Original Article

Astragaloside IV sensitizes non-small cell lung cancer cells to cisplatin by suppressing endoplasmic reticulum stress and autophagy

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Background: Cisplatin is an effective chemotherapeutic drug for treating various cancers including non-small cell lung cancer (NSCLC), but resistance to cisplatin remains the main limitation to its use in clinic. Astragaloside IV (AS-IV), which is derived from *Astragalus membranaceus*, has been proven to participate in various anti-cancer activities including anti-cancer, anti-oxidative, and anti-inflammatory functions.

Method: In this study, we explored the role of AS-IV in cisplatin chemoresistance to NSCLC cells by establishing cisplatin-resistant the NSCLC cell lines, $A549^{Cis}$ and $H1299^{Cis}$.

Results: Cisplatin inhibited viability and promoted apoptosis of $A549^{Cis}$ and $H1299^{Cis}$ cells in a dose-dependent manner. In addition, cisplatin upregulated the levels of autophagy-related proteins (Beclin1, LC3 II/I) and endoplasmic reticulum (ER) stress-related proteins (glucose regulated protein 78: GRP78, protein kinase R (PKR)-like endoplasmic reticulum kinase: PERK), indicating that cisplatin caused autophagy and ER stress in NSCLC cells. However, treatment combined with AS-IV dose-dependently suppressed cell viability and increased the cell apoptosis rate in $A549^{Cis}$ and $H1299^{Cis}$ cells, suggesting that AS-IV elevated the anti-tumor role of cisplatin in NSCLC cells. AS-IV treatment suppressed the expression of GRP78 and Beclin1. Inhibition of ER stress or autophagy both counteracted the inhibitory effect of AS-IV on chemoresistance to cisplatin in NSCLC cells.

Conclusions: AS-IV sensitized NSCLC cells to cisplatin through suppressing ER stress and autophagy. This study provides a novel strategy of cisplatin combined with AS-IV for the treatment of cisplatin-resistant NSCLC patients.

Keywords: Astragaloside IV (AS-IV); non-small cell lung cancer (NSCLC); cisplatin; endoplasmic reticulum stress (ER stress); autophagy

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Introduction

Non-small cell lung cancer (NSCLC) is one of the most common cancers and the primary cause of cancer-related death around the world (1). At present, supplementary therapy used to treat NSCLC patients following surgical operation, and cisplatin is widely considered as a first-line chemotherapeutic agent for NSCLC patients (2). However, cisplatin resistance remains a main obstacle to achieving successful chemotherapy (3). The cytotoxic mechanism of cisplatin includes DNA damage and the suppression of DNA synthesis in cancer cells, which prevent or increase cancer cell death by regulating a range of signaling pathways including autophagy and endoplasmic reticulum (ER) stress (4,5).

The ER is an important organelle for protein folding and maturation in eukaryotic cells. ER stress can be triggered by exposure to chemotherapeutic agents and the accumulation of misfolded proteins (6,7). The accumulation of misfolded proteins in the ER cavity contributes to ER stress and the activation of subsequent unfolded protein response (UPR), thereby initiating the expression of chaperone proteins (8). Moderate ER stress promotes survival of cancer cells and enhances resistance to chemotherapy (9,10).

Autophagy is a common cellular process that degrades aggregated or misfolded proteins in cells and damaged organelles to maintain cell homeostasis (11). It is also a form of programmed cell death, which is closely related to apoptosis (12). Previous studies have reported that autophagy plays a vital role in the drug resistance of cancer cells. Bao *et al.* reported that induction of autophagy contributes to cisplatin resistance in human ovarian cancer cells (13), while Su *et al.* demonstrated that autophagy inhibition enhances cisplatin sensitivity in nasopharyngeal carcinoma cells (14). However, knowledge concerning the precise mechanism of autophagy resistance to cisplatin in NSCLC treatment remains extremely limited.

