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Original Article

Curcumin induces ferroptosis in ovarian cancer cells through the Nrf2/GPX4 regulation axis

Nan Liu[1,2*], Ye-Ting Cui[1,2*], Yi Zheng[3], Shu-Min Fang[3], Li-Xi Liao[3], Ting-Ting Luo[3], Ze-Hui Zhong[3], Xiao-Yu Hu[3], Ming-Hui Zhou[4], Yan-Yang Tu[3]

[1]Guangdong Provincial Science and Technology Expert Workstation, Huizhou Central People's Hospital, Huizhou 516001, Guangdong, China; [2]College of Life Sciences and Health, Wuhan University of Science and Technology, Wuhan 430065, Hubei, China; [3]Science Research Center, Huizhou Central People's Hospital, Huizhou 516001, Guangdong, China; [4]Department of Gynecology, Huizhou Central People's Hospital, Huizhou 516001, Guangdong, China. [*]Equal contributors.

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Abstract: Ovarian cancer (OC) frequently develops acquired resistance to traditional anti-tumor treatments, highlighting the urgent need for novel therapeutic strategies. This study investigated whether curcumin can induce ferroptosis in OC cells through the Nrf2/GPX4 regulation axis, and whether Nrf2 overexpression can confer resistance to curcumin in OC cells. SK-OV-3 and A2780 cells were treated with curcumin, and the effects on cell viability, migration, and invasion were evaluated using Cell Counting Kit-8 (CCK-8), wound healing, Transwell assay, and flow cytometry. Ferroptosis-associated changes were assessed by measuring intracellular Fe^{2+}, malondialdehyde (MDA), and glutathione (GSH) levels, and protein expression of Nrf2, SLC7A11, and GPX4 was analyzed by Western blot. Additionally, Nrf2-overexpressing SK-OV-3 and A2780 cell lines were established for functional evaluation. Our results demonstrated that curcumin inhibited proliferation, migration, and invasion of SK-OV-3 and A2780 cells in a dose-dependent manner, while inducing apoptosis and ferroptosis, as evidenced by elevated reactive oxygen species (ROS), MDA, Fe^{2+} levels, and depletion of GSH. Moreover, curcumin suppressed the Nrf2/GPX4 signaling pathway in these cells. Conversely, Nrf2 overexpression significantly upregulated the protein levels of SLC7A11 and GPX4 and enhanced the survival, migration, and invasion capabilities of SK-OV-3 and A2780 OC cells. Furthermore, Nrf2 overexpression significantly attenuated curcumin-induced apoptosis and ferroptosis in SK-OV-3 and A2780 cells, effectively preserving the antioxidant capacity of OC cells. These findings indicate that curcumin exerts anti-tumor effects in SK-OV-3 and A2780 OC cells by inducing apoptosis and ferroptosis through inhibition of the Nrf2/GPX4 signaling axis. Conversely, overexpression of Nrf2 strengthens the endogenous antioxidant defense system in SK-OV-3 and A2780 OC cells, contributing to curcumin resistance. Therefore, targeted regulation of the Nrf2/GPX4 signaling axis may represent a promising therapeutic strategy to overcome chemotherapy resistance in ovarian cancer.

Keywords: Ovarian cancer, curcumin, Nrf2/GPX4 axis, ferroptosis, apoptosis, oxidative stress

Introduction

Ovarian cancer (OC) is a major cause of cancer-related death among women worldwide [1-4]. The five-year survival rate remains low at 29.2%, largely attributable to the anatomical location of the ovaries and consequent difficulties in early detection [5]. OC is among the deadliest gynecologic malignancies [6, 7], accounting for an estimated 313,959 new cases and 207,252 deaths globally in 2020, with incidence continuing to rise alongside increasing life expectancy [8]. Although the exact pathogenesis remains unclear, established risk factors include genetic predisposition, obesity, smoking and exposure to talc or pesticides [9], loss of the p53 tumor suppressor gene (observed in about 55% of cases), and BRCA mutations [9, 10]. The standard first-line treatment for OC consists of surgical resection followed by chemotherapy (e.g., paclitaxel and carboplatin) [11]. While most patients initially respond well to treatment, around 70% eventually experience disease recurrence, often accompanied by acquired resistance, including cisplatin or multidrug resistance [12]. Hence, novel treatments are urgently needed to overcome chemoresistance and reduce toxicity.

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Curcumin, a natural polyphenolic bioactive component extracted from the rhizome of *Curcuma longa*, has been extensively studied for its anti-inflammatory, anti-tumor, and antioxidant pharmacological activities [13-18]. Clinical studies have investigated its pharmacokinetics, safety, and efficacy across a range of human diseases [19, 20]. A recent comprehensive review highlighted the role of curcumin in OC and its modulation of signaling pathways such as NF-κB, STAT3, and PI3K/AKT/mTOR, contributing to enhanced chemosensitivity and reduced drug resistance [21]. Liu et al. showed that curcumin potentiates the efficacy of paclitaxel in OC via the miR-9-5p/BRCA1 signaling axis [22].

Ferroptosis, a regulated cell death mechanism driven by iron-dependent lipid peroxidation [23], has emerged as a promising alternative to apoptosis, particularly in tumors with dysregulated cell death pathways [24-28]. A growing body of evidence supports the role of curcumin in inducing ferroptosis across various cancer types [29]. For instance, curcumin triggers both apoptosis and ferroptosis in osteosarcoma cells through modulating the Nrf2/GPX4 pathway [30], and suppresses breast cancer tumorigenesis by inducing ferroptosis [31]. Importantly, curcumin has also been shown to induce ferroptosis in OC. For example, Shi et al. reported that the curcumin derivative NL01 induces ferroptosis in OC cells through HCAR1/MCT1 signaling [32]. Despite these advancements, the precise mechanisms by which curcumin exerts cytotoxic effects on ovarian cancer cells and inhibits chemoresistance remain incompletely understood.

In this study, we aimed to investigate whether curcumin can induce ferroptosis in SK-OV-3 and A2780 ovarian cancer cells through the Nrf2/GPX4 signaling axis, and to explore the role of Nrf2 in modulating curcumin sensitivity. Specifically, we sought to determine the effects of curcumin on the expression of key ferroptosis-related proteins, including SLC7A11 and GPX4, as well as on intracellular glutathione levels and lipid peroxidation. Furthermore, we evaluated whether overexpression of Nrf2 confers resistance to curcumin-induced ferroptosis, with the ultimate goal of identifying potential therapeutic strategies to overcome chemoresistance in ovarian cancer.

Materials and methods

Cell lines and drug treatments

Human OC cell lines SK-OV-3 (CL-0215, Procell system Co., Ltd., Wuhan, China) and A2780 (iCell-h004, Saibokang (Shanghai) Biotechnology Co., Ltd., Shanghai, China) were commercially purchased. Cells were cultured in RPMI-1640 medium (11875127, Thermo Fisher Scientific) containing antibiotics (100 μg/mL streptomycin, 100 U/mL penicillin) and 10% fetal bovine serum (FBS) at 37°C in a humidified atmosphere containing 5% CO_2. Curcumin (Sigma-Aldrich, St. Louis, MO, USA) was used to treat SK-OV-3 cells at the concentrations of 0, 10, 20, and 40 μM and to A2780 cells at the concentrations of 0, 7.5, 15, and 30 μM for 48 h, based on a previous report [33].

