A fibroblast activation protein degrader enhances cisplatin sensitivity in non-small cell lung cancer

YONG ZHOU[1], RANHUA LI[1], XIAOBO CHEN[1], CHENG ZHANG[1], YANAN BAO[1], YUE CUI[1], XINGHE TONG[1], TING XIA[1], XUDONG YANG[1], JIQING YANG[2] and XIAOCHUAN YIN[1]

[1]Department of Thoracic Surgery, First Affiliated Hospital of Kunming Medical University, Kunming, Yunnan 650032, P.R. China; [2]Department of Obstetrics, First Affiliated Hospital of Kunming Medical University, Kunming, Yunnan 650032, P.R. China

Received November 26, 2025; Accepted May 29, 2026

DOI: 10.3892/or.2026.9150

Abstract. The therapeutic effect of cisplatin against non-small cell lung cancer (NSCLC), the most common lung cancer, is limited by resistance. In the present study, a fibroblast activation protein (FAP) degrader (Pomalidomide-PEG2-FAP2286: FAP-D) was utilized to enhance cisplatin sensitivity in NSCLC. The study specifically assessed the viabilities of NCI-H1299 and NCI-H460 cells (human NSCLC cell lines) and the growth of heterogeneous tumors in mice. The binding between FAP-D and FAP was studied by molecular docking. The ability of FAP-D to induce FAP and CD26 degradation was examined by western blotting, as was caspase-3 and cleaved caspase-3 expression. The viabilities of H1299 and H460 cells were analyzed using a Cell Counting Kit-8 assay (CCK-8). Cell migration rates were studied via wound-healing assays. Apoptotic features were confirmed in tumors by hematoxylin-eosin staining assay. FAP was degraded by FAP-D in a time- and concentration-dependent manner, whereas CD26 protein expression was not altered by FAP-D. FAP-D exhibited favorable biocompatibility. The half-maximal inhibitory concentration (IC_{50}) of cisplatin was reduced by co-treatment with FAP-D, which could be attributable to the inhibition of cell migration by FAP-D. Heterogeneous tumor growth was also strongly suppressed by cisplatin + FAP-D. The apoptotic features of H1299/H460 cells and tumors were enhanced by cisplatin + FAP-D treatment. In conclusion, the study demonstrated that FAP-D can enhance the cisplatin sensitivity of H1299 cells and NSCLC tumors. The present findings shed new light into promising treatment strategies and demonstrated the potential clinical utility of cisplatin + FAP-D for NSCLC treatment.

Correspondence to: Professor Xiaochuan Yin, Department of Thoracic Surgery, First Affiliated Hospital of Kunming Medical University, 295 Xichang Road, Kunming, Yunnan 650032, P.R. China
E-mail: yxc9701@163.com

Key words: non-small cell lung cancer, cisplatin, fibroblast activation protein, apoptosis

Introduction

Non-small cell lung cancer (NSCLC) accounts for ~85% of all lung cancers (1,2). NSCLC is often classified into three main histological subtypes: Adenocarcinoma, squamous cell carcinoma and large cell carcinoma (1). Although smoking is the main risk factor for NSCLC (3), the incidence of NSCLC is also increasing among non-smokers who are exposure to tobacco (1). The standard treatment of NSCLC consists of surgery, chemotherapy, radiation therapy, targeted therapy and immunotherapy (4). Chemotherapy is the standard treatment modality for early-stage NSCLC (4). Similarly, favorable curative effects have been achieved through advances in radiotherapy techniques (5). Moreover, the most common targeted therapeutic strategy is vascular endothelial growth factor (6-8) or epidermal growth factor receptor inhibition (9,10). However, issues such as drug resistance, systemic toxicity and high costs remain major obstacles for the adoption of these strategies.

For decades, platinum-based chemotherapeutics have dominated the treatment of NSCLC (11-13). Among them, cisplatin has become the most commonly used first-line drug because of its excellent efficacy (14). Unfortunately, chemoresistance often develops during treatment, which seriously limits the clinical utility of cisplatin (14). Usually, combination treatment is a powerful means to overcome this resistance (15).