Astragaloside IV (AS-IV), a major active component of *Astragalus membranaceus*, has anti-cancer, anti-oxidative, and anti-inflammatory functions (15-17). Although AS-IV is a potential treatment drug for NSCLC (17), the relevant mechanism has not been elucidated. Thence, this study aimed to investigate the effect of AS-IV on cisplatin chemosensitivity in NSCLC cells, and the relationship with endoplasmic reticulum stress and autophagy. In the current study, the results of western blot suggested that cisplatin seriously induced increasing of ER stress-related proteins glucose regulated protein 78 (GRP78) and protein kinase R (PKR)-like endoplasmic reticulum kinase (PERK), also enhanced expression levels of autophagy-related proteins Beclin1 and LC3 II/I. Fortunately, treatment combined with AS-IV partly reversed these effects. Thus, we inferred that AS-IV increased the chemosensitivity of NSCLC cells to cisplatin through suppressing ER stress and autophagy.

Methods

Reagents and cell culture

NSCLC cell lines (A549, H1299) were purchased from the American Type Culture Collection (ATCC). Cisplatin-resistant A549 and H1299 cell lines, A549Cis and H1299Cis, were established by constant exposure to cisplatin through a process described previously (18). A549Cis and H1299Cis cells were cultured in RPMI-1640 medium (Gibco, Rockville, MD, USA) supplemented with 2 μM cisplatin and 10% fetal bovine serum (FBS) at 37 ℃ with 5% CO_2. A549Cis and H1299Cis cells were moved to the cisplatin-free medium for 2 weeks before subsequent experiments were performed in order to eliminate the interference of residual cisplatin. AS-IV, cisplatin, and rapamycin were obtained from Sigma (St. Louis, MO, USA).

Cell viability assay

Cell Counting Kit-8 (CCK-8) assay was carried out to detect cell viability. Different groups of cells were seeded into 96-well plates at a density of 2×10^3 cells per well, in triplicate. After cells were treated with each concentration of cisplatin for 24 h, 10 μL/well of CCK-8 solution (Dojindo, Tokyo, Japan) was added, and the cells were incubated in the dark at 37 ℃ for another 2 h. The optical density (OD) was determined under 490 nm.

Cell apoptosis assay

Cell apoptosis was detected by Hoechst 33258 stain analysis. In brief, 2×10^5 cells per well were washed with phosphate-buffered saline (PBS) twice. Then, 1 mL of Hoechst 33258 reagent (Beyotime, Nantong, China) was added to each well, and the cells were incubated at 37 ℃ for 30 min in the dark. Next, the Hoechst 33258 reagent was removed, and cells were washed with PBS 3 times (5 min × 3 times). Morphological changes of apoptotic cells were observed under an inverted fluorescence microscope, and images were captured.

Flow cytometry

Cells were harvested to detecte cell apoptosis after 48 h transfection. Cells were washed with pre-cooled PBS three times, followed by being re-suspended using binding buffer to a concentration of 1×10^6/mL to 5×10^6/mL. Then, 100 μL cell suspension was moved into a 5-mL tube, to which 5 μL of Annexin V/fluorescein isothiocyanate (FITC) and 5 μL of propidium iodide (PI) were added, followed by incubating the tube under the dark for 15 min. Then, 400 μL of 1× Annexin V binding buffer was added into the tube. Cell apoptosis was analyzed using a FACScan flow cytometer (BD Biosciences, USA).

Western blot analysis

The extraction of total protein from the treated cells was carried out using radioimmunoprecipitation assay (RIPA) lysis buffer (Beyotime, Nantong, China). The concentration of protein was quantified with bicinchoninic acid (BCA) protein measurement kit (Thermo Fisher Scientific, USA). Proteins were separated by 10% sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) gel and then transferred onto polyvinylidene fluoride (PVDF) membranes (Millipore, Boston, MA, USA). The membrane was blocked with 5% skim milk at room temperature for 2 h, and then incubated with anti-GRP78 antibody, anti-PERK antibody, anti-Beclin1 antibody, anti-LC3 I/II antibody, and anti-GAPDH antibody (Cell Signaling Technology, USA) at 4 ℃ overnight. Next day, the relative secondary antibody was added, and the membrane was incubated at room temperature for 1 h. Then, enhanced chemiluminescence (ECL) reagent was added, and the membranes were detected by chemiluminescence (GE Healthcare, Piscataway, NJ, USA).

Statistical analysis

All data are presented as the mean ± standard deviation (SD) and were analyzed by SPSS19.0. The Student's *t*-test was used to compare means of two groups and one-way analysis of variance (ANOVA) was used for comparing means of multiple samples. Values of $P<0.05$ were considered statistically significant.