Cell counting Kit-8 (CCK-8) assay

Cell viability following curcumin treatment was measured using the CCK-8 assay at 24-, 48-, and 72-h [34]. In brief, cells were seeded at 5×10^3 cells/well in 96-well plates and allowed to adhere overnight. Cells were treated with curcumin at the indicated concentrations for 48 h. Following treatment, 10 μL of CCK-8 reagent (Dojindo, CK04-500T, Japan) was added to each well, and the plates were incubated for 2 h at 37°C. Absorbance at 450 nm was measured using a microplate reader (Synergy H1m, BioTek, USA), and cell viability was calculated relative to untreated controls. Each group of experiment was repeated at least three times.

Wound healing and Transwell assay

For the wound healing test, cells seeded at 5×10^4/well in 6-well plates and cultured to reach 90% confluence. A scratch was created using a sterile pipette tip and wound closure was monitored by capturing images at 0 and 48 h. For the Transwell invasion assay, 8 μm pore-size chamber (Corning Falcon, 353097, USA) was coated with Matrigel (Corning, 356230, USA). Cells were suspended in 200 μL serum-free medium and added to the upper chamber, while 600 μL of complete medium containing 10% FBS was placed in the lower chamber. After 24 h incubation, invaded cells were fixed by 4% paraformaldehyde, stained with 0.5% crystal violet for 10 min, and visualized under

Table 1. Specific primers for qPCR

Genes	Forward	Reverse
Nrf2	GGTTGCCCACATTCCCAAATC	CAAGTGACTGAAACGTAGCCG
GAPDH	GGACTCATGACCACAGTCCAT	CAGGGATGATGTTCTGGAGAG

an inverted microscope (Olympus IX73, Japan). The number of invaded cells was quantified from three randomly selected fields [35].

Transfection and quantitative real-time PCR (qRT-PCR) assay

Full-length cDNA of human *Nrf2* was cloned into the pLVX-3×FLAG-Puro vector (V013340, Shanghai Newpu Biotechnology Co., Ltd., China) to achieve overexpression in SK-OV-3 and A2780 OC cells. All constructs were verified by sequencing before use. Plasmid DNA was transfected using Lipofectamine 3000 (Invitrogen, Waltham, USA) according to the manufacturer's instructions.

Total RNA was extracted from SK-OV-3 and A2780 OC cells using an RNA extraction kit (TaKaRa, TCH020, Japan), according to the manufacturer's instructions. RNA concentration and purity were detected by NanoDrop spectrophotometer. cDNAs was then synthesized using a reverse transcription kit (TaKaRa, RR047A, Japan), which served as a template for qRT-PCR. qPCR was conducted in 25 μL reactions containing cDNA template, gene-specific primers, and TB Green (TaKaRa, RR420A, Japan) on an CFX96 Real-Time PCR system. Amplification conditions were as follows: at 95°C for 30 s, followed by 40 cycles at 95°C for 5 s and at 60°C for 30 s, with a final melting curve analysis. All experiments were conducted in at least three biological and technical replicates. GAPDH was used as an internal reference gene, and relative gene expression was calculated using the $2^{-\Delta\Delta Ct}$ method. Primer sequences are listed in **Table 1**.

Flow cytometry for apoptosis and ROS assessment

Curcumin-induced apoptosis in A2780 and SK-OV-3 cells was assessed 48 h after treatment using the Annexin V-FITC Apoptosis Detection Kit (E-CK-A211, Elabscience, China) following the manufacturer's instructions. Cells were analyzed by flow cytometry (BD FACSMelody, USA), with Annexin V and PI used to identify early apoptotic and late/necrotic cells, respectively. Unstained and single-stained controls were used for fluorescence compensation. Intracellular reactive oxygen species (ROS) were measured using a DCFH-DA assay kit (Dojindo, R252-100T, Japan) in accordance with the manufacturer's instructions. Cells from each group were detected by Flow Cytometry (BD FACSMelody, USA).

Western blot assay

Cells were lysed in RIPA buffer (Thermo Scientific, 89900, USA) supplemented with a protease inhibitor cocktail (MCE, HY-K0010, USA). After centrifugation (12,000×g, 10 min, 4°C), the supernatant was collected for quantification by BCA Protein Assay Kit (Thermo Scientific, 23227, USA). Equal amounts of protein were separated by SDS-PAGE and transferred onto PVDF membranes. The membranes were blocked with 5% skimmed milk (BD, 232100, USA) for 1 h at room temperature to prevent non-specific binding, followed by incubation overnight at 4°C with primary antibodies: Nrf2 (ab62352, 1:1000, Abcam), SLC7A11 (ab307601, 1:1000, Abcam), GPX4 (ab125066, 1:1000, Abcam), and β-actin (66009-1-Ig, 1:10000, Proteintech). After washing, the membranes were incubated with HRP-conjugated goat-anti-rabbit IgG secondary antibody (RGAR001, 1:10000, Proteintech) for 2 h at room temperature. Target proteins were detected using chemiluminescent reagents (Thermo Fisher, 34577, USA) and visualized with a chemiluminescence imaging system (Alliance Q9 Advanced Manual, Uvitec Limited, Britain). Protein expression was normalized to β-actin (internal reference protein).

ELISA analysis

Intracellular Fe^{2+} levels were measured using the Human Cell Ferrous (Fe^{2+}) Fluorometric Assay Kit (E-BC-F108, Elabscience Biotechnology Co., Ltd., China) according to the manufacturer's protocol.

MDA and GSH detection

Malondialdehyde (MDA) levels were quantified using the Lipid Peroxidation MDA Detection Kit (TBA Colorimetric Method, TO1013, Beijing Leagene Biotechnology Co., Ltd.) following the

manufacturer's protocol. Glutathione (GSH/GSSG) levels were measured using ultra-performance liquid chromatography-mass spectrometry (UPLC-MS) (UPLC-MS-4487, Shanghai Liquid Mass Testing Technology Co., Ltd.).

Statistical analysis

All statistical analyses were performed using GraphPad Prism 8.0.1 software. Data were presented as mean ± SEM. Two-group comparisons were conducted using unpaired t-test, while one-way and two-way repeated measures analysis of variance (ANOVA) were applied for multiple group comparisons, followed by Tukey's or Šídák's post hoc tests as appropriate. A p-value < 0.05 was considered statistically significant. All experiments were independently conducted at least in triplicate.

Results

Curcumin suppressed OC cell proliferation, migration, and invasion

Curcumin treatment significantly decreased the viability of SK-OV-3 and A2780 cells in a dose-dependent manner (**Figure 1A**, **1B**). Similarly, curcumin treatment suppressed the migration of SK-OV-3 and A2780 cells, with stronger effects observed at higher doses (**Figure 1C**, **1D**). Transwell invasion assays further confirmed a dose-dependent suppressive effect of curcumin on the invasive capacity of SK-OV-3 and A2780 cells (**Figure 1E**, **1F**). These results indicate that curcumin exerts potent anti-tumor activity against ovarian cancer cells through the coordinated suppression of proliferation, migration, and invasion.

Curcumin triggered apoptosis and ferroptotic pathways in OC cells

As shown by flow cytometry analysis, curcumin treatment for 48 h induced notable apoptosis in SK-OV-3 cells in a dose-dependent manner (**Figure 2A**, **2B**). Additionally, curcumin triggered oxidative stress, as evidenced by a marked increase in intracellular ROS level (**Figure 2C**, **2D**). ELISA assays further showed that curcumin treatment led to increased Fe^{2+} accumulation (**Figure 2E**) and elevated MDA levels (**Figure 2F**), both of which are key indicators of iron-dependent lipid peroxidation and ferroptosis. These effects were more pronounced at higher curcumin concentrations, suggesting a dose-dependent induction of ferroptosis. Moreover, curcumin significantly reduced intracellular GSH level in SK-OV-3 cells (**Figure 2G**), a key component of the cellular antioxidant defense system. GSH depletion can lead to an imbalance in redox homeostasis and significantly increase the cell's sensitivity to ferroptosis.

