

ORIGINAL RESEARCH

LRRC15 accelerates lung adenocarcinoma cells' proliferation and chemoresistance

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Abstract

Background: Lung adenocarcinoma (LUAD) is one of the most common malignant tumors and poses a serious threat to patient health and survival. Leucine-rich repeat-containing protein 15 (LRRC15) has been reported to act as a promoter in certain cancers, and importantly, its expression has been found to be elevated in LUAD. **Methods:** Protein expression was examined using immunohistochemistry (IHC, n = 6 for tissues) and Western blotting. Cell survival rate (%) and half-maximal inhibitory concentration (IC₅₀) were assessed using the Cell Counting Kit (CCK)-8 assay. Cell proliferation was evaluated through colony formation assays. **Results:** LRRC15 expression was significantly upregulated in LUAD tissues and cell lines, and was associated with poor prognosis. Knockdown of LRRC15 inhibited cell proliferation, and suppression of LRRC15 reduced cisplatin resistance by limiting autophagy. Furthermore, it was demonstrated that LRRC15 promoted autophagy through activation of Unc-51-like autophagy-activating kinase 1 (ULK1). **Conclusions:** These findings indicate that LRRC15 may enhance both proliferation and chemoresistance of LUAD cells by triggering ULK1-mediated autophagy. Therefore, LRRC15 may represent a potential therapeutic target for improving LUAD treatment outcomes.

Keywords

LRRC15; LUAD; Autophagy; Chemoresistance

1. Introduction

Lung cancer remains the leading cause of cancer-related mortality worldwide, with lung adenocarcinoma (LUAD) representing the most common histological subtype and accounting for approximately 40% of all lung cancer deaths [1–3]. Despite advances in diagnostic and therapeutic strategies, a considerable proportion of LUAD cases remain incurable [4], and this poor prognosis is largely attributable to late-stage diagnosis and the frequent emergence of resistance to pharmacological therapies [5]. Therefore, identifying reliable biomarkers and developing effective therapeutic strategies have become urgent priorities in LUAD research.

Leucine-rich repeat-containing protein 15 (LRRC15) is a membrane-associated protein that participates in intercellular and cell-matrix interactions [6]. Accumulating evidence indicates that LRRC15 exerts tumor-promoting effects in several malignancies. For instance, LRRC15 has been shown to facilitate metastasis in ovarian cancer by activating the β 1-integrin/Focal Adhesion Kinase (FAK) signaling pathway [7]. In triple-negative breast cancer, LRRC15 enhances cell migration and invasion by activating the Wnt/ β -catenin pathway [8]. Moreover, LRRC15 antibody-drug conjugates can improve osteosarcoma progression [9]. Importantly, LRRC15 expression has been found to be significantly elevated in LUAD [10], al-

though its functional role in the progression of this malignancy remains poorly understood. Autophagy, a conserved cellular degradation and recycling mechanism, plays an essential role in sustaining metabolic homeostasis and removing damaged organelles, thereby supporting tumor cell growth and survival [11, 12]. Although autophagy-targeted strategies have been introduced into clinical settings, the underlying regulatory mechanisms remain incompletely defined in many cancers, including LUAD [13].

The present study was designed to investigate the regulatory role of LRRC15 in autophagy in LUAD cells and reveal, for the first time, that LRRC15 could promote LUAD cell proliferation and chemoresistance by activating Unc-51-like autophagy-activating kinase 1 (ULK1)-mediated autophagy, providing novel insights into the potential of LRRC15 as a therapeutic target for improving outcomes in LUAD.

2. Materials and methods

2.1 LUAD patients

LUAD patients (n = 57) were enrolled from October 2023–February 2025 at Jiangyin People's Hospital. The obtained information from LUAD patients were recorded in Table 1.

LUAD tumor tissues (n = 6) and matched adjacent normal tissues (n = 6) were collected from LUAD patients undergoing

TABLE 1. Correlation between LRRC15 expression and clinical characteristics of patients with LUAD.

Variables	Cases (n = 57, %)		High (n = 27, %)		Low (n = 30, %)		χ^2	<i>p</i>
Age (yr)								
≥55	27	47.37	15	55.56	12	40.00	1.379	0.240
<55	30	52.63	12	44.44	18	60.00		
Gender								
Male	31	54.39	15	55.56	16	53.33	0.028	0.866
Female	26	45.61	12	44.44	14	46.67		
T stage								
T1	28	49.12	19	70.37	9	30.00	10.284	0.016
T2	17	29.82	6	22.22	11	36.67		
T3	7	12.28	1	3.70	6	20.00		
T4	5	8.77	1	3.70	4	13.33		
N stage								
N0	24	42.11	18	66.67	6	20	13.628	0.001
N1	23	40.35	5	18.52	18	60		
N2	10	17.54	4	14.81	6	20		
TNM stage								
I	15	26.32	13	48.15	2	6.67	13.330	0.001
II	26	45.61	10	37.04	16	53.33		
III	16	28.07	4	14.81	12	40.00		

LUAD patients were enrolled from Jiangyin People’s Hospital to participate in the study. T: Tumor; N: Node; TNM: Tumor Node Metastasis.

treatment at Jiangyin People’s Hospital for IHC assay.