Results

Cisplatin inhibited cell viability and induced apoptosis in cisplatin-resistant NSCLC cells

In order to estimate the cytotoxicity of cisplatin treatment on cisplatin-resistant NSCLC cells, A549Cis and H1299Cis cells were incubated with each dose of cisplatin for 24 h. CCK-8 assay was used to detect the cell viability rate. The data showed that cisplatin application suppressed cell viability in both A549Cis and H1299Cis cells (*Figure 1A*). Meanwhile, results from Hoechst 33258 stain analysis revealed that cisplatin dose-dependently induced apoptosis in A549Cis and H1299Cis cells (*Figure 1B*). Hence, we can surmise that cisplatin inhibited cell viability and induced apoptosis in cisplatin-resistant NSCLC cells.

Cisplatin induced ER stress and autophagy in cisplatin-resistant NSCLC cells

To further investigate whether ER stress and autophagy are related to cisplatin-induced cell apoptosis in A549Cis and H1299Cis cells, we examined the expression of ER stress-related and autophagy-related proteins following cisplatin treatment by Western blot. After A549Cis and H1299Cis cells were treated with each concentration of cisplatin (0, 20, and 60 μM) for 24 h respectively, the expression of GRP78 and PERK (two kinds of ER stress-related proteins) and autophagy-related proteins (Beclin1, LC3 II/I) significantly increased in a dose-dependent manner (*Figure 2A*,*B*,*C*,*D*). These results indicate that cisplatin induced ER stress and autophagy in A549Cis and H1299Cis cells.

AS-IV augmented the anti-tumor effect of cisplatin dose-dependently

The effect of AS-IV on the chemoresistance of NSCLC cells to cisplatin was explored. The results suggested that the combination of AS-IV and cisplatin suppressed cell viability and increased the cell apoptosis rate in A549Cis and H1299Cis cells in a dose-dependent manner compared with the cisplatin 20 μM treatment group (*Figure 3A*,*B*,*C*,*D*). These findings demonstrate that AS-IV enhanced the anti-tumor effect of cisplatin in NSCLC cells in a dose-dependent manner.