Consistent results were observed in A2780 cells. Curcumin treatment significantly increased A2780 cell apoptosis in a dose-dependent manner (**Figure 2H**, **2I**), accompanied by elevated ROS levels, intracellular Fe^{2+} concentration, and MDA content, while GSH levels was significantly decreased (**Figure 2J-N**). These findings demonstrate that curcumin effectively induces apoptosis in SK-OV-3 and A2780 OC cells and simultaneously activate ferroptosis-related signaling pathways, both in a dose-dependent manner.

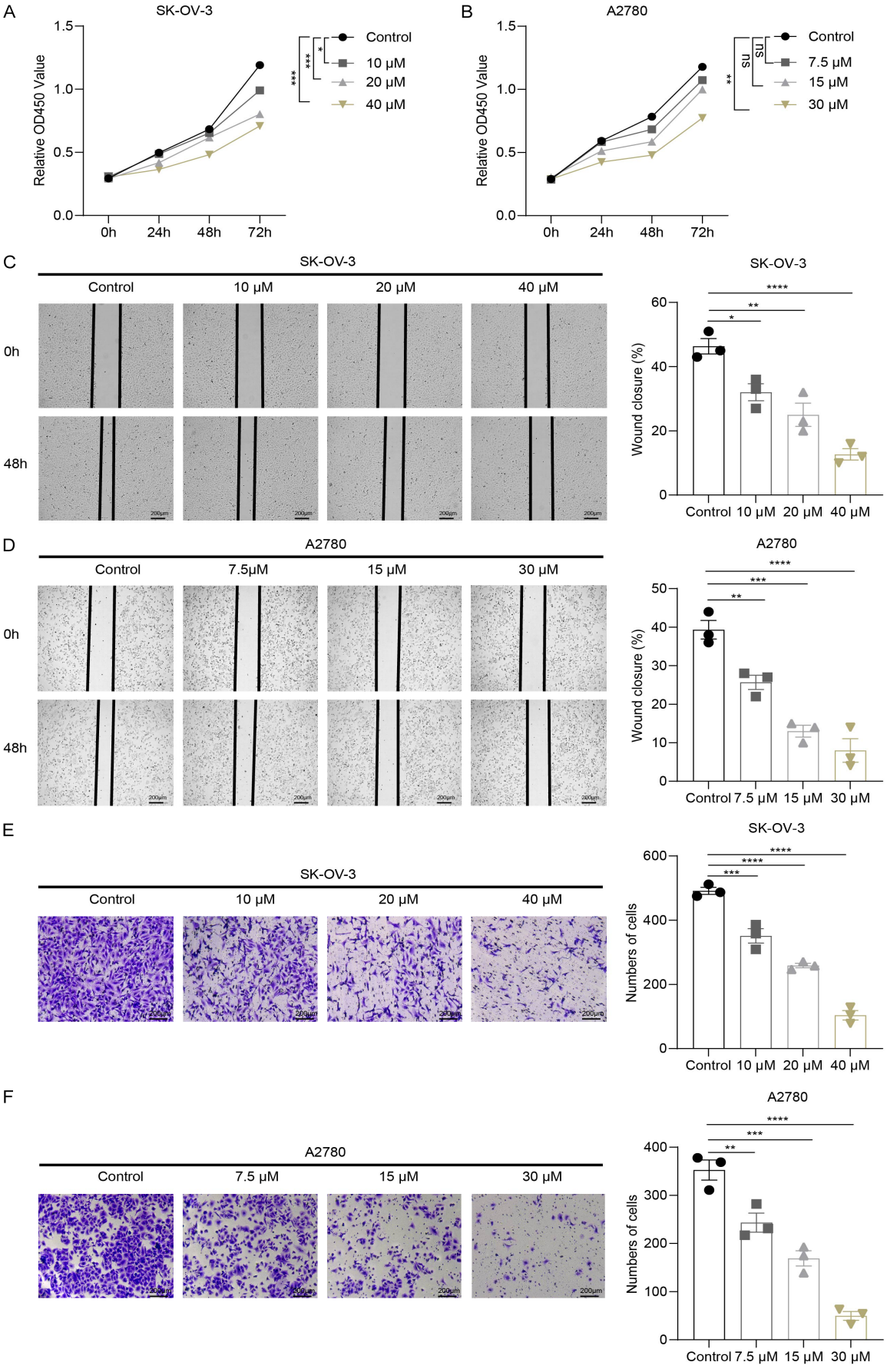
Curcumin downregulated the level of Nrf2/GPX4 axis in OC cells

To explore the role of Nrf2/GPX4 axis in curcumin-induced ferroptosis, the expression of key proteins (Nrf2, SLC7A11, and GPX4) was detected by Western blot. In SK-OV-3 and A2780 cells, curcumin treatment significantly inhibited the expression Nrf2, SLC7A11 and GPX4 protein in dose-dependent manner (**Figure 3A**, **3B**), suggesting that curcumin can suppress the Nrf2/GPX4 signaling pathway in SK-OV-3 and A2780 OC cells.

To further examine the role of the Nrf2/GPX4 axis in OC progression, Nrf2-overexpressing SK-OV-3 and A2780 OC cell lines (Nrf2-OE) were established. qRT-PCR and Western blot analyses indicated that the mRNA and protein levels of Nrf2 in the Nrf2-OE cells were significantly increased compared with control cells (**Figure 3C-E**). In addition, western blot showed that Nrf2 overexpression notably upregulated SLC7A11 and GPX4 protein levels in both SK-OV-3 (**Figure 3F**) and A2780 cells (**Figure 3G**).

Nrf2 overexpression increased the proliferative, migratory, and invasive capabilities of OC cells

CCK-8 assays revealed that Nrf2 overexpression notably increased the viability of SK-OV-3


A
SK-OV-3
Relative OD450 Value
1.5
1.0
0.5
0.0
0h
24h
48h
72h
Control
10 μM
20 μM
40 μM
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A2780
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Control
7.5 μM
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SK-OV-3
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Figure 1. Curcumin suppressed OC cell proliferation, migration, and invasion. A, B. Cell Counting Kit-8 (CCK-8) assay for cell proliferation assessment. C, D. Wound healing assay for cell migration (Scale bar: 200 μm, ×100). E, F. Transwell invasion assay for cell invasion (Scale bar: 200 μm, ×200). Notes: ****$P < 0.0001$, ***$P < 0.001$, **$P < 0.01$, *$P < 0.05$.