Meanwhile, fibroblast activation protein (FAP) a type-II transmembrane serine protease, expressed almost exclusively to pathological conditions including fibrosis, arthritis and cancer. Across most cancer types, FAP plays critical roles in tumor proliferation, tumor invasion, angiogenesis and drug resistance, and elevated FAP is associated with worse clinical outcomes (16-18). Previous research demonstrated that treatment strategies targeting FAP in combination with other approaches such as chemotherapy, radiotherapy and immunotherapy could strengthen treatment efficacy (17,18). However, the role of FAP degradation in enhancing cisplatin sensitivity of NSCLC is unclear. Thus, the present study investigated the effect of FAP degradation on the therapeutic effect of cisplatin against NSCLC.

Materials and methods

Reagents. Cisplatin (cat. no. HY-17394; CAS no. 15663-27-1) was purchased from MedChemExpress. Human anti-CD26

polyclonal antibody (cat. no. 29403-1-AP), human anti-FAP polyclonal antibody (cat. no. 11779-1-AP), human anti-caspase-3 polyclonal antibody (cat. no. 19677-1-AP), HRP-conjugated goat anti-rabbit IgG (H+L) secondary antibody (cat. no. SA00001-2) and human anti-cleaved caspase 3 polyclonal antibody (cat. no. 25128-1-AP) were purchased from Proteintech Group, Inc. Pomalidomide-PEG2-FAP2286: FAP-D was obtained from Shanghai Apeptide Co., Ltd. Protein extraction kit (cat. no. R0018M), Cell-Counting Kit-8 (CCK-8; cat. no. c0038), radioimmunoprecipitation assay buffers (cat. no. P0013B) and bicinchoninic acid (BCA) protein concentration assay kit (cat. no. P0012) were purchased from Beyotime Institute of Biotechnology. NCI-H1299 cells (cat. no. SCSP-589) were purchased from National Collection of Authenticated Cell Cultures. All other reagents, chemicals and cell lines were local.

Molecular docking. Molecular docking was performed using AutoDock Vina 1.2.0 (19). Concerning the docking parameters of the receptor, the center coordinates of the docking box (center X, center Y and center Z) were set to (38.034, 0.53 and 69.455). The number of grid points in each direction of XYZ was set to 60x60x60, the docking accuracy exhaustiveness was 25 and the output binding conformation was set to 100. The docking results were visualized using PyMOL (version 2.5.0) (20) and LigPlot+(version 2.3) (21). The structure of human FAP alpha was obtained from Protein Data Bank (https://www.rcsb.org/structure/1Z68).

Protein degradation. NCI-H1299 cells ($5x10^5$ cells/ml) were cultured in 96-well plates. FAP-D was added to each well (Final concentrations: 0.01, 0.05, 0.1, 0.25, 0.5, 1, 5, 10 and 20 μM), and cells were cultured at 37˚C for 12 h. Then, proteins were extracted from cells for western blotting. The protocols assessing the effects of FAP-D on protein degradation in H460 cells and effects of time on protein degradation were similar.

CCK-8 assay. H1299 cells ($1x10^5$ cells/ml) were cultured in 96-well plates. FAP-D was added to each well (final concentrations: 0.5, 1, 5, 10 and 20 μM), and cells were cultured at 37˚C for 24 h. Then, the culture medium was discarded, and cell viability was determined according to the standard CCK-8 assay protocol using the EnVision microplate reader (Revvity, Inc.). For half-maximal inhibitory concentration (IC_{50}) assessment, FAP-D (0 or 5 μM) was added to each well, and cells were cultured at 37˚C for 12 h. The culture medium was discarded, and cisplatin was added to each well (final concentrations: 0.01, 0.05, 0.1, 0.5, 1, 5, 10, 50, 100, and 500 μM), after which cells were cultured at 37˚C for 12 h. After discarding the culture medium, cell viability was determined according to the standard CCK-8 assay protocol using the EnVision microplate reader. Volume of CCK-8 used was 20 μl and the solutions were incubated at 37˚C for 2 h. The absorbance at 450 nm of solutions cultured without drugs was defined as 100%. The protocols of effects of FAP-D and cisplatin + FAP-D on cell viabilities of H460 cells were similar. Unless otherwise stated, all experiments were repeated three times.