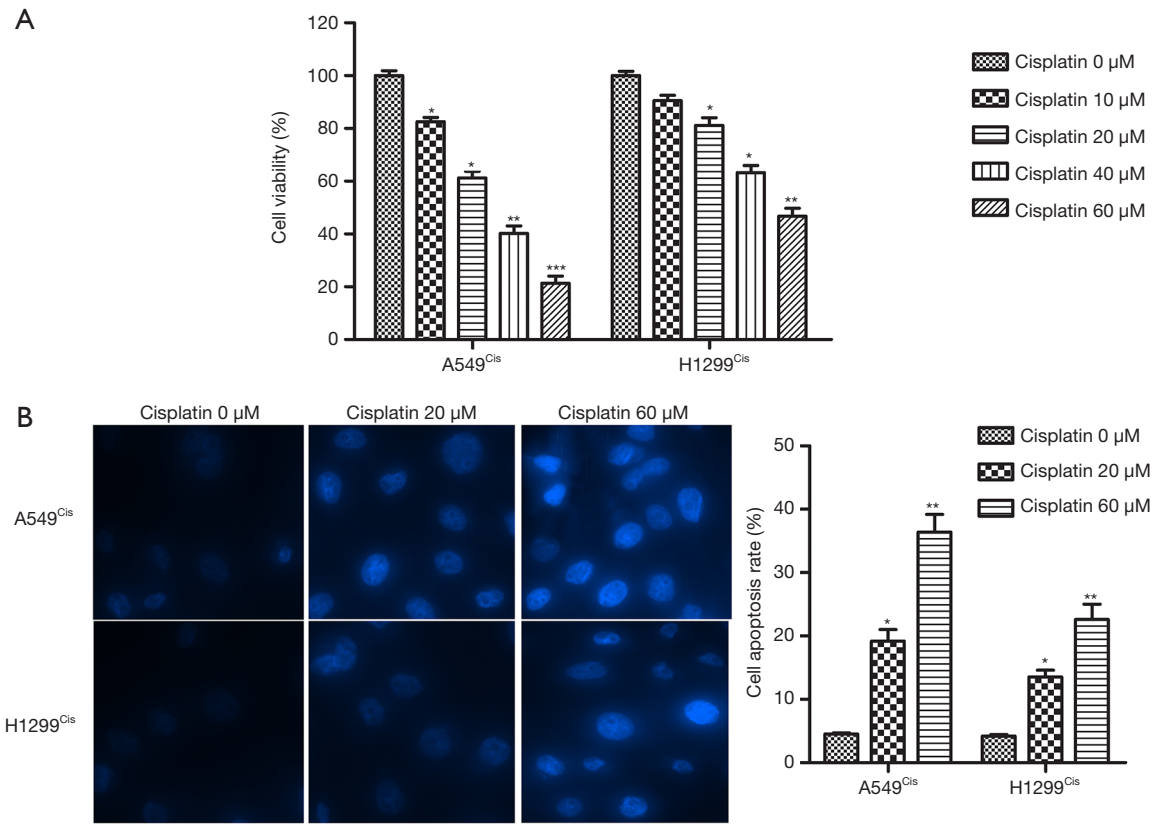

Figure 1 Cisplatin inhibited cell viability and induced apoptosis in cisplatin-resistant NSCLC cells. Cisplatin-resistant NSCLC cell lines, A549^{Cis} and H1299^{Cis}, were established and treated with each concentration of cisplatin. (A) Cell viability was measured by CCK-8 assay. (B) Cell apoptosis was detected by Hoechst 33258 stain analysis (×400 magnification). Data are expressed as mean ± SD of three independent experiments. *P<0.05, **P<0.01, and ***P<0.001 compared with the cisplatin 0 μM group. NSCLC, non-small cell lung cancer.

AS-IV sensitized NSCLC cells to cisplatin through suppressing ER stress and autophagy

We further examined the molecular changes of NSCLC cells under AS-IV cotreatment to reveal the underlying mechanism of AS-IV sensitization in the chemosensitivity to cisplatin. Western blot results revealed that the expressions of GRP78 and Beclin1 were both markedly downregulated after co-administration with AS-IV (*Figure 4A*), indicating that AS-IV might augment the antitumor effect of cisplatin through inhibiting ER stress and autophagy. To verify our hypothesis, autophagy activator, rapamycin (100 nM), and ER stress inducer, tuniamycin (5 μg/mL), were used to treat the cells. Our data showed that both rapamycin and tuniamycin treatment increased cell viability and decreased cell apoptosis in A549Cis and H1299Cis cells, as compared with the AS-IV 16 ng/mL group. This suggests that induction of autophagy or ER stress counteracted the inhibitory effect of AS-IV on chemoresistance to cisplatin in NSCLC cells (*Figure 4B,C,D,E*). Our data demonstrate that AS-IV sensitized NSCLC cells to cisplatin through suppressing ER stress and autophagy.

Discussion

NSCLC is one of the most common malignant tumors, with cisplatin being the predominant first-line chemotherapy for NSCLC patients. However, acquired drug resistance limits the application of cisplatin (19). As a chemotherapeutic agent, cisplatin causes DNA lesioning and the suppression of DNA synthesis in cancer cells. Cisplatin-caused DNA damage can activate various signaling pathways which induce cell death, mainly through apoptosis-related pathways (20). Recent research indicates that cisplatin-