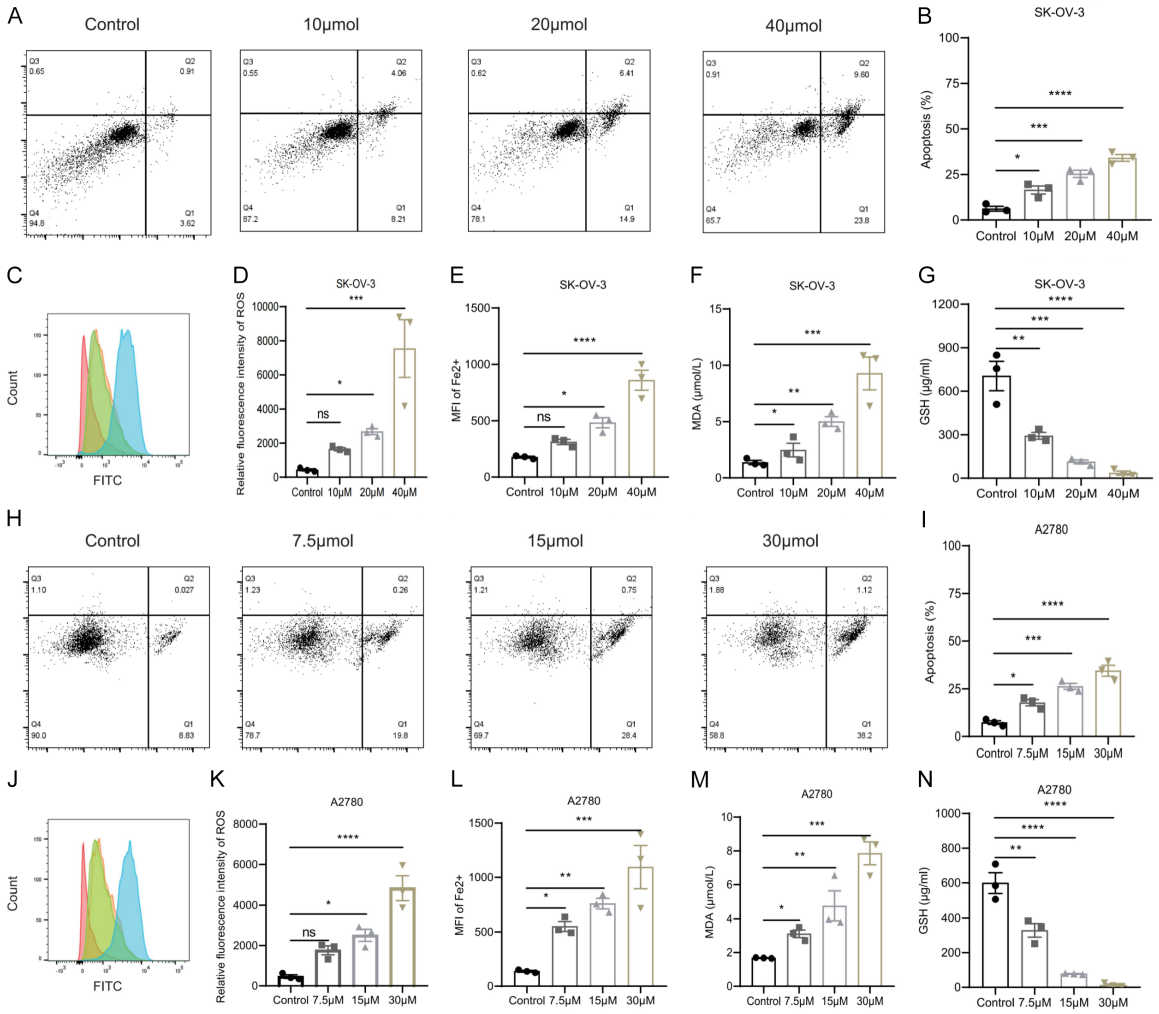

Figure 2. Curcumin induced apoptosis and ferroptosis in OC cells. A, B. Flow cytometry analysis of apoptosis in SK-OV-3 cells. C, D. Intracellular reactive oxygen species (ROS) levels in SK-OV-3 cells detected by flow cytometry. E. Fe^{2+} levels in SK-OV-3 cells detected by ELISA. F, G. Determination of malondialdehyde (MDA) and glutathione (GSH) levels in SK-OV-3 cells. H, I. Flow cytometry analysis of apoptosis in A2780 cells. J, K. Flow cytometry analysis of ROS in A2780 cells. L. Fe^{2+} levels in A2780 cells measured with ELISA. M, N. Detection of MDA and GSH levels in A2780 cells. Notes: ****$P < 0.0001$, ***$P < 0.001$, **$P < 0.01$, *$P < 0.05$.

and A2780 OC cells (**Figure 4A**, **4B**). Wound healing assays further showed that Nrf2-OE cells exhibited enhanced migration compared with control cells (**Figure 4C**, **4D**). Consistently, Transwell assays indicated that Nrf2 overexpression significantly promoted the invasiveness of SK-OV-3 and A2780 cells (**Figure 4E**, **4F**). Collectively, these results suggest that Nrf2 could promote proliferation, migration and invasion of SK-OV-3 and A2780 OC cells.

Nrf2 overexpression inhibited apoptosis, enhanced antioxidant defense, and suppressed ferroptosis in OC cells

We further evaluated apoptosis, oxidative stress, iron homeostasis, and antioxidant capacity in SK-OV-3 and A2780 cells. Flow cytometry analysis indicated that Nrf2 overexpression significantly inhibited apoptosis in SK-OV-3 cells (**Figure 5A**, **5B**), indicating a role for Nrf2 in pro-