Wound-healing assay. H1299 or H460 cells were cultured in serum-free medium without/with cisplatin (5 μM, 24 h) or cisplatin (5 μM) + FAP-D (5 μM; cells were cultured with FAP-D for 12 h and then with cisplatin for 12 h). Cells were then cultured to confluence and scratched with a cell scraper. The debris was removed via washes with the culture medium. The cells were subsequently cultured in an incubator for 24 h. The images were acquired by microscopy and analyzed using ImageJ software (version 1.52a; National Institutes of Health).

Western blotting. The samples were prepared according as follows: cells were lysed using the radioimmunoprecipitation assay buffers and the solutions were centrifuged (14,000 x g 10 min). The protein concentrations were obtained using BCA assay. The samples were separated through 10% sodium dodecyl sulfate polyacrylamide gel electrophoresis and then transferred onto polyvinylidene difluoride membranes (transfer current set to 250 mA). The membranes were blocked in 5% milk at room temperature for 1 h, and then were incubated with primary antibodies (FAP antibody: Dilution, 1:1,000; CD26 antibody: Dilution, 1:1,500; caspase-3 antibody: Dilution, 1:1,000; and cleaved caspase 3 antibody: Dilution, 1:1,000) at 4˚C. Membranes were then washed with Tris-buffered saline with Tween-20 (0.05%) buffer and incubated with horseradish peroxidase-modified secondary antibodies (1:10,000) at room temperature for 1 h. Lastly, the membranes were imaged through Amersham™ ImageQuant™ 800 western blot imaging systems. The densitometric analysis were performed from ImageJ software (1.52a; National Institutes of Health)

Animal experiments. The animal experiments were approved by the institutional animal ethics committee of Kunming Medical University (approval no. kmmu20241355; Kunming, China). BALB/c mice were purchased from the Department of Experimental Zoology, Kunming Medical University (Kunming, China). All clinical procedures were conducted in accordance with the relevant provisions of the Declaration of Helsinki. The studies were additionally conducted in accordance with local legislation and institutional requirements. Body weights of mice were ~18-19 g (healthy, 5-6 weeks old). Mice were fed at 25˚C in the standard animal experiment lab and the humidity were maintained at 53%. The feeds and water were replaced every 3 days. The light/dark cycle was set as 12 h light/12 h dark. For biosafety experiments, BALB/c mice were randomly divided into two groups (n=5/group): PBS (control) group and FAP-D group. Mice in the FAP-D group were first anesthetized with 3% isoflurane via inhalation and then intraperitoneally injected with FAP-D (3 mg/kg, once daily for 7 days). Mice in the control group were first anesthetized with 3% isoflurane via inhalation and then intraperitoneally injected with phosphate-buffered saline (PBS). After treatment, mice were sacrificed via spinal dislocation, and the major organs were collected for analysis. For intervention experiments, nude BALB/c mice were randomly divided into three groups (n=6/group): PBS (control) group, cisplatin group, and cisplatin + FAP-D group. The mice were first subcutaneously injected with H1299 cells ($5x10^6$ cells, 100 μl, in the right sides of the mice back) and monitored for 10 days to permit tumor growth. After tumor formation, mice in the cisplatin group were first anesthetized with 3% isoflurane via inhalation and then intratumorally injected with cisplatin (20 mg/kg, once every 3 days, 3 times). Then, the body weight and volume were recorded every 3 days. After treatment, mice

