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ORIGINAL RESEARCH

Erianin Suppresses Pancreatic Cancer Progression by Inducing Cell Cycle Arrest and Ferroptosis

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Background: Pancreatic cancer is a highly aggressive malignancy with limited therapeutic options and poor prognosis. Erianin, a natural product, has shown anti-cancer properties in various malignancies, but its effects on pancreatic cancer and the underlying mechanisms remain poorly understood.

Aim: This study aimed to evaluate the anti-tumor effects of erianin on pancreatic cancer cells and to explore the regulatory mechanisms involved.

Methods: PANC-1 and ASPC-1 pancreatic cancer cells were treated with erianin at different concentrations. Cell viability and proliferation were assessed using the Cell Counting Kit-8 (CCK-8) assay and colony formation assay. Cell cycle distribution was analyzed by flow cytometry. Ferroptosis was evaluated by measuring levels of Fe^{2+}, total iron, and lipid reactive oxygen species (ROS). Western blotting was used to detect</mark> the expression of cell cycle regulators and ferroptosis-related proteins.

Results: Erianin significantly suppressed pancreatic cancer cell viability and proliferation in a dose-dependent manner. It induced G0/G1 phase arrest, accompanied by downregulation of cyclin D1 and cyclin A. Furthermore, erianin promoted ferroptosis, as evidenced by increased Fe^{2+}, total iron, and lipid ROS levels, along with reduced glutathione peroxidase 4 (GPX4) and solute carrier family 7 member 11 (SLC7A11) expression. The ferroptosis inhibitor Ferrostatin-1 reversed these effects, validating ferroptosis as a critical mechanism in erianin's anti-cancer activity.

Conclusion: Erianin exerts potent anti-tumor effects on pancreatic cancer cells by inducing cell cycle arrest and ferroptosis. These findings establish erianin as a promising therapeutic candidate for pancreatic cancer treatment.

Keywords: erianin, ferroptosis, cell cycle, pancreatic cancer

Introduction

Pancreatic cancer is one of the deadliest malignancies, ranking as the seventh leading cause of cancer-related deaths worldwide with an estimated 495,773 new cases and 466,003 deaths in 2020.[1] Alarmingly, the global incidence of pancreatic cancer has more than doubled over the past two decades, a trend that cannot be solely explained by population aging.[1,2] Pancreatic cancer stands as a prominent contributor to cancer-related mortality on a global scale. Its worldwide prevalence has increased by over two-fold in the last two decades.[1] While a significant portion of this rise can be attributed to the aging of populations worldwide, it's crucial to acknowledge that there are specific modifiable risk factors associated with pancreatic cancer.[2] These include factors like obesity, diabetes, alcohol consumption, and cigarette smoking.[3] Despite advances in cancer therapy, pancreatic cancer remains highly lethal with a 5-year survival rate of only about 10%, largely due to late diagnosis, aggressive tumor biology, and limited treatment efficacy.[3,4] The established treatment approach for patients diagnosed with resectable pancreatic cancer typically involves surgical removal of the tumor, followed by adjuvant chemotherapy.[4] However, the prognosis of patients with pancreatic cancer remains poor attributed to the development of drug resistance and recurrence.[4] Therefore, it is urgently needed to explore novel therapeutic approaches for pancreatic cancer.

Since the identification of ferroptosis as an iron-dependent form of non-apoptotic cell death in 2012, there has been mounting interest in the process and function of ferroptosis.[5,6] Ferroptosis is caused by a redox imbalance between the production of oxidants and antioxidants (eg, glutathione (GSH)), which is driven by the abnormal expression and activity of multiple redox-active enzymes that produce or detoxify free radicals and lipid oxidation products (eg, malondialdehyde (MDA)).[7,8] This form of

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regulated cell death is characterized by the accumulation of iron-dependent lipid peroxides, leading to oxidative damage to cellular membranes and eventual cell death.[7] Unlike apoptosis, ferroptosis exhibits unique characteristics such as iron dependency and lipid peroxidation, making it a promising alternative strategy to target cancer cells, particularly those resistant to traditional therapies.[9] In recent years, ferroptosis has been shown to play a critical role in overcoming therapeutic resistance in cancer cells, including pancreatic cancer.[10] For example, pancreatic cancer cells often upregulate antioxidant defense systems such as the cystine/glutamate antiporter (system Xc^-) and glutathione peroxidase 4 (GPX4) to resist oxidative stress and avoid cell death. Ferroptosis-inducing agents can disrupt these defenses, offering a novel approach to tackle drug resistance and recurrence in pancreatic cancer. Given the inherent resistance of pancreatic cancer to apoptosis, targeting ferroptosis represents a promising therapeutic avenue.[10]