Written informed consent was obtained from all participants. The study was performed in compliance with the Helsinki Declaration and approved by the Ethics Committee of the Affiliated Jiangyin Clinical College of Xuzhou Medical University (Approval no. 2024-154).

2.2 IHC assay

Paraffin-embedded tumor (n = 6) and normal tissues (n = 6) were sectioned at a thickness of 4 μm, followed by dewaxing and rehydration. After blocking, the sections were incubated with a primary antibody against LRRC15 (1:1000; ab150376; Abcam, Shanghai, China) for 12 h, and subsequently with a secondary antibody (1:1000; ab6721; Abcam, Shanghai, China) for 2 h. The antigen-antibody complex was visualized using 3,3'-Diaminobenzidine (DAB) staining, and nuclei were counterstained with hematoxylin. Stained sections were examined and imaged using a light microscope (L200, Nikon, Tokyo, Japan).

2.3 Cell lines and cell culture

Human Embryonic Kidney (HEK)293 cells and LUAD cell lines (A549 and H1975) were purchased from the American Type Culture Collection (ATCC, USA). All cells were cultured in Dulbecco’s Modified Eagle’s Medium (DMEM) (11965084, Gibco, Carlsbad, CA, USA) supplemented with 10% fetal bovine serum, and maintained in an incubator at 37 °C with

5% CO₂. For drug treatment, cells were exposed either to Retinoic Acid (RA, an autophagy activator, 50 nM; S1039, Selleck Chemicals, Shanghai, China) to induce autophagy or to LYN-1604 (an effective and selective agonist of ULK1, 2 μM; S8597, Selleck Chemicals, Shanghai, China) to activate ULK1.

2.4 Cell transfection

Small interfering RNAs (siRNAs) targeting LRRC15 (si-LRRC15) and the corresponding negative Control (si-NC) were purchased from GenePharma company (Shanghai, China). Transfections were performed using Lipofectamine 2000 (11668019, Invitrogen, Carlsbad, CA, USA) following the manufacturer’s instructions.

2.5 Western blot

Proteins extracted from LUAD cells were separated by 10% Sodium Dodecyl Sulfate-Polyacrylamide Gel Electrophoresis (SDS-PAGE) and transferred to Polyvinylidene Fluoride (PVDF) membranes (Beyotime, Shanghai, China). After blocking, the membranes were incubated with primary antibodies, then with Horseradish Peroxidase (HRP)-conjugated secondary antibody (1:1000; ab7090). After 2 h of incubation, the corresponding protein bands were visualized using an enhanced chemiluminescence detection kit (89880, Thermo Fisher Scientific, Inc., Waltham, MA, USA).

The primary antibodies used were: LRRC15 (1:1000;

ab150376; Abcam, Shanghai, China), Microtubule-associated protein 1A/1B-light chain 3B (LC3B, 1:2000; ab192890), Beclin (1:2000; ab207612), p62 (1:5000; ab109012), p-ULK1 (1:5000; ab133747), ULK1 (1:1000; ab167139), and Glyceraldehyde-3-Phosphate Dehydrogenase (GAPDH, 1:1000; ab8245).

2.6 CCK-8 assay

LUAD cells were seeded into 96-well plates, and 10 μ L of Cell Counting Kit (CCK-8) solution (CK04, Dojindo Laboratories, Kumamoto, Japan) was added to each well. After incubation for 2 h, the absorbance at 450 nm was measured using a spectrophotometer (ND-ONE-W, Thermo Fisher Scientific, Waltham, MA, USA). Cell viability and half-maximal inhibitory concentration (IC₅₀) values were subsequently calculated.

2.7 Colony formation assay

LUAD cells were seeded into 6-well plates and cultured for 14 days to allow colony formation. The resulting colonies were fixed with 4% paraformaldehyde and stained with 0.1% crystal violet, after which the number of colonies was counted.

2.8 Statistical analysis

Data are presented as mean $\pm$ standard deviation (SD). Statistical analyses were conducted using GraphPad Prism 9 (GraphPad Software, La Jolla, CA, USA). Comparisons between two groups were performed using Student's *t*-test, whereas multiple group comparisons were assessed using one-way analysis of variance (ANOVA). A *p*-value < 0.05 was considered statistically significant.

3. Results

3.1 LRRC15 was upregulated in LUAD and associated with poor prognosis

LRRC15 expression was significantly elevated in LUAD tissues compared with normal counterparts (Fig. 1A), which was then validated by IHC analysis and demonstrated increased LRRC15 protein levels in tumor samples (Fig. 1B). Consistently, Western blot analysis revealed higher LRRC15 protein expression in LUAD cell lines compared with HEK293 cells (Fig. 1C). Kaplan-Meier survival analysis indicated that elevated LRRC15 expression was significantly correlated with poorer prognosis in LUAD patients (Fig. 1D). In addition, clinical correlation analysis showed that LRRC15 expression was significantly associated with T (Tumor) stage ($p = 0.016$), N (Node) stage ($p = 0.001$), and TNM (Tumor Node Metas-