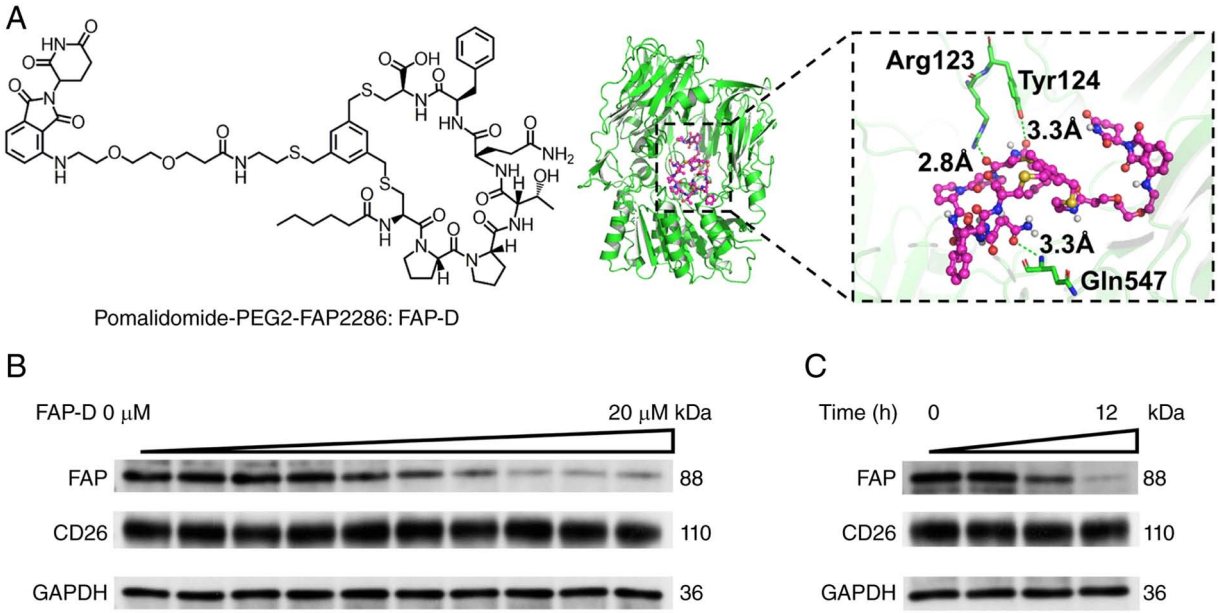

Figure 1. (A) Chemical formula of FAP-D and the binding model between FAP-D and FAP (PDB: 1z68). (B) Western blotting of FAP (n=3) and CD26 expression in H1299 cells treated with different concentrations of FAP-D (0, 0.01, 0.05, 0.1, 0.25, 0.5, 1, 5, 10 and 20 μM) for 12 h. (C) Western blotting of FAP (n=3) and CD26 expression in H1299 cells treated with 5 μM FAP-D for 0, 3, 6, or 12 h. FAP, fibroblast activation protein; FAP-D, FAP degrader.

were sacrificed via spinal dislocation, and the tumors were weighed and then sliced or mashed for further experiments. Mice in the cisplatin + FAP-D group were first anesthetized with 3% isoflurane via inhalation and then intratumorally injected with FAP-D (1.5 mg/kg, once every 3 days, three times), followed by an intraperitoneal injection of cisplatin (20 mg/kg, once every 3 days, three times) after 12 h. Mice were euthanized after 21 days or upon reaching tumor volume ≥2.000 mm^3 or >20% body weight loss, with tumors processed for analysis. The other protocols were similar.

Statistical analysis. Statistical analysis was performed using GraphPad Prism 9.0 (Dotmatics) and Origin 9 software (OriginLab Corporation). All data are determined from at least three independent experiments and presented as the mean ± standard deviation (SD). Statistical significance was assessed by ANOVA followed by Dunnett post-hoc test. $P<0.05$ was considered to indicate a statistically significant difference.

Results

FAP degradation. FAP-D consisted of three components: Pomalidomide, the FAP-binding peptide FAP 2286, and a linker (Diethylene glycol, Fig. 1A). The results of high-performance liquid chromatography and mass spectrometry are presented in Figs. S1 and S2. Molecular docking exhibited that several hydrophobic interactions and hydrogen bonds were formed between FAP-D and FAP (Figs. 1A and S3). Specifically, Arg123, Tyr124 and Gln547 in FAP formed hydrogen bonds with oxygen atoms in FAP-D. Trp623, Leu571, Ala554, Val552, Ile367, Phe350, Phe579, Gly349, Phe351, Val352, Ala207 and Ile398 in FAP formed hydrophobic interactions with FAP-D. The binding energy between FAP-D and FAP was -10.484 kcal/mol. These results suggested the binding force between FAP-D and FAP was strong. Western blotting demonstrated that FAP degradation increased as the FAP-D concentration increased (Figs. 1B and S4). Conversely, CD26 was not degraded by FAP-D, supporting the selectivity of FAP-D. In addition, FAP was degraded by FAP-D within 12 h (Figs. 1C and S5). These findings indicate that FAP-D is an ideal FAP degrader.