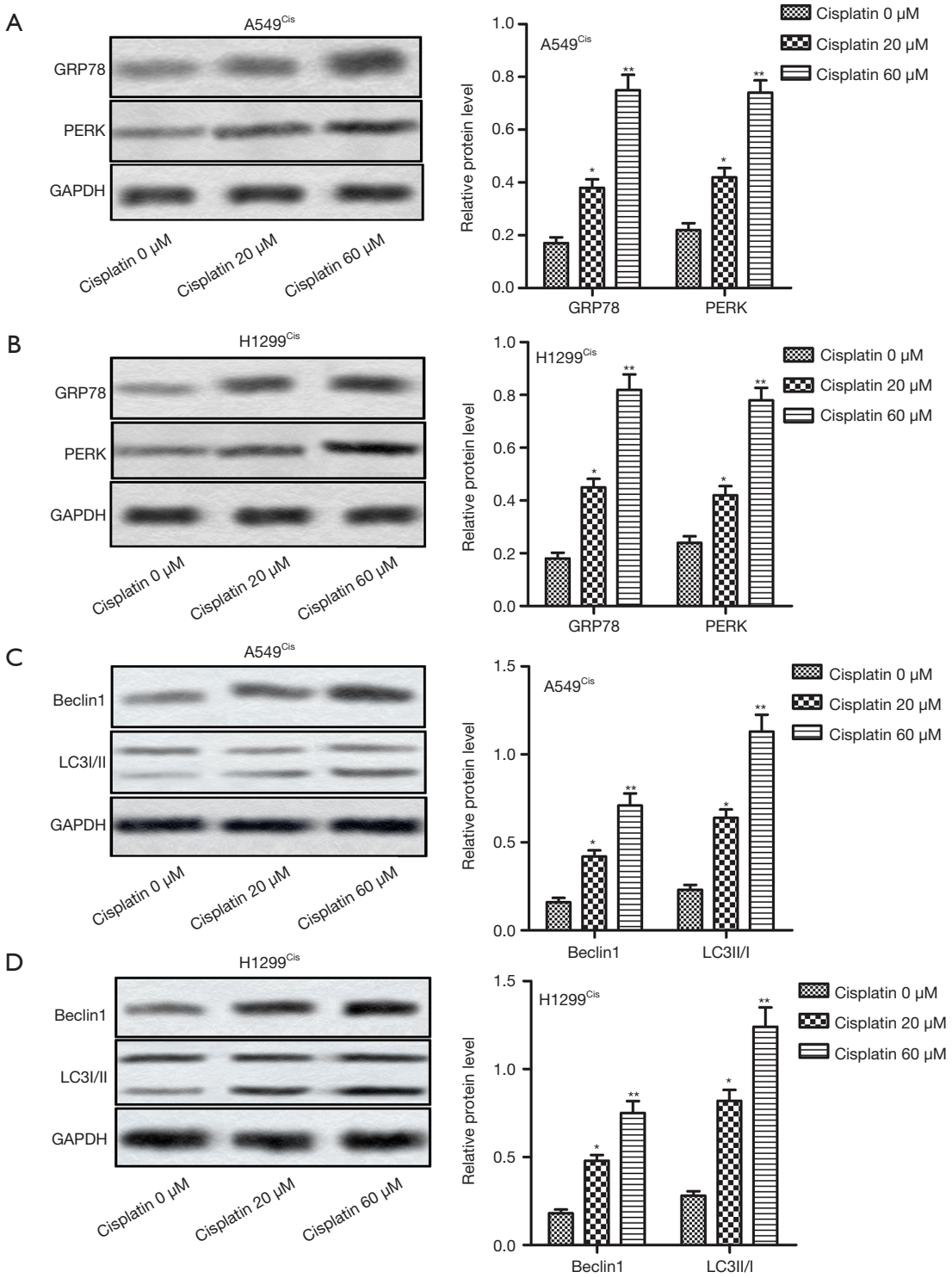

Figure 2 Cisplatin induced ER stress and autophagy in cisplatin-resistant NSCLC cells. A549^{Cis} and H1299^{Cis} cells were treated with each concentration of cisplatin. (A,B,C,D) Relative expression of GRP78, PERK, Beclin1, and LC3I/II in A549^{Cis} and H1299^{Cis} cells were determined by Western blot. Data are expressed as mean ± SD of three independent experiments. *P<0.05 and **P<0.01 compared with cisplatin 0 μM group. ER, endoplasmic reticulum; NSCLC, non-small cell lung cancer.