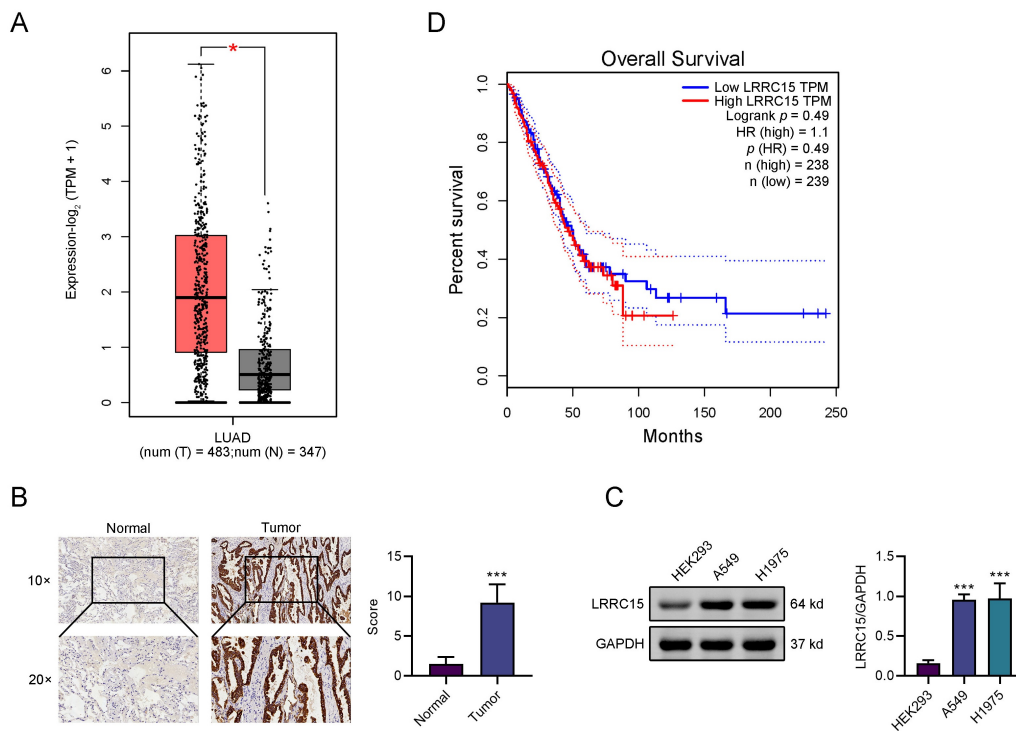


FIGURE 1. LRRC15 was upregulated in LUAD and associated with poor prognosis. (A) LRRC15 mRNA expression levels in normal and LUAD tissues were analyzed using the GEPIA online database. * $p < 0.05$ vs. the Normal group. (B) LRRC15 protein expression in normal tissues (n = 6) and LUAD tissues (n = 6) was evaluated by IHC. (C) LRRC15 protein expression in HEK293, A549, and H1975 cells was examined by Western blot. *** $p < 0.001$ vs. the HEK293 group. (D) Kaplan-Meier survival analysis of LUAD patients with high versus low LRRC15 expression was performed using TCGA data. LUAD: Lung adenocarcinoma; LRRC15: Leucine-rich repeat-containing protein 15; TPM: Transcripts Per Million; HR: Hazard Ratio; GAPDH: Glyceraldehyde-3-Phosphate Dehydrogenase; HEK: Human Embryonic Kidney; T: Tumor; N: Normal; num: number.

tasis) stage ($p = 0.001$) (Table 1). Collectively, these results demonstrate that LRRC15 is upregulated in LUAD and is strongly correlated with adverse clinical outcomes.

3.2 Knockdown of LRRC15 inhibited LUAD cell proliferation

The efficiency of LRRC15 knockdown was confirmed by a significant reduction in its protein expression (Fig. 2A). Functional analyses demonstrated that silencing LRRC15 significantly decreased cell viability (Fig. 2B) and suppressed cell proliferative ability, as evidenced by reduced colony formation (Fig. 2C). Taken together, these findings indicate that LRRC15 plays an essential role in supporting LUAD cell growth, and its knockdown markedly impairs proliferative capacity.

3.3 Suppression of LRRC15 reduced cisplatin resistance by inhibiting autophagy

Knockdown of LRRC15 led to a marked decrease in Microtubule-associated protein 1A/1B-light chain 3 (LC3)-II/LC3-I and Beclin protein levels, accompanied by an increase in p62 expression, indicating reduced autophagic flux (Fig. 3A). Consistently, the IC₅₀ of cisplatin was significantly reduced in LRRC15-silenced cells, reflecting enhanced drug

sensitivity. Notably, this effect was reversed when cells were treated with RA, an autophagy activator, thereby restoring resistance to cisplatin (Fig. 3B). These findings suggest that LRRC15 promotes cisplatin resistance in LUAD cells, at least in part, through its regulation of autophagy.