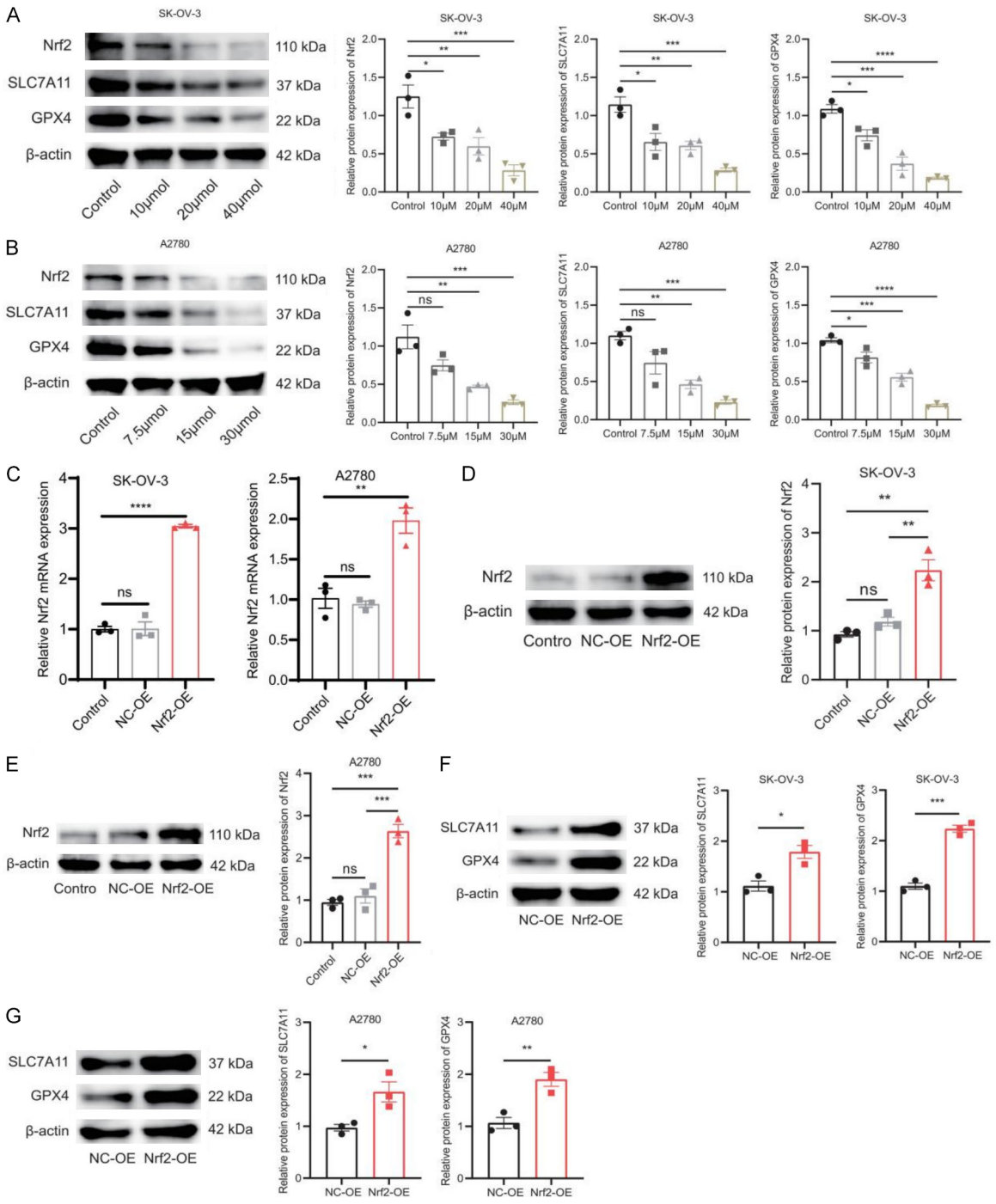

Figure 3. Effects of curcumin on the expression of Nrf2/GPX4 axis protein. A, B. Western blot analysis of Nrf2, SLC7A11, GPX4 protein expression in SK-OV-3 and A2780 cells after curcumin treatment. C-E. Effects of Nrf2 overexpression on the mRNA and protein levels of Nrf2 in SK-OV-3 and A2780 cells detected by qPCR and Western blot. F, G. Western blot analysis of SLC7A11, GPX4 protein expression in cells with *Nrf2* overexpression. Notes: ns is no significant, $****P < 0.0001$, $***P < 0.001$, $**P < 0.01$, $*P < 0.05$.

moting OC cell survival. Consistently, intracellular ROS levels were significantly reduced in Nrf2 overexpression group (**Figure 5C**, **5D**), indicating that Nrf2 activation enhanced cellular antioxidant defense. Moreover, Nrf2 overexpression significantly reduced intracellular Fe^{2+} and MDA levels in SK-OV-3 cells (**Figure 5E**, **5F**), suggesting protection against iron overload

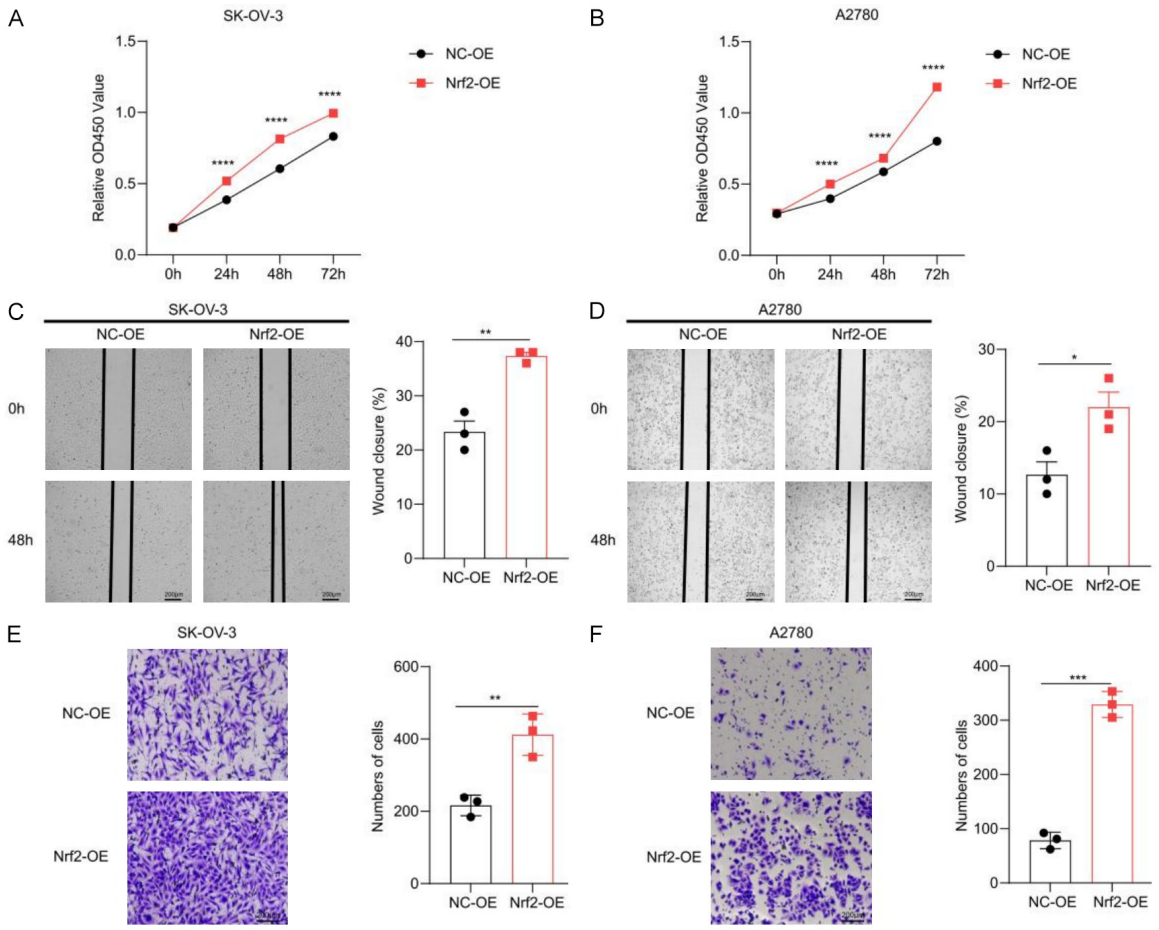

Figure 4. Effects of Nrf2 overexpression on proliferation, migration, and invasion in A2780 and SK-OV-3 cells. A, B. Cell proliferation assessed using the CCK-8 assay. C, D. Cell migration measured by wound healing assay (Scale bar: 200 μm, ×100). E, F. Cell migration measured by Transwell invasion assay (Scale bar: 200 μm, ×200). Notes: ****P < 0.0001, ***P < 0.001, **P < 0.01, *P < 0.05.

and lipid peroxidation. In contrast, GSH levels were significantly increased in Nrf2 overexpression group (**Figure 5G**), suggesting enhanced antioxidant defense. Consistently, in A2780 cells, Nrf2 overexpression reduced apoptosis and ROS levels (**Figure 5H-K**), decreased Fe^{2+} and MDA content (**Figure 5L**, **5M**), and significantly increased GSH levels (**Figure 5N**). These findings collectively demonstrate that Nrf2 protects OC cells against ferroptosis and oxidative stress.

Nrf2 overexpression attenuated the anti-tumor effects of curcumin by sustaining the Nrf2/GPX4 axis in OC cells

WB results showed that after treatment with curcumin, the level of SLC7A11 and GPX4 in SK-OV-3 and A2780 cells were significantly increased in the Nrf2 overexpression group compared with the control cells (**Figure 6A-C**), suggesting that Nrf2 overexpression impaired the inhibitory effect of curcumin on Nrf2/GPX4 axis. In addition, CCK-8 assay demonstrated that Nrf2 overexpression significantly enhanced the proliferation of SK-OV-3 and A2780 cells after curcumin treatment (**Figure 6D**), indicating that activation of Nrf2/GPX4 axis enhanced cell vitality of SK-OV-3 and A2780 cells under curcumin exposure. Meanwhile, Nrf2 overexpression significantly enhanced migration and invasion in SK-OV-3 and A2780 cells after curcumin treatment (**Figure 6E-H**). These results collectively demonstrate that Nrf2 overexpression attenuates the inhibitory effect of curcumin on proliferation, migration and invasion of OC cells via the Nrf2/GPX4 pathway.