Several compounds extracted from Dendrobium chrysotoxum, such as confusarin, chrysotobibenzyl, and chrysotoxene, have been reported as potential anti-tumor agents.[11,12] Notably, erianin, a bibenzyl compound, is considered the chemical marker for quality control of Dendrobium chrysotoxum and has emerged as a highly promising anti-tumor agent with documented efficacy against various cancers, including osteosarcoma, melanoma, hepatoma, breast cancer, lung cancer, gastric cancer, and bladder cancer.[13–19] Erianin's mechanisms of action have been linked to the induction of apoptosis in cancer cells.[15,18] Recently, erianin has been shown to inhibit the growth and stemness of pancreatic cancer cells through mechanisms involving the inhibition of the MAPK signaling pathway.[20] However, the role of ferroptosis in erianin's anti-pancreatic cancer activity remains unexplored. This connection is particularly significant due to the potential of ferroptosis to overcome drug resistance, a hallmark of pancreatic cancer. Given that erianin is a natural compound with a favorable safety profile and multi-targeting potential, it represents an attractive candidate for developing novel therapies against pancreatic cancer.

The present study aims to evaluate the anti-tumor effects of erianin on pancreatic cancer progression and to elucidate the involvement of ferroptosis in this process. Specifically, we investigated whether erianin induces ferroptosis in pancreatic cancer cells and explored the underlying molecular mechanisms. Our findings provide new insights into the anti-cancer mechanisms of erianin and support its potential as a ferroptosis-inducing agent for pancreatic cancer treatment.

Materials and Methods

Reagents and Chemicals

Erianin (purity ≥98%, HPLC) was purchased from MedChemExpress (Monmouth Junction, NJ, USA; catalog no. HY-N0376). Cell Counting Kit-8 (CCK-8) was obtained from Beyotime Biotechnology (Shanghai, China; catalog no. C0038). Propidium iodide (PI) and RNase A were from Sigma-Aldrich (St. Louis, MO, USA; catalog nos. P4170 and R6513, respectively). BODIPY™ 581/591 C11 was purchased from Thermo Fisher Scientific (Waltham, MA, USA; catalog no. D3861). The Iron Assay Kit was acquired from Abcam (Cambridge, UK; catalog no. ab83366). Antibodies against GPX4 (catalog no. ab125066), SLC7A11 (catalog no. ab175186), cyclin D1 (catalog no. ab134175), and cyclin A (catalog no. ab181591) were purchased from Abcam. All other chemicals were of analytical grade.

Cell Culture

Pancreatic cancer cell lines PANC-1 and ASPC-1 were purchased from American Type Culture Collection (ATCC; Manassas, VA, USA). Cells were cultured in DMEM (Gibco, Grand Island, NY, USA) supplemented with 10% fetal bovine serum (FBS; Gibco) and 1% penicillin-streptomycin (Gibco) at 37°C in a humidified atmosphere containing 5% CO2. Cells were passaged every 2–3 days and used within 20 passages. All cell lines were regularly tested for mycoplasma contamination and found negative. These cell lines were selected as representative models for pancreatic cancer due to their distinct biological characteristics. PANC-1 is derived from a poorly differentiated pancreatic carcinoma and exhibits high metastatic potential, while ASPC-1 originates from a moderately differentiated adenocarcinoma and reflects different pathological features of the disease. Together, they provide complementary models for studying pancreatic cancer progression and treatment responses.

Cell Counting Kit 8 (CCK-8)

Cell viability was measured using the CCK-8 assay (Beyotime) according to the manufacturer's instructions. Briefly, cells were seeded in 96-well plates at a density of 5×10^3 cells per well and incubated overnight for attachment. The next day, cells were treated with erianin at various concentrations (0, 1.25, 2.5, 5, 10, and 20 μM) for 24, 48, and 72 h. After treatment, 10 μL of CCK-8 reagent was added to each well and incubated for 2 h at 37°C. Absorbance was measured at 450 nm using a microplate reader (Thermo Fisher Scientific). Each experiment was performed in triplicate and repeated three times independently.

Colony Formation Assay

For colony formation assay, cells were seeded in 6-well plates at a density of 1000 cells per well and allowed to adhere overnight. The next day, cells were treated with erianin (0, 2.5, 5, and 10 μM) for 10 days, with the medium replaced every 3 days. After incubation, cells were washed with PBS, fixed with 4% paraformaldehyde for 15 min, and stained with 0.1% crystal violet for 20 min. The plates were washed with distilled water, air-dried, and colonies (defined as >50 cells) were counted under a light microscope (Olympus, Tokyo, Japan).