3.4 LRRC15 induced ULK1-mediated autophagy

Suppression of LRRC15 led to a reduction in the protein levels of p-ULK1/ULK1, LC3-II/LC3-I, and Beclin, accompanied by an elevation in p62 expression, indicating that autophagy was inhibited (Fig. 4A). Importantly, treatment with LYN-1604, a ULK1 activator, reversed these molecular changes and restored autophagic activity. Functionally, the reduction in cell survival caused by LRRC15 knockdown was counteracted by LYN-1604 treatment (Fig. 4B). Similarly, the inhibitory effect of LRRC15 suppression on cell proliferation was alleviated following LYN-1604 administration (Fig. 4C). Together, these findings demonstrate that LRRC15 promotes autophagy in LUAD cells through an ULK1-dependent mechanism.

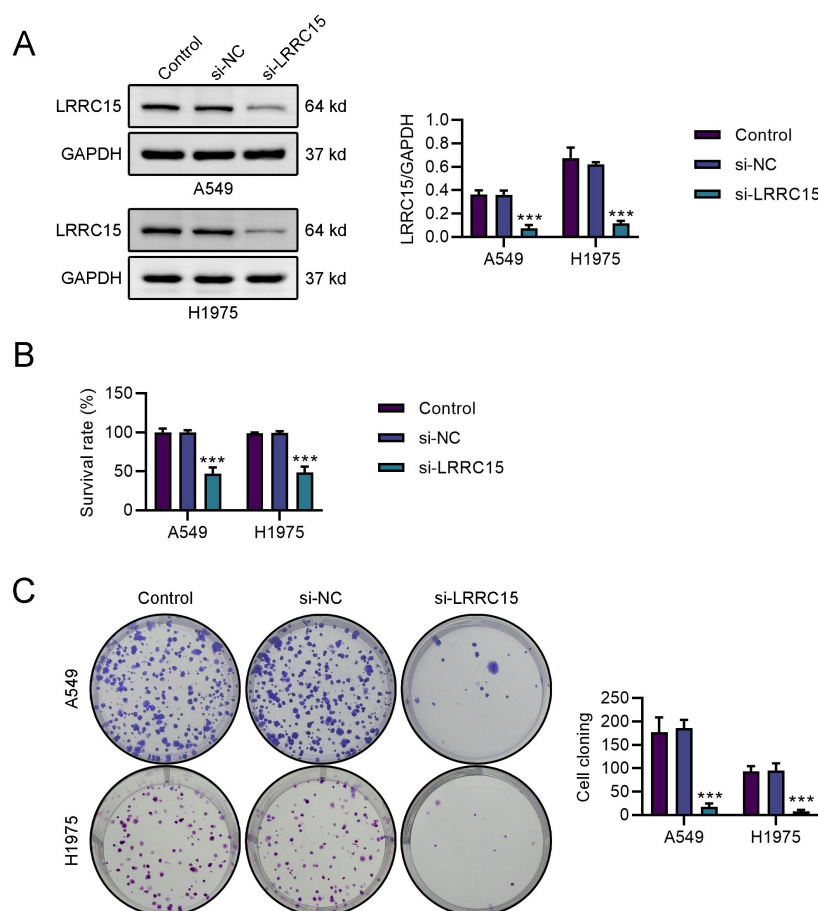


FIGURE 2. Knockdown of LRRC15 inhibited LUAD cell proliferation. LUAD cells were divided into Control, si-NC, and si-LRRC15 groups. (A) LRRC15 protein expression was evaluated by Western blot. *** $p < 0.001$ vs. the si-NC group. (B) Cell viability was assessed using the CCK-8 assay. *** $p < 0.001$ vs. the si-NC group. (C) Cell proliferation was determined using colony formation assay. *** $p < 0.001$ vs. the si-NC group. LRRC15: Leucine-rich repeat-containing protein 15; GAPDH: Glyceraldehyde-3-Phosphate Dehydrogenase; NC: Negative Control.