Enhancement of the cisplatin sensitivity of H1299 cells by FAP-D. Considering the degradation performance of FAP-D, its effect on the cisplatin sensitivity of H1299 cells was explored. First, the effects of FAP-D on H1299 cell viability were studied. As presented in Fig. 2A, the viability of H1299 cells was reduced from 100 to 80% in response to increasing FAP-D concentration, suggesting that FAP degradation has little effect on cell viability. Second, FAP degradation was found to reduce the IC_{50} of cisplatin in H1299 cells (1.36 μM vs. 5.71 μM, Fig. 2B), indicating enhanced cisplatin sensitivity. In addition, the mobility of H1299 cells treated with cisplatin + FAP-D was reduced (Fig. 2C and D). This result suggested that the extracellular matrix, which is responsible for proliferation and migration, was destroyed by FAP-D, leading to reduced cell viability. Lastly, the expression of cleaved caspase 3 (a major index of apoptosis) was increased by treatment with cisplatin + FAP-D (Figs. 2E and S6). These results reveal that the cisplatin sensitivity of H1299 cells was enhanced by FAP-D, resulting in strengthened apoptosis. Similarly, these results were confirmed through H460 cells (Figs. S7A-E and S8).

Therapeutic effects of cisplatin + FAP-D in vivo. The *in vivo* therapeutic effects of cisplatin + FAP-D were then studied. First, the potential *in vivo* toxicity of FAP-D was investigated. As presented in Fig. 3, no damage was observed in the major organs (heart, liver, spleen, lungs and kidneys) of mice treated with FAP-D, indicating its favorable biocompatibility.