Cell Cycle Analysis

For cell cycle analysis, cells were seeded in 6-well plates and treated with erianin (0, 5, and 10 μM) for 24 h. Cells were then harvested, washed with PBS, and fixed in 70% ice-cold ethanol overnight at 4°C. After fixation, cells were washed with PBS and stained with a solution containing 50 μg/mL PI, 100 μg/mL RNase A, and 0.1% Triton X-100 in PBS for 30 min at 37°C in the dark. Cell cycle distribution was analyzed using a BD FACSCanto II flow cytometer (BD Biosciences), and data were processed using FlowJo software (version 10.6.2; Tree Star, Ashland, OR, USA).

Characterization of Ferroptosis

Ferroptosis was assessed by measuring lipid ROS, Fe^{2+}, and total iron levels, as well as by Western blotting of ferroptosis-related proteins.

Lipid ROS detection: Cells were treated with erianin (0, 5, and 10 μM) for 24 h, then incubated with 5 μM BODIPY™ 581/591 C11 at 37°C for 30 min. After washing with PBS, lipid ROS levels were analyzed by flow cytometry (excitation/emission: 581/591 nm).

Iron assay: Intracellular Fe^{2+} and total iron levels were measured using the Iron Assay Kit (Abcam) according to the manufacturer's instructions. Briefly, cells were lysed in iron assay buffer, and the lysates were centrifuged at 16,000 × g for 10 min. The supernatant was mixed with iron reducer (for total iron) or assay buffer (for Fe^{2+}) and incubated with iron probe for 60 min at 37°C. Absorbance was measured at 593 nm.

Western blotting: Total proteins were extracted using RIPA buffer (Beyotime) and quantified by BCA assay. Proteins (30 μg per lane) were separated by SDS-PAGE and transferred to PVDF membranes. After blocking with 5% non-fat milk, membranes were incubated with primary antibodies (1:1000 dilution) overnight at 4°C, followed by HRP-conjugated secondary antibodies (1:5000) for 1 h at room temperature. Protein bands were visualized using ECL reagent (Millipore, Billerica, MA, USA) and analyzed by ImageJ software (NIH, Bethesda, MD, USA).

Statistics Analysis

Statistical analysis was performed using GraphPad Prism 7.0 (GraphPad Software, San Diego, CA, USA). Data are presented as mean ± standard deviation (SD) of at least three independent experiments. Differences between two groups were analyzed by Student's *t*-test, and differences among multiple groups were analyzed by one-way ANOVA followed by Tukey's post hoc test. Statistical significance was set at $P < 0.05$.

Results

Cytotoxicity of Erianin to Pancreatic Cancer Cells

To evaluate the anti-proliferative effects of erianin, we calculated its IC50 values (concentration inhibiting 50% cell viability) in PANC-1 and ASPC-1 pancreatic cancer cells. Erianin significantly suppressed cell growth in a dose-dependent manner, with higher concentrations exerting stronger inhibitory effects (Figure 1A). Morphological changes in treated cells—including shrinkage, rounding, and reduced confluency—further supported its cytotoxicity.

Colony formation assays corroborated these findings (Figures 1B and C). At 20 μM erianin, PANC-1 cells exhibited 43.21 ± 5.19% relative colony formation (vs control: 100.21 ± 8.21%; 57% reduction, $p<0.01$). Similarly, ASPC-1 cells showed 44.19 ± 5.27% colony formation (vs control: 98.92 ± 9.04%; 55% reduction, $p<0.01$). These results demonstrate erianin's potent suppression of long-term proliferative capacity.

Erianin Induces Cell Cycle Arrest of Pancreatic Cancer Cells

To investigate the effect of erianin on cell cycle progression, flow cytometry analysis was conducted on PANC-1 and ASPC-1 pancreatic cancer cells treated with 0, 10, or 20 nM erianin. As shown in Figure 2A and B, erianin treatment led to a dose-dependent alteration in cell cycle distribution. Quantitative analysis (Figure 2C) indicated a significant accumulation of cells in the G0/G1 phase. Specifically, the proportion of G0/G1 phase cells increased from 45.2% (control) to 58.1% (10 nM) and 68.7% (20 nM) in PANC-1 cells, and from 42.8% to 54.3% and 65.3% in ASPC-1 cells (all $p < 0.01$). Correspondingly, the percentages of cells in the S and G2/M phases decreased. These findings suggest that erianin effectively induces G0/G1 phase arrest in pancreatic cancer cells.