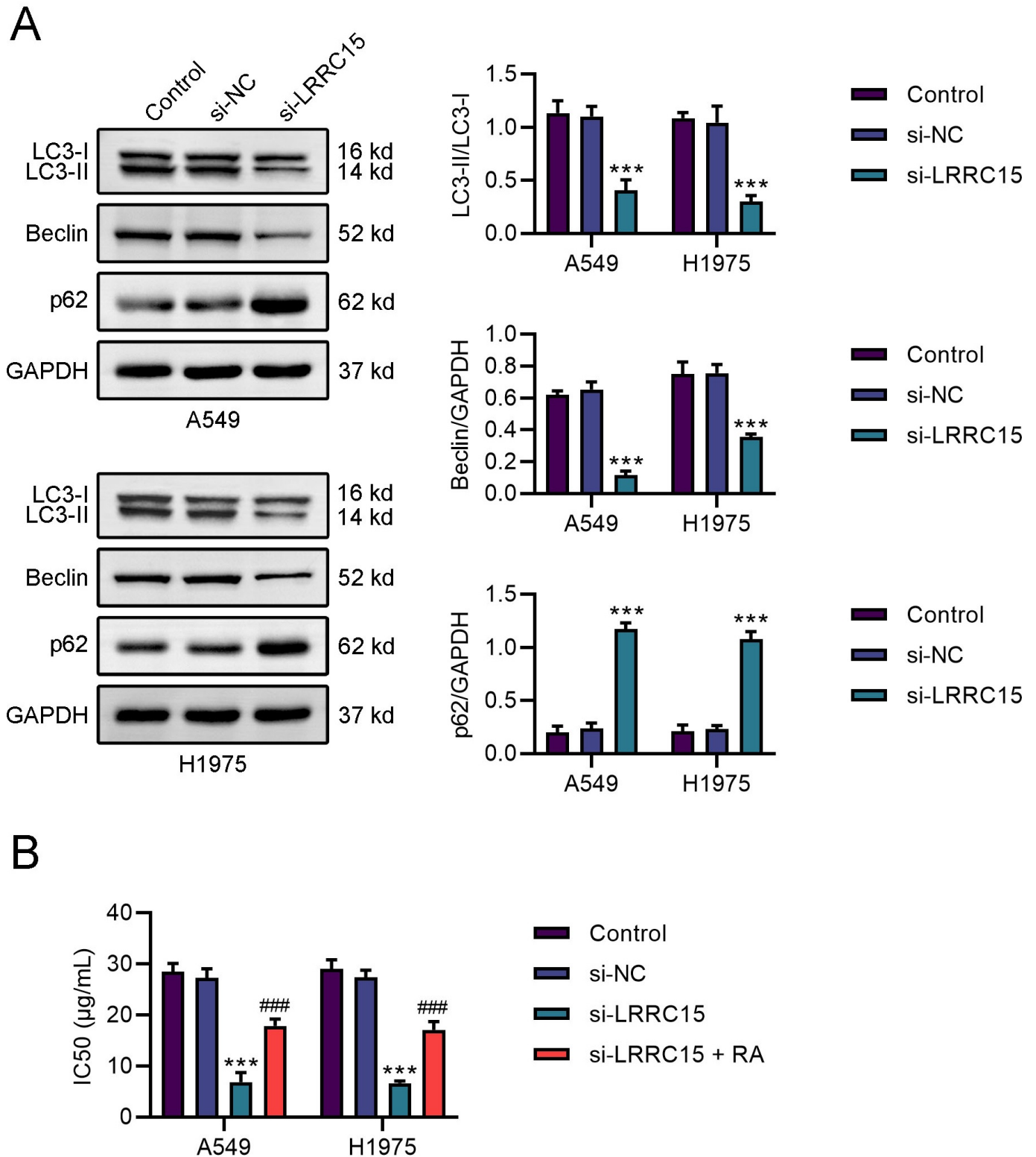


FIGURE 3. LRRC15 knockdown reduced cisplatin resistance by inhibiting autophagy. (A) Protein levels of LC3-I, LC3-II, Beclin, and p62 were analyzed by Western blot in Control, si-NC, and si-LRRC15 groups. *** $p < 0.001$ vs. the si-NC group. (B) IC₅₀ values of cisplatin were measured using the CCK-8 assay. Groups included Control, si-NC, si-LRRC15, and si-LRRC15 + RA. *** $p < 0.001$ vs. the si-NC group; ### $p < 0.001$ vs. the si-LRRC15 group. LRRC15: Leucine-rich repeat-containing protein 15; IC₅₀: inhibitory concentration; GAPDH: Glyceraldehyde-3-Phosphate Dehydrogenase; NC: Negative Control; RA: Retinoic Acid; LC3: Microtubule-associated protein 1A/1B-light chain 3.