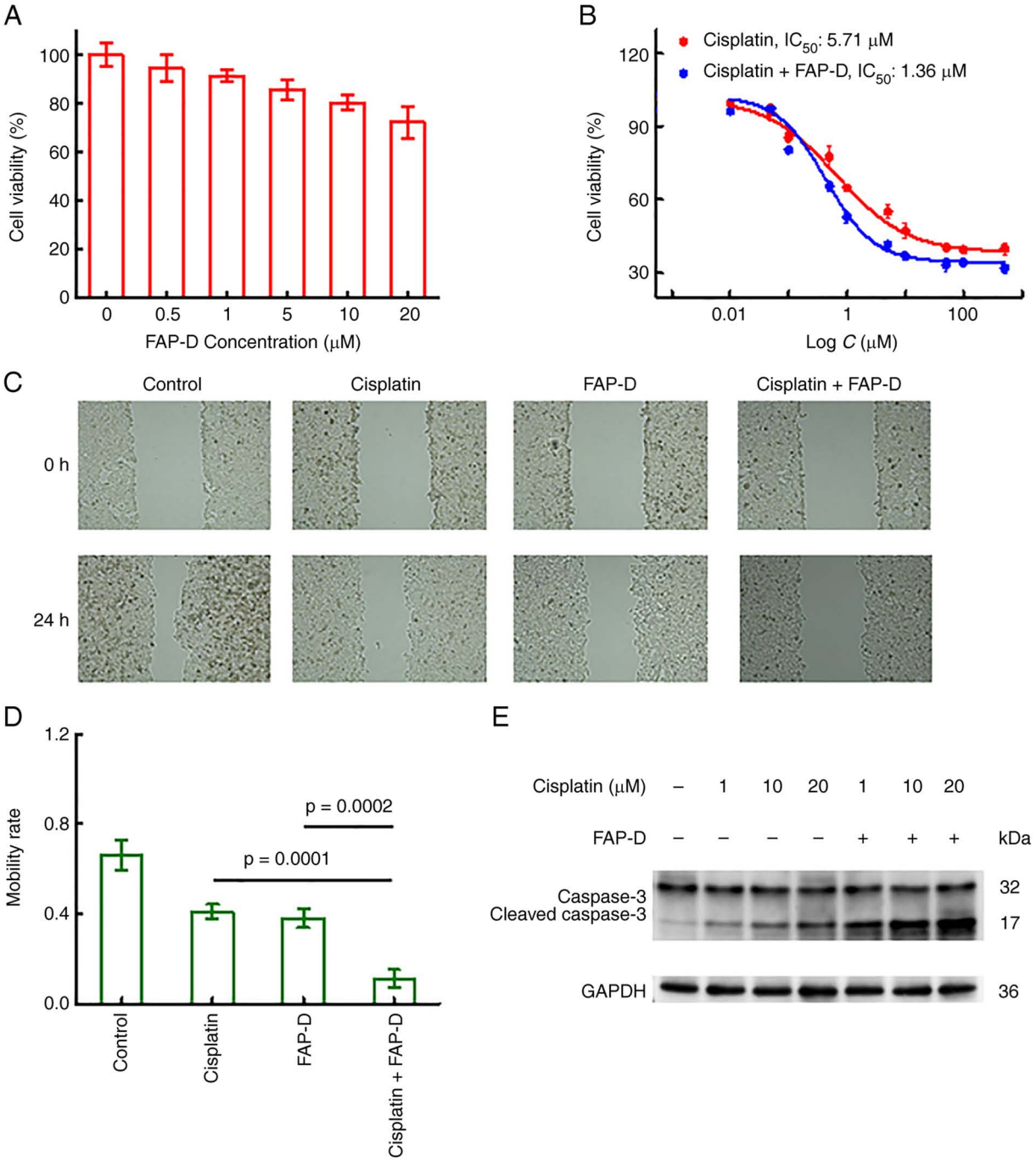

Figure 2. (A) Effect of different concentrations of FAP-D (24 h of treatment) on H1299 cell viability. (B) Effects of cisplatin or cisplatin + FAP-D concentrations (treatment for 24 h) on H1299 cell viabilities. (C) Images of wounded H1299 cells in the different groups. Conditions: cisplatin (5 μM, 24 h), FAP-D (5 μM, 24 h), and cisplatin + FAP-D (5 μM FAP-D for 12 h followed by 5 μM cisplatin for 12 h). (D) The statistical results from 2C. ANOVA test (n=3). (E) Western blotting of caspase 3 and cleaved caspase 3 (Cle. Cas 3, n=3) expression in different groups of H1299 cells. Cells were treated with cisplatin (1, 10, or 20 μM, 24 h) or cisplatin + FAP-D (5 μM FAP-D for 12 h followed by 1, 10, or 20 μM cisplatin for 12 h). FAP, fibroblast activation protein; FAP-D, FAP degrader.

After confirming the biocompatibility of FAP-D, the *in vivo* therapeutic effects of cisplatin + FAP-D were systematically examined. As illustrated in Fig. 4A, the tumor volumes of mice treated with cisplatin alone were smaller than those in control mice. Interestingly, tumor growth was inhibited in mice pre-treated with FAP-D, as confirmed by tumor weight (Fig. 4B). Moreover, H&E and TUNEL staining revealed that apoptosis was enhanced in the tumors of mice co-treated with FAP-D (Fig. 4C and D). In addition, no significant changes in body weights were observed (Fig. S9). These results reveal that apoptosis was enhanced by FAP-D in tumors.

Discussion

Cisplatin resistance has become a serious issue in NSCLC (22-24), which can be overcome by combination treatment strategies (15). In the past, a high response rate with modest side effects could be achieved in stage IIIB and IV NSCLC by the combination of gemcitabine and cisplatin (25).