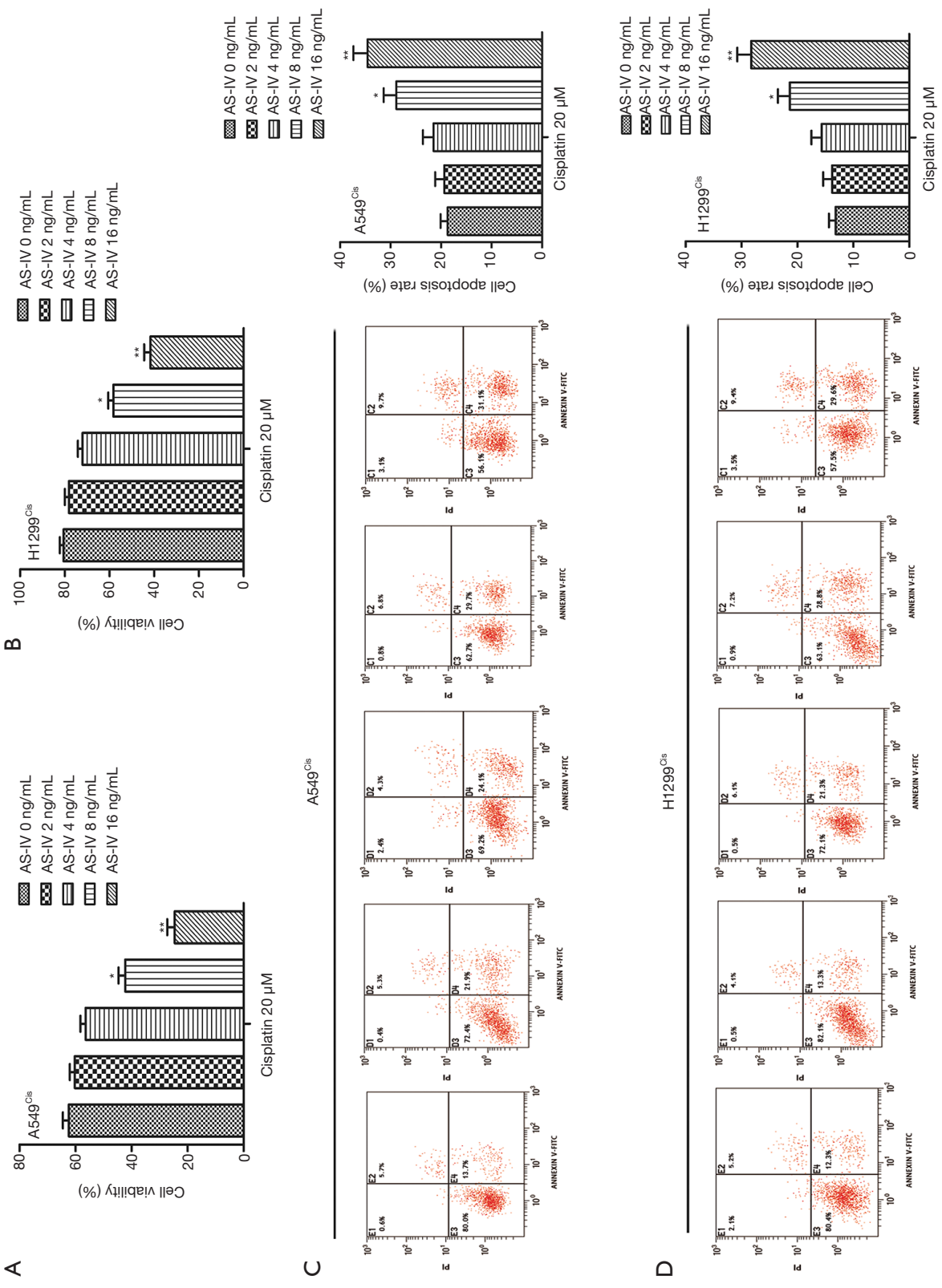

Figure 3 AS-IV augmented the antitumor effect of cisplatin dose-dependently. $A549^{Cis}$ and $H1299^{Cis}$ cells were treated with 20 μM cisplatin combined with different concentrations of AS-IV. (A,B) Cell viability was detected through CCK-8 assay. (C,D) Cell apoptosis rate was assessed by flow cytometry. Data are expressed as mean ± SD of three independent experiments. *P<0.05 and **P<0.01 compared with AS-IV 0 ng/mL group. AS-IV, astragaloside IV.