Erianin Enhances Ferroptosis of Drug Resistant Pancreatic Cancer Cells

Treatment with erianin significantly increased intracellular ferrous ion levels (Figure 3A and B), total iron content (Figure 3C and D), and lipid reactive oxygen species (ROS) accumulation (Figure 3E and F) in a dose-dependent manner in both PANC-1 and ASPC-1 cells. Western blot analysis revealed that erianin downregulated the expression of key ferroptosis inhibitors GPX4 and SLC7A11, with more pronounced suppression observed at higher doses.

To confirm the role of ferroptosis in erianin's anti-cancer effects, we co-treated cells with the ferroptosis inhibitor ferrostatin-1 (Fer-1). Fer-1 treatment substantially reversed erianin-induced cytotoxicity, as demonstrated by restored cell viability in CCK-8 assays (Figure 4A and B). Additionally, Fer-1 attenuated erianin-mediated increases in Fe^{2+}, total iron, and lipid ROS levels (Figure 4C–H). The downregulation of cyclin D1, cyclin A, GPX4, and SLC7A11 by erianin was also rescued upon Fer-1 co-treatment. These results collectively demonstrate that erianin exerts its anti-tumor effects in pancreatic cancer cells primarily through induction of ferroptosis.

Discussion

Cancers are featured with uncontrolled cell proliferation, for which inducing cell death and repressing cell cycle have been considered as ideal therapies. Erianin has garnered extensive research attention in various diseases, including inflammatory conditions and cancers. Accumulating evidence has reported that erianin showed inhibitory effects on the growth of several types of cancer, including bladder cancer, lung cancer, hepatocellular carcinoma, triple-negative breast cancer, and more.[16,18,20–23] Our findings suggested that erianin treatment inhibited the growth of pancreatic cancer cells and induced cell cycle arrest in a dose-dependent manner, accompanied with obvious incidence of ferroptosis.

Research on erianin has documented the occurrence of apoptosis and cell cycle arrest in cancers treated with erianin. For instance, erianin treatment was found to enhance both apoptosis and autophagy in oral squamous cell carcinoma cells, achieved by regulating the MAPK signaling pathway.[21] In osteosarcoma, erianin induced autophagy, apoptosis, and G2/M cell cycle arrest by targeting the ROS/JNK signaling pathway.[15] A consistent pattern was observed with down-regulated expression of Cyclin D1 and Cyclin A and the subsequent accumulation of cells at the G0/G1 phase. This finding suggests that erianin primarily arrests the cell cycle at the G0/G1 phase, potentially through a mechanism involving modulation of key cell cycle regulators, including Cyclin D1 and Cyclin A. The regulation of these molecules,