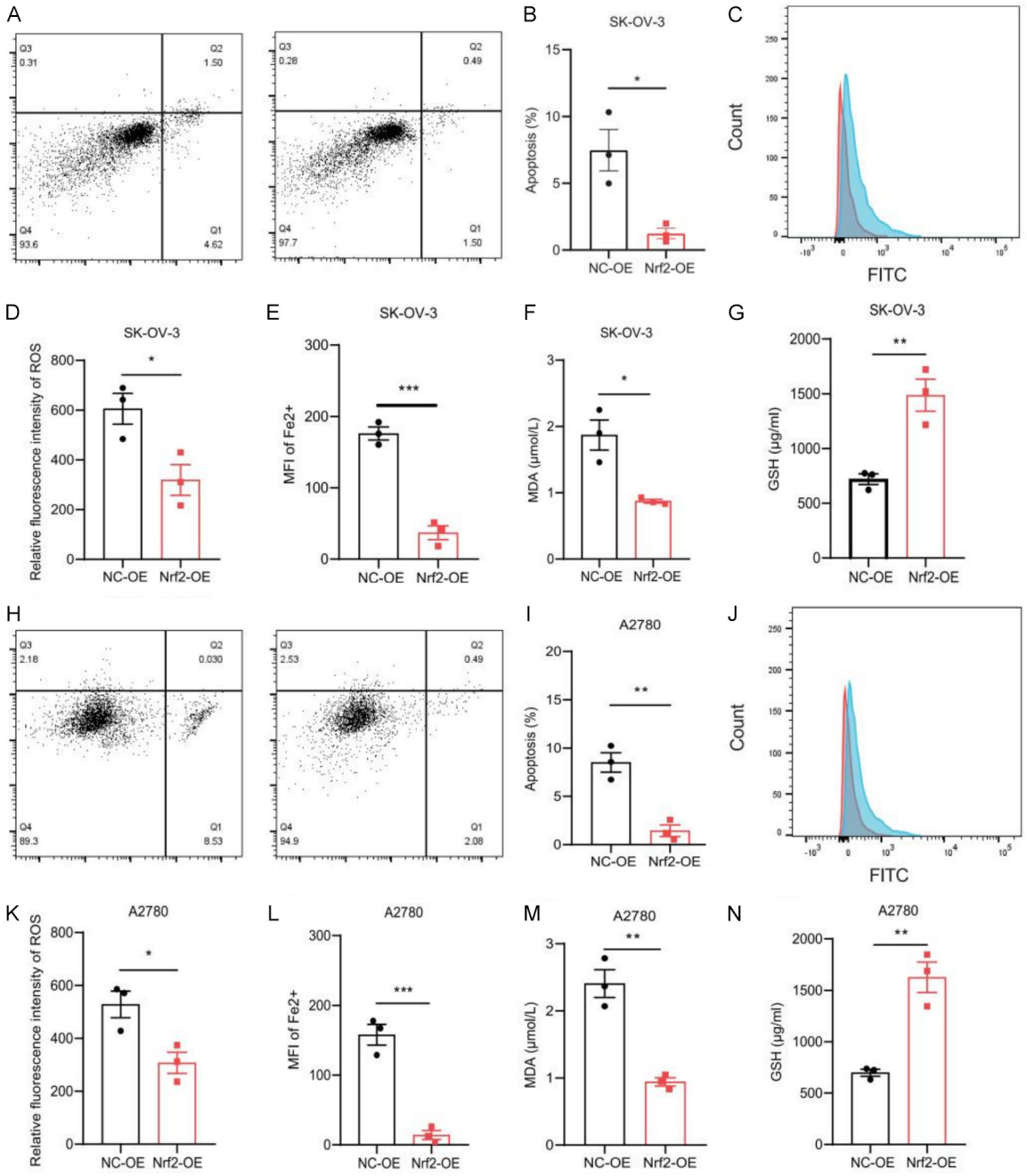

Figure 5. Effects of Nrf2 overexpression on apoptosis, ROS production, and oxidative stress markers in A2780 and SK-OV-3 cells. A. Flow cytometry analysis of apoptosis in oe-NC and oe-Nrf2 groups. B. Quantification of apoptotic percentage in SK-OV-3 cells under oe-NC and oe-Nrf2 conditions. C, D. Flow cytometry histograms showing FITC fluorescence intensity for ROS measurement (blue: oe-NC; red: oe-Nrf2). E-G. Levels of Fe^{2+}, malondialdehyde (MDA) and glutathione (GSH) levels in SK-OV-3 cells. H-N. Apoptosis, ROS production, Fe^{2+}, MDA, and GSH levels in A2780 cells. Notes: ***$P < 0.001$, **$P < 0.01$, *$P < 0.05$.

Nrf2 overexpression conferred resistance to curcumin-induced apoptosis, oxidative stress, and ferroptosis in OC cells

To evaluate the role of Nrf2 in modulating cellular response to curcumin, we measured apoptosis, oxidative stress, iron homeostasis, lipid peroxidation, and antioxidant capacity in SK-OV-3 and A2780 cells transfected with control (NC-OE) or Nrf2-overexpressing (Nrf2-OE) vectors. Flow cytometry revealed that Nrf2 overexpression significantly inhibited curcumin-indu-