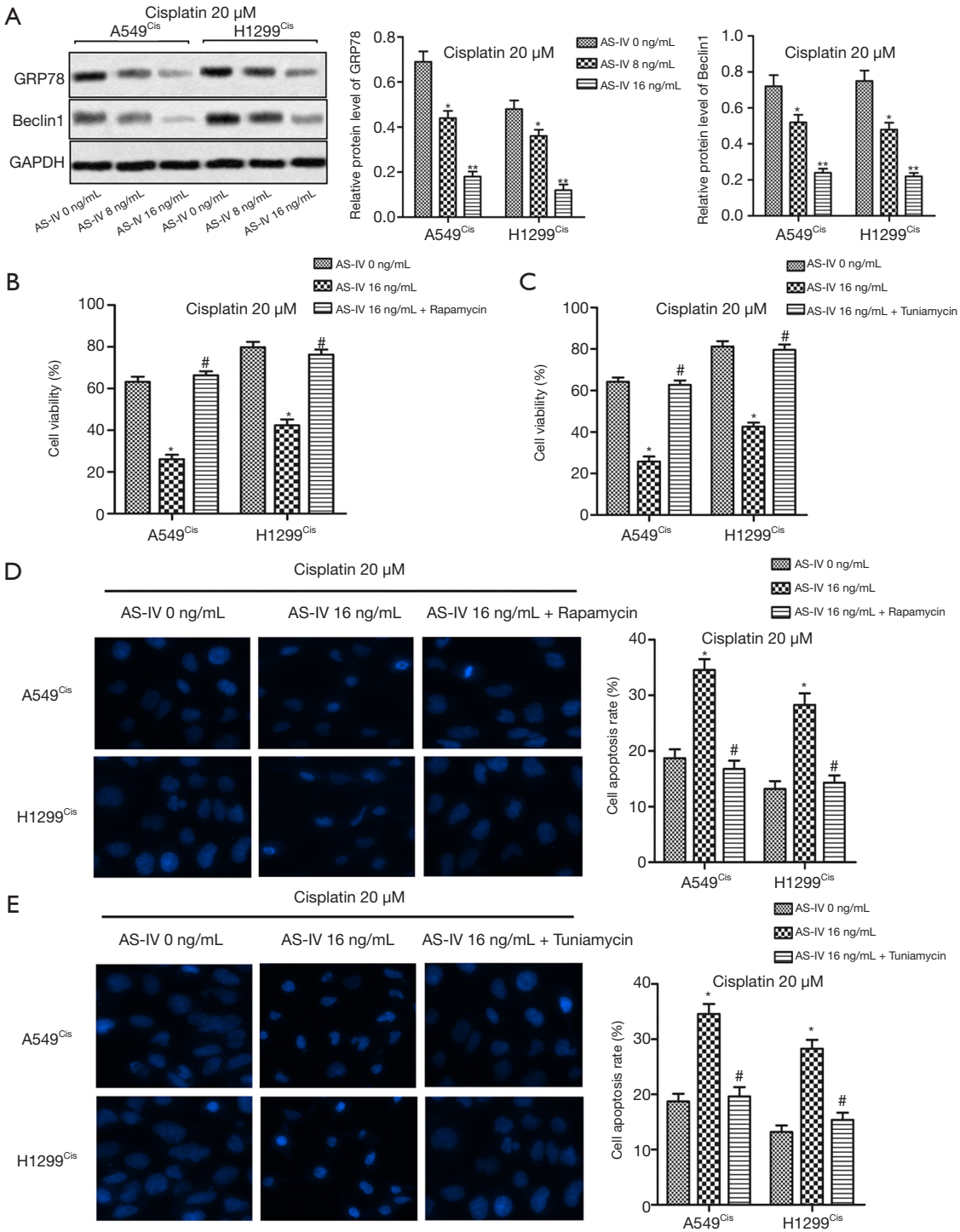

Figure 4 AS-IV sensitized NSCLC cells to cisplatin through suppressing ER stress and autophagy. A549^{Cis} and H1299^{Cis} cells were treated with 20 μM cisplatin combined with AS-IV along with rapamycin or tuniamycin. (A) Relative expression of GRP78 and Beclin1 in A549^{Cis} and H1299^{Cis} cells were assessed by Western blot. (B,C) Cell viability was measured through CCK-8 assay. (D,E) Cell apoptosis rate was assessed by Hoechst 33258 stain analysis (×400 magnification). Data are expressed as mean ± SD of three independent experiments. *P<0.05 and **P<0.01 compared with the AS-IV 0 ng/mL group; #P<0.05 compared with the AS-IV 16 ng/mL group. AS-IV, astragaloside IV; NSCLC, non-small cell lung cancer.

induced ER stress and autophagy can inhibit cisplatin-induced apoptosis in cancer cells (5). Therefore, suppressing ER stress and autophagy induced by cisplatin might help to augment the anti-tumor effect of cisplatin. In our present study, we found that AS-IV, a major active component of *Astragalus membranaceus*, can sensitize NSCLC cells to cisplatin by suppressing ER stress and autophagy.