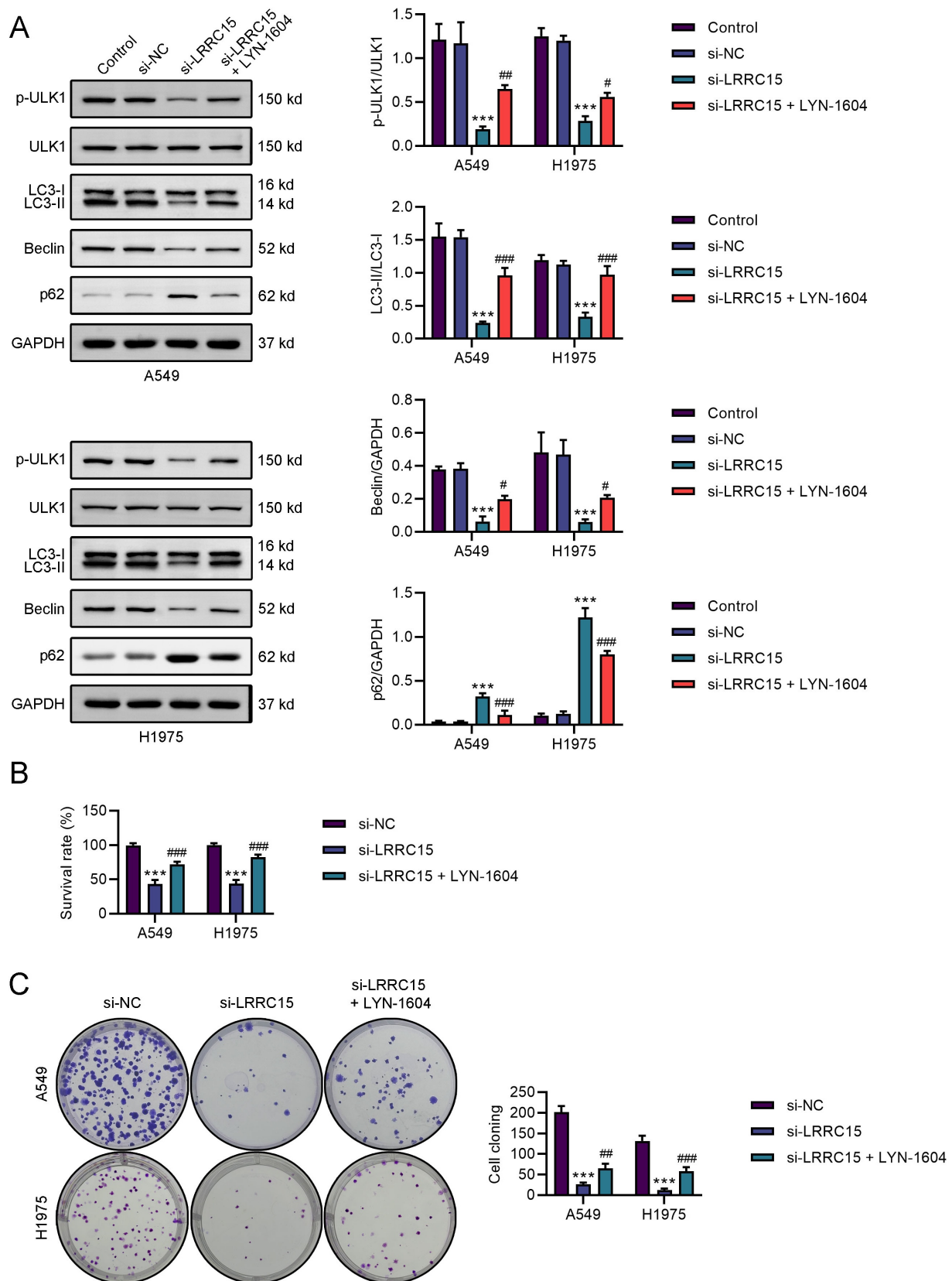


FIGURE 4. LRRC15 promoted autophagy through ULK1 activation. Cells were grouped into Control, si-NC, si-LRRC15, and si-LRRC15 + LYN-1604. (A) Protein levels of p-ULK1, ULK1, LC3-I, LC3-II, Beclin, and p62 were detected by Western blot. (B) Cell survival rate (%) was evaluated using the CCK-8 assay. (C) Cell proliferation was assessed using the colony formation assay. *** $p < 0.001$ vs. the si-NC group; # $p < 0.05$, ## $p < 0.01$, ### $p < 0.001$ vs. the si-LRRC15 group. LRRC15: Leucine-rich repeat-containing protein 15; GAPDH: Glyceraldehyde-3-Phosphate Dehydrogenase; NC: Negative Control; LC3: Microtubule-associated protein 1A/1B-light chain 3; ULK1: Unc-51-like autophagy-activating kinase 1; LYN-1604: an effective and selective agonist of ULK1.

4. Discussion

LRRC15 has previously been reported as a tumor-promoting factor in several malignancies [7–9]. Its overexpression has also been confirmed in LUAD [10]; however, its specific role in LUAD progression has remained poorly defined. In this study, we demonstrated that LRRC15 expression was markedly elevated in LUAD tissues and cell lines, and its upregulation was associated with unfavorable prognosis. Furthermore, silencing LRRC15 significantly suppressed cell proliferation, thereby suggesting that LRRC15 contributes to the growth of LUAD cells.

Autophagy, which is typically maintained at a low basal level, can be rapidly activated in response to various stressors and environmental stimuli [14]. Accumulating evidence indicates that autophagy exerts a dual role in tumor biology and has been recognized as a critical mechanism underlying chemoresistance, including resistance to cisplatin [15]. Previous studies have highlighted the importance of autophagy in mediating cisplatin resistance across multiple cancers. For example, the COP9 Signalosome Subunit 3 (COPS3)/Forkhead Box O3 (FOXO3) axis was found to promote cisplatin resistance in osteosarcoma through regulation of autophagy [16]. In gastric cancer, circCUL2/miR-142-3p/Rho Associated Coiled-Coil Containing Protein Kinase 2 (ROCK2) signaling enhanced autophagy and thereby increased cisplatin resistance [17]. In ovarian cancer, both Low-Density Lipoprotein Receptor (LDLR) [18] and SHC Binding and Spindle Associated 1 (SHCBP1) [19] were shown to contribute to autophagy-driven cisplatin resistance. Conversely, E74-Like ETS Transcription Factor 1 (ELF1) inhibited autophagy to weaken cisplatin resistance in lung cancer [20]. In LUAD, the miR-125b/RAR Related Orphan Receptor A (RORA)/BCL2 Interacting Protein 3 Like (BNIP3L) axis has been implicated in modulating autophagy and influencing cisplatin sensitivity [21]. Despite these advances, the role of LRRC15 in regulating autophagy-dependent cisplatin resistance in LUAD had not been clarified. In the present study, we demonstrated that suppression of LRRC15 reduced cisplatin resistance, at least in part, through inhibition of autophagic activity.