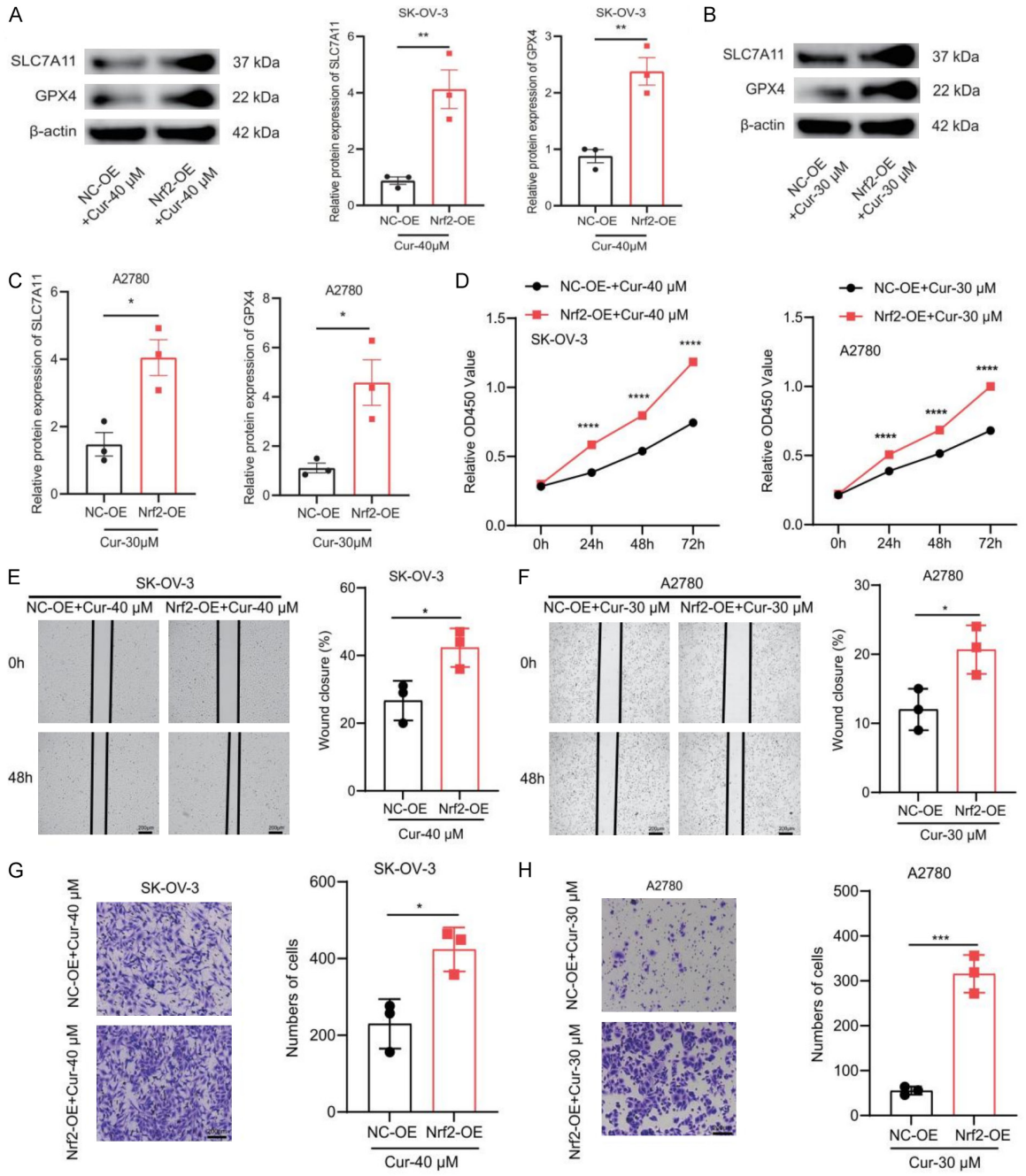

Figure 6. Impacts of Nrf2 overexpression on curcumin-mediated regulation of protein expression, cell proliferation, migration, and invasion. A-C. Western blot analysis of SLC7A11 and GPX4 protein expression in OC cells. D. Cell proliferation assessed by CCK-8 assay. E, F. Cell migration evaluated by Wound healing assay (Scale bar: 200 μm, ×100). G, H. Cell invasion measured by Transwell invasion assay (Scale bar: 200 μm, ×200). Notes: ****P < 0.0001, ***P < 0.001, **P < 0.01, *P < 0.05.

ced apoptosis in SK-OV-3 cells (**Figure 7A**, **7B**), indicating a protective role of Nrf2 against curcumin-induced cell death. Consistently, flow cytometry showed that intracellular ROS level was significantly decreased in Nrf2-OE cells treated with curcumin (**Figure 7C**, **7D**), suggesting effective suppression of oxidative stress. In addition, Nrf2 overexpression notably reduced both Fe^{2+} and MDA levels in curcumin-treated SK-OV-3 cells (**Figure 7E**, **7F**), while maintaining higher GSH levels (**Figure 7G**), indicating preserved antioxidant capacity and enhanced re-

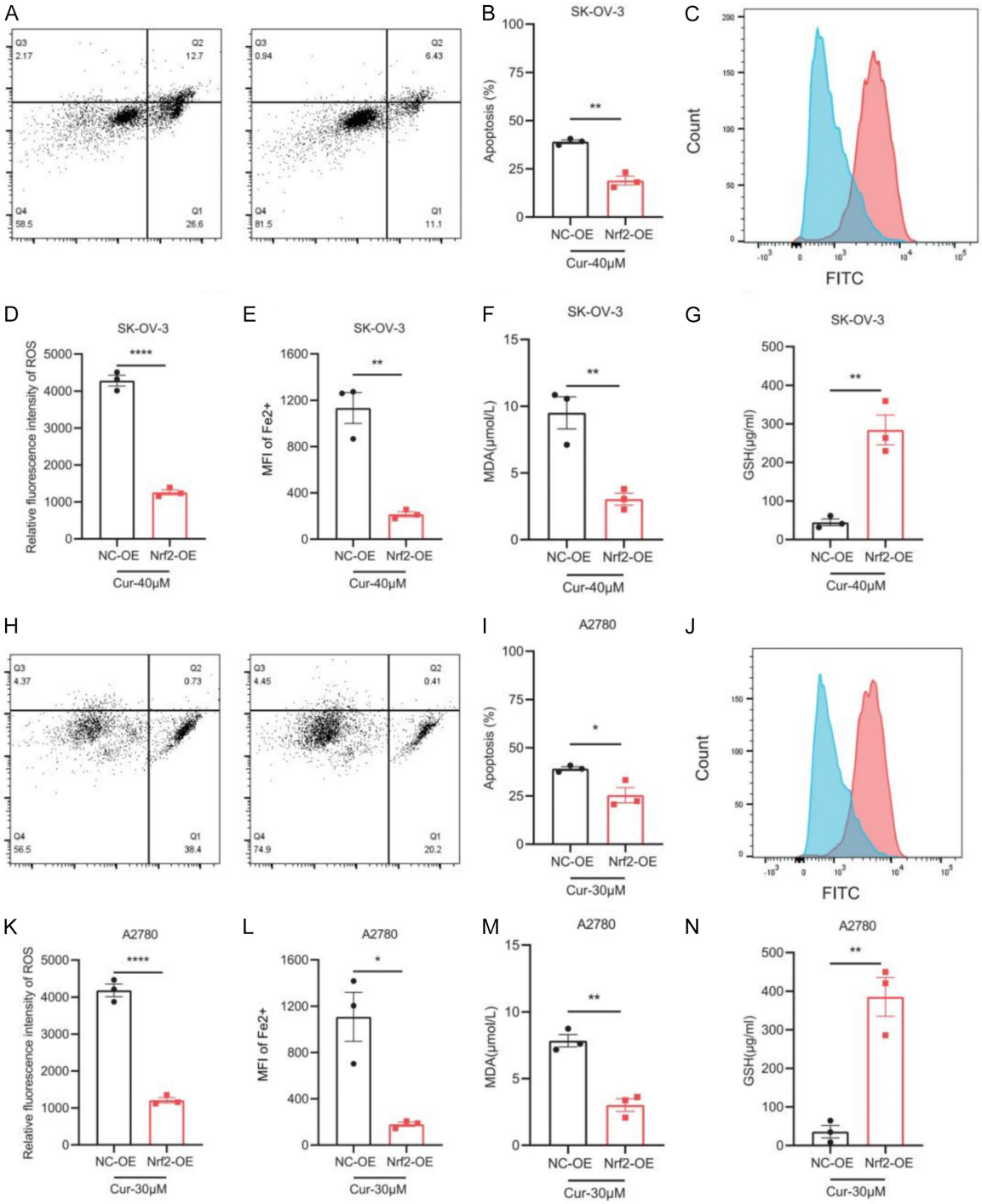

Figure 7. Effects of Nrf2 Overexpression on apoptosis, ROS production, and oxidative stress markers in SK-OV-3 and A2780 cells treated with curcumin. A-D. Flow cytometry analysis of apoptosis and ROS production in Nrf2-overexpressing SK-OV-3 cells treated with curcumin. E-G. Levels of Fe^{2+}, malondialdehyde (MDA) and glutathione (GSH) levels in Nrf2-overexpressing SK-OV-3 cells treated with curcumin. H-N. Determination of apoptosis, ROS production, Fe^{2+}, MDA and GSH levels in Nrf2-overexpressing A2780 cells treated with curcumin. Notes: $****P < 0.0001$, $**P < 0.01$, $*P < 0.05$.

sistance to oxidative stress. Similar results were observed in the A2780 cells, where Nrf2 overexpression simultaneously decreased apoptosis, ROS, Fe^{2+}, MDA levels, while increasing GSH content under curcumin treatment (**Figure 7H-N**).