ER is an essential intracellular organelle in eukaryotic cells with multiple functions including protein synthesis, protein folding, stress reaction, and calcium ion level modulation (21). It was reported that changes in the tumor cell microenvironment or the effects of anti-tumor drugs can provoke ER stress, resulting in the accumulation of unfolded proteins in the ER lumen (22,23). ER stress can trigger a UPR, which decreases the burden of protein processing in the ER and increases the level of ER molecular chaperones such as GRP78 and the ER stress sensor protein, PERK (4). It has been shown that mild ER stress promotes cell survival through UPR to mitigate ER stress (24). However, severe ER stress can cause cell apoptosis by activating the downstream apoptotic signaling pathway (25). Lin *et al.*'s study reported that human lung cancer cells acquired cisplatin-resistance through ER stress (26). Zhang *et al.* also indicated that cisplatin induced ER stress in U251 human glioma cells (4). Similarly, our present study suggests that cisplatin suppressed cell viability and triggered apoptosis in cisplatin-resistant NSCLC cells; the application of cisplatin upregulated the expression of GRP78 and PERK, meaning that cisplatin induced ER stress in NSCLC cells dose-dependently.

Autophagy is a common process in cellular health. Autophagy maintains cell homeostasis by degrading the intracellular aggregation of misfolded proteins and damaged organelles (11). The key event of autophagy is autophagosome formation, and Beclin1 is integral in this process. LC3-II is involved in autophagosomal membrane formation associated with the completion of various cell processes. The ratio of LC3-II to LC3-II I is used to evaluate autophagy levels (27). Abundant research suggests that autophagy plays an important role in regulating chemoresistance in multiple types of cancer cells. A study by Fukuda *et al.* reported that autophagy was related to endometrial tumor growth and cisplatin resistance, and that the inhibition of autophagy overcame the cisplatin resistance of endometrial cancer cells (28). Furthermore, the inhibition of autophagy was reported to enhance cisplatin-induced cell death and apoptosis in human ovarian cancer cells (13). The present study found that cisplatin increased the expression of Beclin1 and promoted transformation of LC3-I to LC3-II, suggesting that cisplatin advances autophagy in NSCLC cells.

Recently, traditional Chinese medicine has gained significant attention because of its potential antitumor activities. AS-IV is a major active ingredient of *Astragalus membranaceus*, a medicinal plant commonly used in East Asia (29). Accumulating evidence suggests that AS-IV can exert multiple anti-inflammatory and anti-oxidative functions, and it has been used often for the treatment of cardiovascular diseases (30), exerting its anti-tumor effects to this end. AS-IV was also observed inhibiting colorectal cancer epithelial–mesenchymal transition by promoting miR-134 expression level which dramatically inhibited the recombinant human cAMP responsive element binding protein (CREB1) signaling pathway, and therefore enhanced the sensitivity to chemotherapy (31). Additionally, it was also shown that AS-IV also sensitizes NSCLC cells to gefitinib via the regulation of Sirtuin 6 (SIRT6) (32). In the current study, our results demonstrated that cisplatin treatment combined with AS-IV dramatically enhanced cisplatin sensitivity in NSCLC cells and enhanced the anti-tumor effect of cisplatin. Moreover, we also found that AS-IV inhibited the expression of GRP78 and Beclin1, indicating that AS-IV suppresses ER stress and autophagy in NSCLC cells dose-dependently. Inhibition of ER stress or autophagy both counteracted the inhibitory effect of AS-IV on chemoresistance to cisplatin in NSCLC cells. Our results confirm that AS-IV can sensitize NSCLC cells to cisplatin through suppressing ER stress and autophagy.

In summary, this study found that cisplatin triggers autophagy and ER stress which, in turn, increases chemoresistance in NSCLC cells. However, the combination of AS-IV and cisplatin can sensitize NSCLC cells to cisplatin and enhance the antitumor effect of cisplatin by suppressing ER stress and autophagy. These findings provide support for the potential clinical application of AS-IV on cisplatin-resistant NSCLC patients.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jtd-20-2098). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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