ULK1, a serine/threonine kinase, functions as a critical upstream regulator in the initiation of autophagy [22, 23]. Given its central role, ULK1-mediated autophagy has become a major focus in cancer research. Several studies have highlighted its diverse functions in tumor biology. For example, miR-937 was reported to enhance ovarian cancer progression by regulating ULK1-mediated autophagy through F-Box Protein 16 (FBXO16) [24], whereas the Tripartite Motif Containing 27 (TRIM27)/Serine/Threonine Kinase 38 Like (STK38L) axis inhibited ULK1-dependent autophagy and thereby facilitated tumor development [25]. In gastric cancer, Fat mass and obesity-associated protein (FTO) was shown to aggravate cisplatin resistance via modulation of ULK1-mediated autophagy [26], while in esophageal squamous cell carcinoma, Butyrophilin Subfamily 3 Member A1 (BTN3A1) contributed to radiation resistance through ULK1-driven autophagy [27]. In contrast, Death-Associated Protein Kinase 3 (DAPK3) was found to induce ULK1-mediated autophagy

and suppress gastric cancer progression [28]. LRRC15 can modulate the Phosphatidylinositol 3-Kinase (PI3K)/protein kinase B (AKT)/Mechanistic Target of Rapamycin (mTOR) signaling pathway. Importantly, the activity of ULK1 is precisely regulated by key energy/stress-responsive kinases, such as mTOR and AMP-Activated Protein Kinase (AMPK) [29]. These findings provide theoretical justification for our proposed hypothesis model of “transmembrane protein LRRC15 → upstream kinase (mTOR) → ULK1 phosphorylation → autophagy initiation”. In this work, our results confirmed that LRRC15 promotes autophagy in LUAD cells through a ULK1-dependent mechanism.

5. Conclusions

In conclusion, this study provides the first evidence that LRRC15 promotes LUAD cell proliferation and contributes to drug resistance by regulating ULK1-mediated autophagy. These findings suggest that LRRC15 may represent a potential therapeutic target; however, further *in vivo* experiments and clinical investigations are required to validate its translational feasibility. Several limitations should also be acknowledged, including the lack of exploration of other cellular processes, such as exosome secretion, stemness, and immune responses, the absence of *in vivo* validation, the relatively small sample size, the omission of analyses of the immune microenvironment, and the lack of clinical verification. Further investigations using *in vivo* models, such as nude mice or orthotopic transplantation systems, are still needed to confirm the role of LRRC15 and to provide a stronger basis for clinical application.

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

CH and HYB—designed the study and carried them out. CH, HYB and YJS—supervised the data collection; analyzed the data; interpreted the data; prepare 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

Ethical approval was obtained from the Ethics Committee of Affiliated Jiangyin Clinical College of Xuzhou Medical University (Approval no. 2024-154). Written informed consent was obtained from a legally authorized representatives for anonymized patient information to be published in this article.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