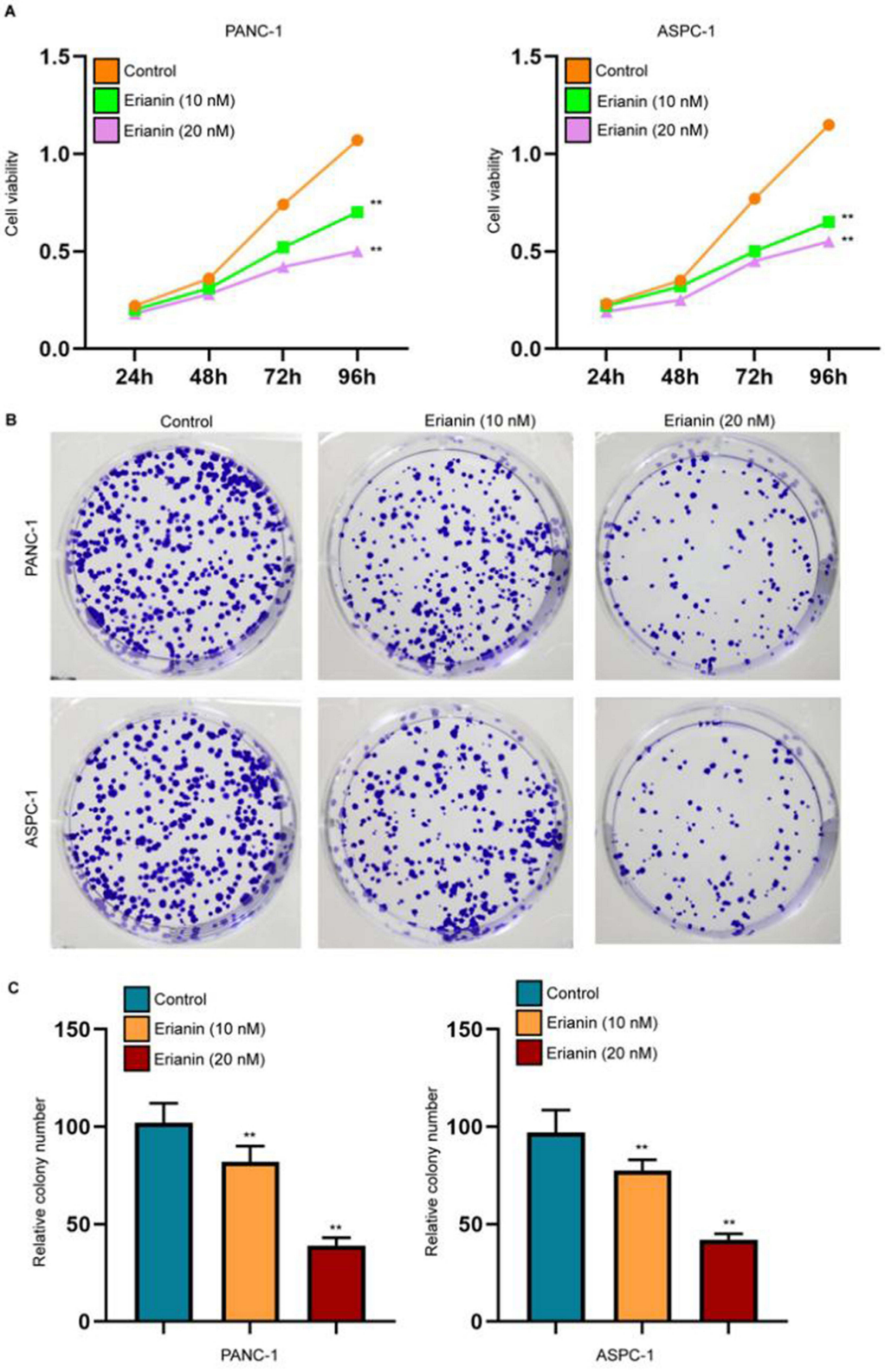

Figure 1 Cytotoxicity of erianin to pancreatic cancer cells. (**A**) Growth curves and IC_{50} values. (**B**) Colony images. (**C**) Quantified colony numbers (mean ± SD, n=3). **p<0.01 vs control.

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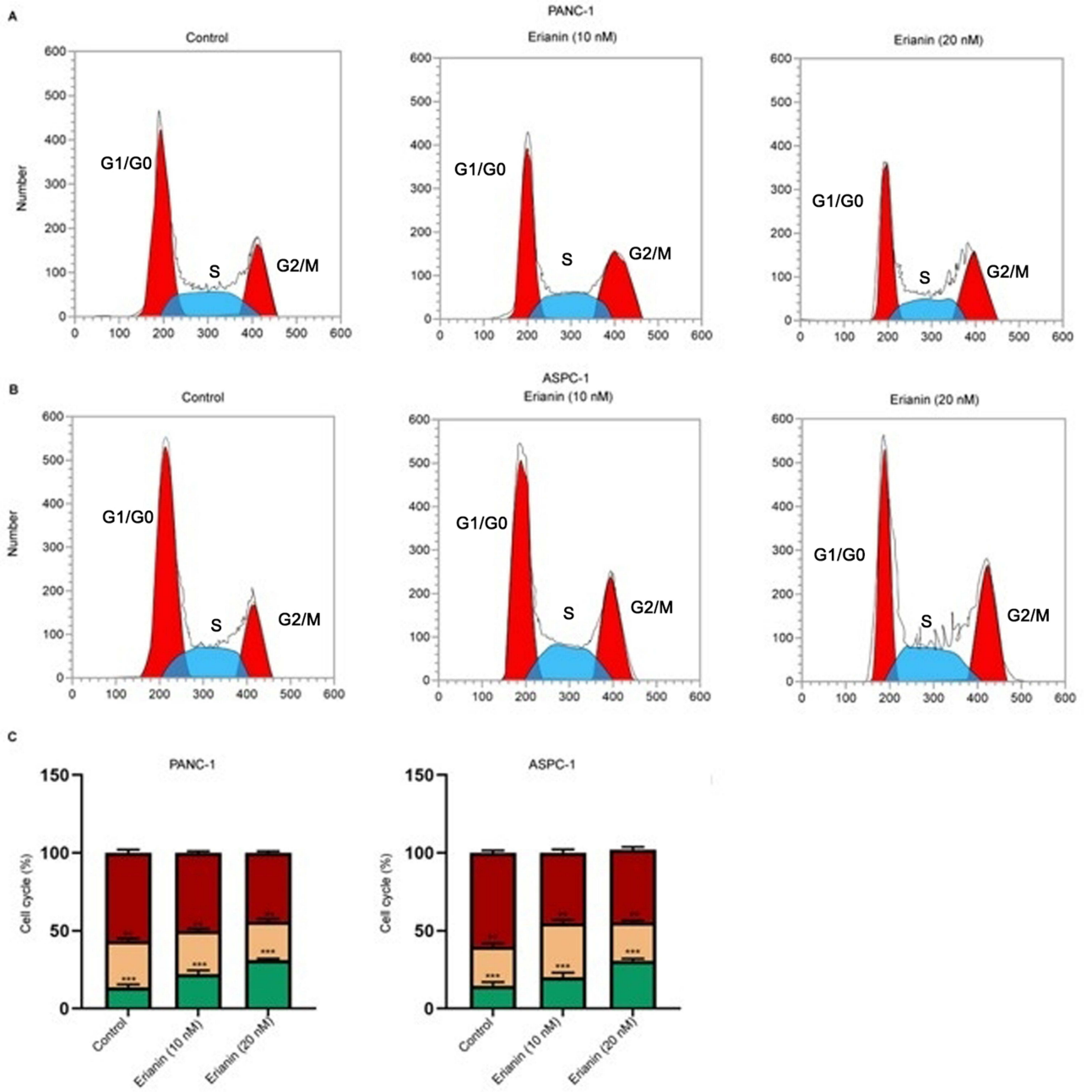