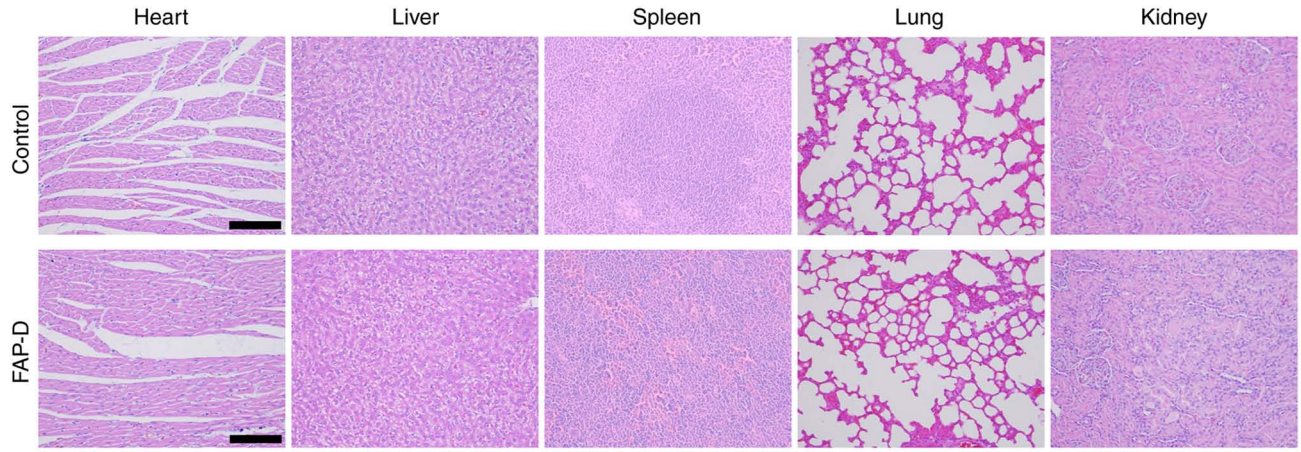

Figure 3. Images of heart, liver, spleen, lung and kidney tissue from mice treated without or with FAP-D. Scale bar, 50 μm. Magnification, x100. FAP-D, fibroblast activation protein-degrader.