- [1] Florez N, Kiel L, Riano I, Patel S, DeCarli K, Dhawan N, *et al.* Lung cancer in women: the past, present, and future. *Clinical Lung Cancer*. 2024; 25: 1–8.
- [2] Wei X, Li X, Hu S, Cheng J, Cai R. Regulation of ferroptosis in lung adenocarcinoma. *International Journal of Molecular Sciences*. 2023; 24: 14614.
- [3] Testa U, Pelosi E, Castelli G. Molecular characterization of lung adenocarcinoma combining whole exome sequencing, copy number analysis and gene expression profiling. *Expert Review of Molecular Diagnostics*. 2022; 22: 77–100.
- [4] Wang S, Wang R, Hu D, Zhang C, Cao P, Huang J. Machine learning reveals diverse cell death patterns in lung adenocarcinoma prognosis and therapy. *npj Precision Oncology*. 2024; 8: 49.
- [5] Li Z, Zhuang X, Pan CH, Yan Y, Thummalapalli R, Hallin J, *et al.* Alveolar differentiation drives resistance to KRAS inhibition in lung adenocarcinoma. *Cancer Discovery*. 2024; 14: 308–325.
- [6] Ray U, Pathoulas CL, Thirusangu P, Purcell JW, Kannan N, Shridhar V. Exploiting LRRC15 as a novel therapeutic target in cancer. *Cancer Research*. 2022; 82: 1675–1681.
- [7] Ray U, Jung DB, Jin L, Xiao Y, Dasari S, Sarkar Bhattacharya S, *et al.* Targeting LRRC15 inhibits metastatic dissemination of ovarian cancer. *Cancer Research*. 2022; 82: 1038–1054.
- [8] Yang Y, Wu H, Fan S, Bi Y, Hao M, Shang J. Cancer-associated fibroblast-derived LRRC15 promotes the migration and invasion of triple-negative breast cancer cells via Wnt/ β -catenin signalling pathway regulation. *Molecular Medicine Reports*. 2022; 25: 2.
- [9] Slemmons KK, Mukherjee S, Meltzer P, Purcell JW, Helman LJ. LRRC15 antibody-drug conjugates show promise as osteosarcoma therapeutics in preclinical studies. *Pediatric Blood & Cancer*. 2021; 68: e28771.
- [10] Li Y, Cai Y, Ji L, Wang B, Shi D, Li X. Machine learning and bioinformatics analysis of diagnostic biomarkers associated with the occurrence and development of lung adenocarcinoma. *PeerJ*. 2024; 12: e17746.
- [11] Debnath J, Gammoh N, Ryan KM. Autophagy and autophagy-related pathways in cancer. *Nature Reviews Molecular Cell Biology*. 2023; 24: 560–575.
- [12] Xu HM, Hu F. The role of autophagy and mitophagy in cancers. *Archives of Physiology and Biochemistry*. 2022; 128: 281–289.
- [13] Yuan W, Fang W, Zhang R, Lyu H, Xiao S, Guo D, *et al.* Therapeutic strategies targeting AMPK-dependent autophagy in cancer cells. *Biochimica et Biophysica Acta—Molecular Cell Research*. 2023; 1870: 119537.
- [14] Palmer JE, Wilson N, Son SM, Obrocki P, Wrobel L, Rob M, *et al.* Autophagy, aging, and age-related neurodegeneration. *Neuron*. 2025; 113: 29–48.
- [15] Li X, Zhou Y, Li Y, Yang L, Ma Y, Peng X, *et al.* Autophagy: a novel mechanism of chemoresistance in cancers. *Biomedicine & Pharmacotherapy*. 2019; 119: 109415.
- [16] Niu J, Yan T, Guo W, Wang W, Ren T, Huang Y, *et al.* The COPS3-FOXO3 positive feedback loop regulates autophagy to promote cisplatin resistance in osteosarcoma. *Autophagy*. 2023; 19: 1693–1710.
- [17] Peng L, Sang H, Wei S, Li Y, Jin D, Zhu X, *et al.* circCUL2 regulates gastric cancer malignant transformation and cisplatin resistance by modulating autophagy activation via miR-142-3p/ROCK2. *Molecular Cancer*. 2020; 19: 156.
- [18] Liu L, Sun YH, An R, Cheng RJ, Li N, Zheng JH. LDLR promotes autophagy-mediated cisplatin resistance in ovarian cancer associated with the PI3K/AKT/mTOR signaling pathway. *The Kaohsiung Journal of Medical Sciences*. 2023; 39: 779–788.
- [19] Qi G, Ma H, Teng K, Gai P, Gong Y, Chen J, *et al.* SHCBP1 promotes cisplatin resistance of ovarian cancer through AKT/mTOR/Autophagy pathway. *Apoptosis*. 2025; 30: 83–98.
- [20] Zhao L, Wu X, Zhang Z, Fang L, Yang B, Li Y. ELF1 suppresses autophagy to reduce cisplatin resistance via the miR-152-3p/NCAM1/ERK axis in lung cancer cells. *Cancer Science*. 2023; 114: 2650–2663.
- [21] Liu L, Guo NA, Li X, Xu Q, He R, Cheng L, *et al.* miR-125b reverses cisplatin resistance by regulating autophagy via targeting RORA/BNIP3L axis in lung adenocarcinoma. *Oncology Research*. 2024; 32: 643–658.
- [22] Liu L, Yan L, Liao N, Wu WQ, Shi JL. A review of ULK1-mediated autophagy in drug resistance of cancer. *Cancers*. 2020; 12: 352.
- [23] Zachari M, Ganley IG. The mammalian ULK1 complex and autophagy initiation. *Essays in Biochemistry*. 2017; 61: 585–596.
- [24] Zhang Z, Liu X, Chu C, Zhang Y, Li W, Yu X, *et al.* MIR937 amplification potentiates ovarian cancer progression by attenuating FBXO16 inhibition on ULK1-mediated autophagy. *Cell Death & Disease*. 2024; 15: 735.
- [25] Yang Y, Zhu Y, Zhou S, Tang P, Xu R, Zhang Y, *et al.* TRIM27 cooperates with STK38L to inhibit ULK1-mediated autophagy and promote tumorigenesis. *The EMBO Journal*. 2022; 41: e109777.
- [26] Zhang Y, Gao LX, Wang W, Zhang T, Dong FY, Ding WP. M⁶ a demethylase fat mass and obesity-associated protein regulates cisplatin resistance of gastric cancer by modulating autophagy activation through ULK1. *Cancer Science*. 2022; 113: 3085–3096.
- [27] Yang W, Cheng B, Chen P, Sun X, Wen Z, Cheng Y. BTN3A1 promotes tumor progression and radiation resistance in esophageal squamous cell carcinoma by regulating ULK1-mediated autophagy. *Cell Death & Disease*. 2022; 13: 984.
- [28] Li GM, Li L, Li MQ, Chen X, Su Q, Deng ZJ, *et al.* DAPK3 inhibits gastric cancer progression via activation of ULK1-dependent autophagy. *Cell Death & Differentiation*. 2021; 28: 952–967.
- [29] Kim J, Kundu M, Viollet B, Guan KL. AMPK and mTOR regulate autophagy through direct phosphorylation of Ulk1. *Nature Cell Biology*. 2011; 13: 132–141.

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