Figure 2 Erianin induces cell cycle arrest in pancreatic cancer cells. (**A** and **B**) Flow cytometry profiles of PANC-1 and ASPC-1 cells treated with erianin (0, 10, 20 nM). (**C**) Quantitative distribution of cell cycle phases: green = G0/G1 phase, Orange = S phase, brown = G2/M phase. Data are presented as mean ± SD (n = 3). *p < 0.01, p < 0.05 vs control (one-way ANOVA with Dunnett's test).

which are known to be critical in the G1/S phase transition, may provide insight into the anti-proliferative effects of erianin in pancreatic cancer cells.

Ferroptosis is a novel programmed cell death form that is induced by abnormal iron metabolism,[24–27] and an increasing number of studies have identified the involvement of ferroptosis during initiation and development of cancers.[28,29] Iron, as an essential reactive element in various biological processes, exists in two oxidation states, ferrous [Fe^{2+}] and ferric [Fe^{3+}], and abnormal Fe^{2+} accumulation could initiate ferroptosis.[30] Ferroptosis has been found to play a crucial role in various aspects of cancer initiation and progression. It has been reported that erianin triggered ferroptotic cell death of lung cancer cells via a Ca^{2+}/CaM-dependent mechanism and concurrently inhibited cell migration.[20] In