Discussion

Ovarian cancer (OC) is a lethal gynecological malignancy that poses a major threat to women's health [4]. Due to nonspecific symptoms and limited effective screening tools, over 70% of cases are diagnosed at advanced stages [36]. Moreover, OC is prone to metastasis, contributing to high recurrence rates and frequent development of chemoresistance [37]. Traditional Chinese Medicine (TCM) holds promise for cancer therapy, with multiple bioactive components known to induce apoptosis in OC cell via signaling such as PI3K/AKT, Wnt/β-catenin, STAT3, NF-κB and Nrf2 [38]. In this study, curcumin triggered apoptosis and promoted ferroptosis, thereby suppressing the proliferation, migration, and invasion of OC cells. Mechanistically, curcumin suppressed the Nrf2/GPX4 signaling pathway, a central regulator of ferroptosis and cellular redox homeostasis [39]. Furthermore, Nrf2 overexpression significantly attenuated curcumin-induced ferroptosis and restored cancer cell survival, migration, and invasion, suggesting that Nrf2/GPX4 axis is critical mediator of curcumin's antitumor effects in OC. Importantly, these findings indicate that natural compounds targeting ferroptosis, such as curcumin, may have therapeutic potential in antitumor treatment, especially in reversing the clinical challenge of chemotherapy resistance in ovarian cancer. By elucidating the Nrf2/GPX4 pathway as a central node in curcumin-induced cell death, this study provides a mechanistic foundation for developing novel, multi-modal therapies that leverage both apoptotic and non-apoptotic cell death pathways in OC.

Accumulating evidence indicate that the natural compound curcumin has significant antitumor activity and shows potential clinical application value in the treatment of various malignancies [40-42], including OC [43, 44]. As a broad-spectrum anticancer agent, this natural polyphenolic compound can selectively induce cancer cell death via multiple biological pathways while exhibiting minimal toxicity to normal cells [45]. These pathways include apoptosis induction, autophagy modulation, cell cycle arrest, suppression of metastasis, and anti-inflammatory effects [46]. Our findings are consistent with previous reports, indicating that curcumin suppresses tumor growth by inducing apoptosis and oxidative stress [47]. Importantly, our study extended these observations by demonstrating that curcumin can also trigger ferroptosis in OC cells [48]. Tang et al. reported that curcumin induces ferroptosis in non-small cell lung cancer, characterized by iron overload, GSH depletion, and lipid peroxidation, through autophagy activation, thereby inhibiting tumor cell proliferation [49]. Moreover, Shi et al. demonstrated that the curcumin derivative NL01 induces ferroptosis in OC via the HCAR1/MCT1 signaling pathway [32].

The Nrf2/GPX4 axis has been widely recognized as a key regulator of ferroptosis [50]. For example, salidroside ameliorates cognitive impairment by suppressing neuronal ferroptosis through Nrf2/GPX4 activation in mice [51], and the LuQi formula alleviates cardiomyocyte ferroptosis by activating the Nrf2/GPX4 pathway in heart failure [52]. Our study showed that curcumin downregulated Nrf2, SLC7A11, and GPX4 in OC cells, further supporting its role in sensitizing cancer cells to ferroptosis. Notably, Nrf2 overexpression restored GPX4 expression and reversed the antitumor effects of curcumin, highlighting that inhibition of the Nrf2/GPX4 axis is essential for curcumin-induced ferroptosis.

In addition, conventional therapies primarily target apoptosis, a pathway commonly impaired in drug-resistant cancers [53]. The emergence of ferroptosis has opened new avenues for overcoming chemoresistance in OC [54]. Our findings demonstrated that curcumin effectively induced ferroptosis in OC cells, at least partly through suppressing the Nrf2/GPX4 signaling axis, positioning ferroptosis induction as a promising alternative to conventional cytotoxic therapies. Nrf2 functions as a master regulator of the antioxidant response, maintaining cellular redox homeostasis by upregulating antioxidant enzymes GPX4 and cysteine transporters such as SLC7A11 [55, 56]. For example, kaempferol activates the Nrf2/SLC7A11/GPX4 signaling pathway to attenuate OGD/R-induced ferroptosis [57], and tripterygium glycosides sensitize drug-resistant OC cells to chemotherapy by triggering NRF2/GPX4-mediated ferroptosis [58]. While Nrf2 activation is generally cytoprotective in normal tissues, its persistent activation in cancer cells can promote tumor survival under stress and confer resistance to oxidative damage-inducing agents [59]. Our results showed that Nrf2 overexpression significantly reduced ROS and lipid peroxidation level while

increasing GSH content, thereby counteracting curcumin-induced oxidative stress and ferroptosis in OC cells. This cytoprotective phenotype was accompanied by upregulation of downstream effectors, including SLC7A11 and GPX4, which are key components of the glutathione-dependent antioxidant defense system that directly neutralize lipid peroxides [60]. Collectively, these results indicate that Nrf2 activation confers resistance to curcumin in OC cells by enhancing antioxidant capacity, highlighting its role as a key determinant of ferroptosis sensitivity in this context [61]. Furthermore, our data suggest that intrinsic *Nrf2* activity within OC cells acts as a molecular switch controlling redox balance and therapeutic response to ferroptosis inducers such as curcumin. This aligns with growing evidence that hyperactivation of the Nrf2 pathway, often caused by mutations in KEAP1 or Nrf2 itself, contributes to aggressive cancer phenotypes and treatment resistance [62, 63]. Therapeutically, our findings suggest that OC with high Nrf2 activity may resist ferroptosis-based treatments, and that combining curcumin with Nrf2 inhibitors or directly targeting downstream effectors such as GPX4 could enhance ferroptosis and overcome resistance.

This study also has several limitations. First, the current findings are primarily based on two OC cell lines, and *in vivo* validation is needed to ascertain the antitumor and ferroptosis-modulating effects of curcumin. Second, the upstream regulators and downstream effectors of the Nrf2/GPX4 axis remain to be fully elucidated. Third, assessment using patient-derived samples and clinical trials is required to establish clinical relevance. Future research should aim to identify biomarkers predicting responsiveness to curcumin and to develop combination strategies that co-activate apoptosis and ferroptosis. Finally, the roles of additional ferroptosis regulators, including ACSL4 and FSP1, warrant further investigation to fully clarify mechanism underlying curcumin's effects in OC.

Conclusion

Curcumin exerts potent antitumor effects on OC cells by inducing apoptosis and activating ferroptosis through inhibition of the Nrf2/GPX4 signaling pathway. These findings enhance the mechanistic understanding of curcumin's antitumor activity and provide a foundation for potential therapeutic strategies targeting ferroptosis in ovarian cancer.

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Disclosure of conflict of interest

None.

Abbreviations

OC, Ovarian cancer; CCK-8, Cell Counting Kit-8; PI, Propidium Iodide; FITC, Fluorescein Isothiocyanate; DCFH-DA, 2',7'-Dichlorodihydrofluorescein diacetate; GPX4, Glutathione Peroxidase 4; Nrf2, Nuclear factor erythroid 2-related factor 2; SLC7A11, Solute Carrier Family 7 Member 11; ROS, Reactive Oxygen Species; MDA, Malondialdehyde; GSH, Glutathione.

Address correspondence to: Yan-Yang Tu, Science Research Center, Huizhou Central People's Hospital, No. 41, Geiling North Road, Huizhou 516001, Guangdong, China. Tel: +86-15029090988; E-mail: tufmmu@188.com; Ming-Hui Zhou, Department of Gynecology, Huizhou Central People's Hospital, No. 41, E Ling North Road, Huicheng District, Huizhou 516001, Guangdong, China. Tel: +86-13437770321; E-mail: ppa66@163.com

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