOR/c-Myc signaling pathway remain incompletely understood. Evidence from *in vivo* studies of other cancers has shown that NUA2 exerts strong oncogenic effects in various malignancies, influencing biological behaviors such as tumor growth, invasion, and metastasis in living systems [19]. Moreover, *in vivo* research on other tumor types has demonstrated that NUA2 may promote tumor development and progression through its involvement in multiple pathways, including cellular metabolic regulation [8]. These findings indicate that corresponding *in vivo* experiments should also be conducted in EC to validate and expand upon the results of the present study.

5. Conclusions

Collectively, our findings indicate that NUA2 not only promotes EC progression by governing ferroptosis via the mTOR/c-Myc pathway but also represents a viable therapeutic target, thereby laying the conceptual groundwork for targeting ferroptosis in EC treatment.

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

DDY—designed the study and carried them out. DDY, RHZ, XFZ—supervised the data collection; analyzed the data. DDY, RHZ—interpreted the data. DDY, XFZ—prepared 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.

ACKNOWLEDGMENT

Not applicable.

FUNDING

This work was supported by Zhejiang Province Traditional Chinese Medicine Science and Technology Plan Project (Grant No. 2025ZX215).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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How to cite this article: Dandan Yao, Ruhui Zheng, Xiangfan Zhu. Knockdown of NUA2 promotes ferroptosis by regulating the mTOR/c-Myc signaling pathway to inhibit endometrial cancer cell progression. *European Journal of Gynaecological Oncology*. 2026; 47(1): 78-85. doi: 10.22514/ejgo.2026.009.