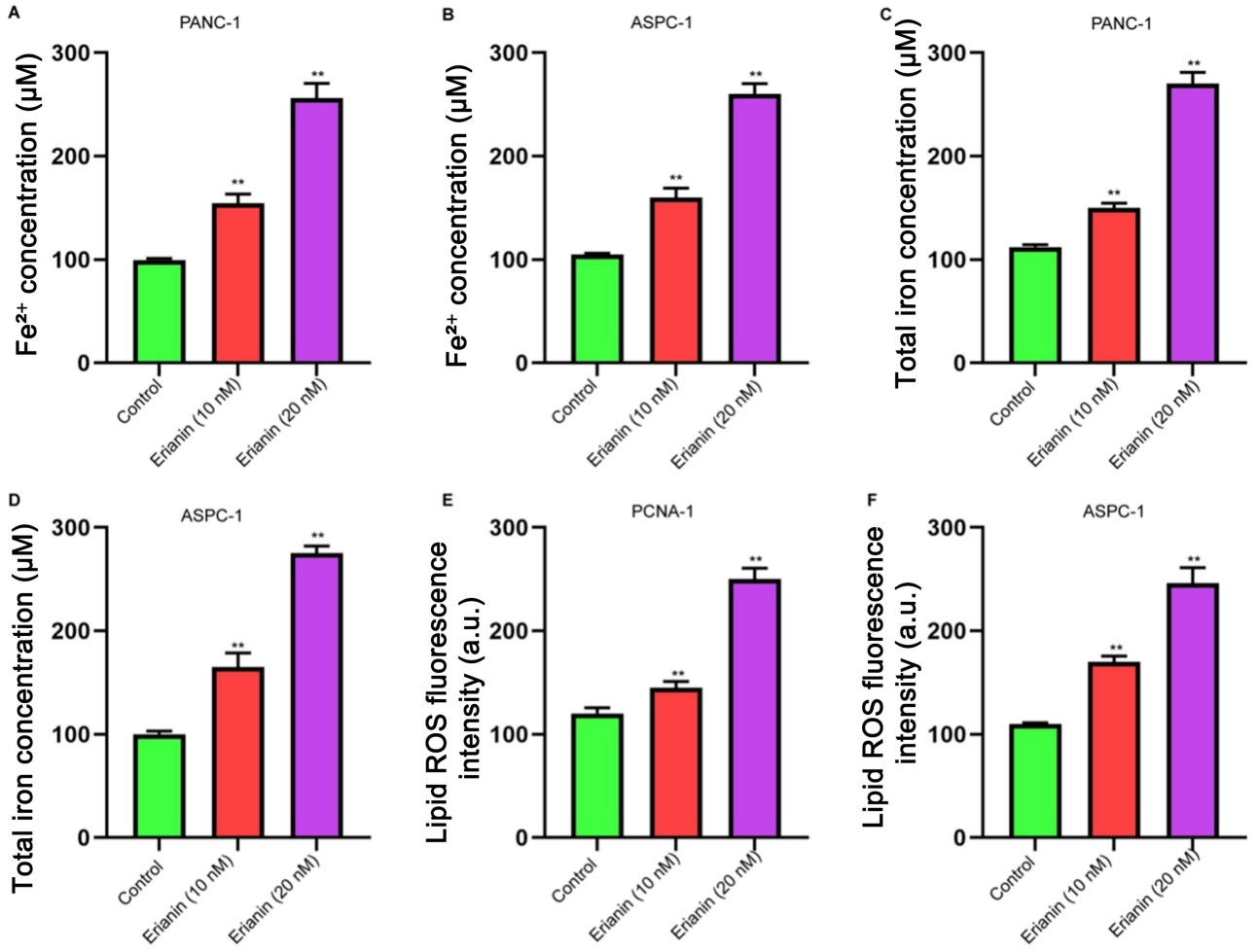

Figure 3 Erianin disrupts iron homeostasis and induces lipid peroxidation. (**A** and **B**) Fe2+ levels, (**C** and **D**) total iron, (**E** and **F**) lipid ROS in PANC-1/ASPC-1 cells treated 24h (mean ± SD, n=3). **p<0.01 vs control (Dunnett's test).

bladder cancer cells, erianin was observed to deactivate nuclear factor E2-related factor 2 (NRF2) and facilitate the reduction of glutathione levels while promoting the production of lipid ROS, suggesting the induction of ferroptosis.[16]

Similarly, this study found that erianin treatment in vitro led to a decrease in GPX4 and SLC7A11 protein levels and a significant increase in Fe^{2+}, total iron, and lipid ROS levels in pancreatic cancer cells. This supports ferroptosis as a major mechanism of erianin's antitumor action. Recent studies also highlight the pivotal role of ferroptosis in mediating drug sensitivity in pancreatic cancer, indicating potential synergy with chemotherapeutics.[10,31]

Beyond erianin, other natural compounds such as artesunate, curcumin, and sulfasalazine have also been identified as ferroptosis inducers in various cancer types. For example, artesunate promotes ferroptosis by increasing ROS production and iron overload in pancreatic and breast cancer cells,[9] while curcumin triggers ferroptosis in colorectal cancer by regulating GPX4 and NRF2 expression.[32] Compared to these compounds, erianin exhibits a potent ferroptosis-inducing effect, even at relatively low concentrations, highlighting its unique therapeutic potential for addressing pancreatic cancer drug resistance.

Given the critical role of ferroptosis in overcoming drug resistance, combining erianin with standard therapies such as gemcitabine or nab-paclitaxel may enhance treatment efficacy. Indeed, ferroptosis inducers have been shown to sensitize cancer cells to chemotherapeutic agents by disrupting redox homeostasis.[33,34] These findings suggest that erianin could be a promising candidate in combination strategies to improve therapeutic outcomes.

While this study emphasizes ferroptosis as the primary mechanism of cell death induced by erianin in pancreatic cancer cells, previous reports have identified apoptosis as the dominant mode in other cancer types, such as osteosarcoma

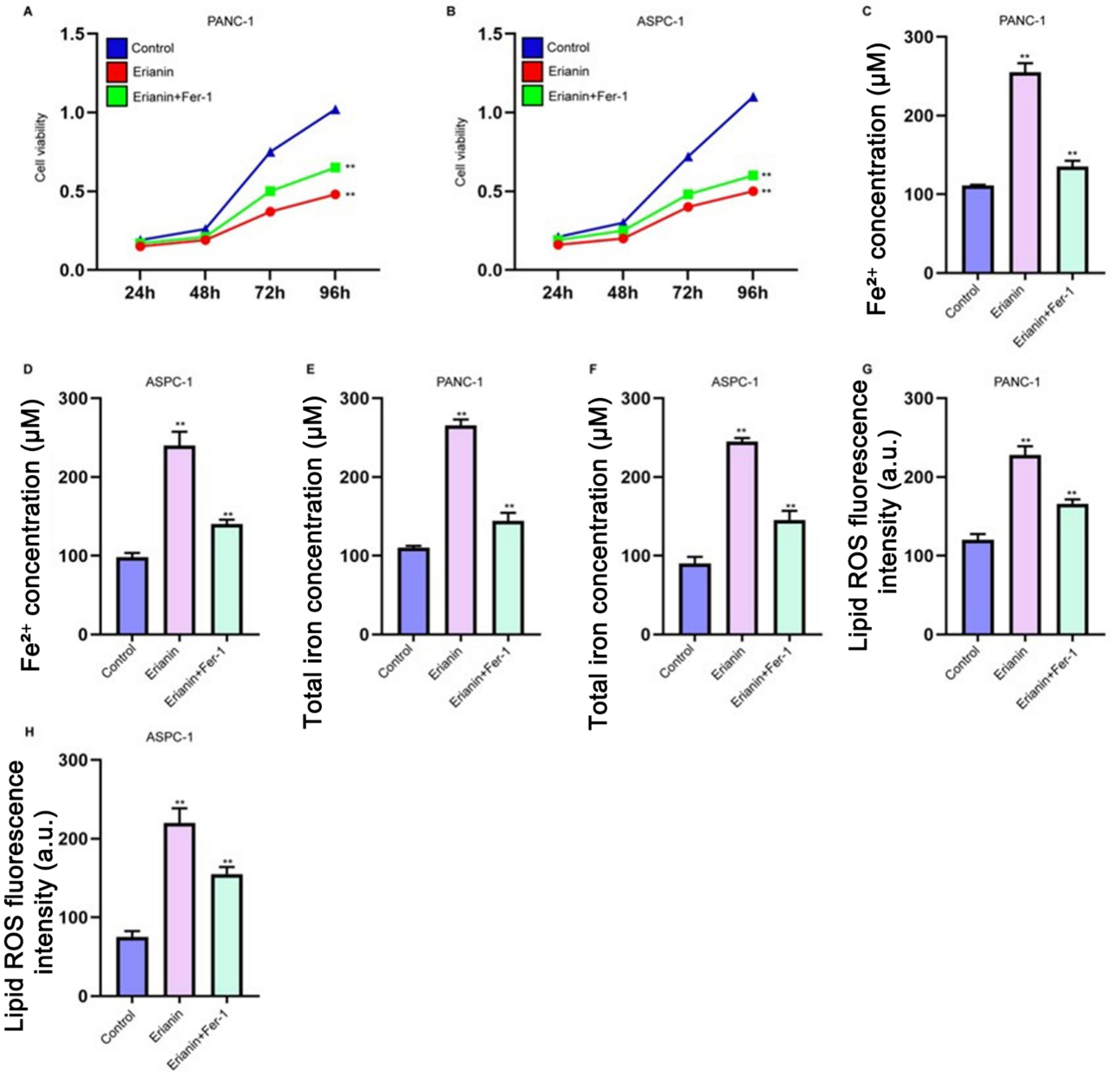

Figure 4 Ferrostatin-1 antagonizes erianin-induced ferroptosis. (**A** and **B**) Viability over 96h (mean ± SD, n=3). (**C**–**H**) Fe2+ /iron/lipid ROS after 24h co-treatment. **p<0.01 vs control (two-way ANOVA).

and oral squamous cell carcinoma.[15,21] This discrepancy may arise from differences in cell type, intracellular iron metabolism, or experimental conditions, such as erianin concentration and treatment duration. Furthermore, the potential off-target effects of erianin on non-cancerous cells in vivo remain unexplored. Future research should address these limitations by evaluating the safety profile and specificity of erianin in vivo.

Conclusion

In summary, the findings of this study provide new insights into the anti-tumor mechanisms of erianin, particularly its ability to induce ferroptosis in pancreatic cancer cells. These results contribute to the growing body of evidence supporting ferroptosis as a promising therapeutic strategy for cancers characterized by drug resistance.

Furthermore, given the critical challenge of drug resistance in pancreatic cancer treatment, erianin may offer a potential solution by sensitizing resistant cells to standard therapies such as gemcitabine or nab-paclitaxel. This could make erianin a valuable candidate for combination therapy in overcoming resistance.

Future investigations should focus on elucidating the detailed molecular pathways underlying erianin-induced ferroptosis, evaluating its in vivo efficacy and toxicity, and exploring its role in combination with conventional chemotherapeutic agents. Such studies will be crucial for establishing erianin's potential as part of a novel therapeutic approach to treat pancreatic cancer and other drug-resistant cancers.

Disclosure

The authors report no conflicts of interest in this work.

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