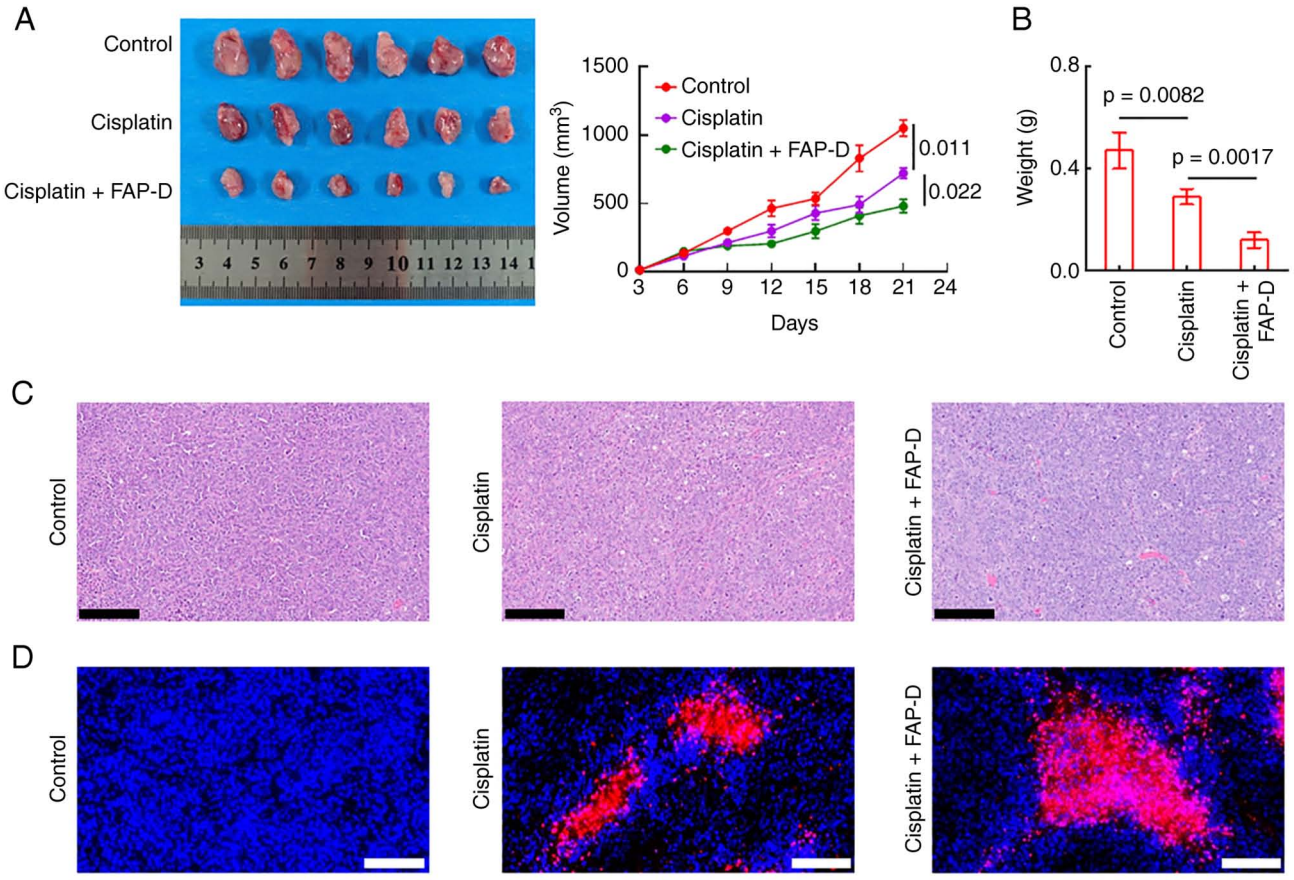

Figure 4. (A) Left: tumors from mice in the control, cisplatin and cisplatin + FAP-D group. Right: the tumor volumes of mice in the different groups. (n=6). (B) Tumor weights of mice in the different groups (n=6/group; ANOVA test). (C) H&E staining results of tumors from mice in the different groups. Scale bar, 50 μm. (D) TUNEL staining results of tumors from mice in the different groups. Scale bar, 20 μm. Magnification, x200. FAP-D, fibroblast activation protein-degrader.

Additionally, cisplatin-etoposide combination chemotherapy achieved success (26). Meanwhile, combinations of traditional Chinese medicine and cisplatin have emerged as effective strategies (27,28). Moreover, the treatment efficacy of chemotherapy can be strengthened by targeting FAP (17,18). In light of the development of nanotechnology in recent years, novel nanoparticles co-loaded with cisplatin and oridonin were developed for NSCLC treatment (29). Unfortunately, treatment efficacy can be restricted by resistance or side effects from other drugs. Thus, an auxiliary medicine with low drug resistance is urgently needed for cisplatin-based combination regimens.

Protein degraders with the advantages of high selectivity, catalytic dosages and extremely low drug resistance (30,31) are ideal candidates for this purpose. In the present study, a

FAP-D was pioneered instead of a FAP inhibitor to eliminate side effects. FAP was degraded by FAP-D with excellent selectivity (Fig. 1). As expected, the IC_{50} of cisplatin in H1299 cells was lowered by combined treatment with FAP-D (Fig. 2), suggesting enhanced cisplatin sensitivity. In addition, H1299/H460 cell apoptosis was strengthen by this combination strategy (Figs. 2 and S7) and FAP-D exhibited favorable biocompatibility (Fig. 3). *In vivo*, apoptosis in tumors was more strongly induced in mice co-treated with FAP-D (Fig. 4). Compared with previous results (32), the dosage of FAP-D used in the present study was lower, and the biocompatibility was excellent, highlighting the advantages of FAP-D.

In the present study, the therapeutic effects of cisplatin + FAP-D on H1299 cells and heterogeneous tumors were investigated systematically. The results demonstrated that the cisplatin sensitivity of H1299 cells and tumors was enhanced by co-treatment with FAP-D. The present findings revealed the great clinical utility of cisplatin + FAP-D for NSCLC treatment.

The present study establishes a link between FAP-D co-treatment and enhanced cisplatin sensitivity in NSCLC. However, several limitations exist: The therapeutic effects of such method on the organoids models are lack. Moreover, patient-derived tumor xenograft models are also worth exploring. Finally, the deep molecular mechanism of the role of the cisplatin + FAP-D needs to be investigated. All the aforementioned approaches represent important directions for our future investigations.

Acknowledgements

The authors would like to thank Dr Joe Barber Jr. from Liwen Bianji (Edanz) (www.liwenbianji.cn) for editing the English text of a draft of this manuscript.

Funding

The present study was supported by the Doctoral Research Fund Project of the First Affiliated Hospital of Kunming Medical University (grant nos. 2022BS031 and 2023BS013), the Yunnan Provincial Department of Education Science Research Fund Projects (grant nos. 2025J0175 and 2025J0177), the Yunnan Fundamental Research Kunming Medical University Projects (grant nos. 202501AY070001-063 and 202301AY070001-205), the Key Clinical Specialty of Thoracic Surgery in Yunnan (grant no. 300067-3) and the Science and Technology Department of Yunnan (grant no. 202401AT070066).

Availability of data and materials

The data generated in the present study are included in the figures and/or tables of this article.

Authors' contributions

YZ, RL, XC and CZ conducted all experiments and analyzed the data. YZ, RL, XC, CZ, YB, YC, XT and TX assisted in data acquisition, data analysis and drafted the manuscript. XY and JY performed the MD assays and assisted in data analysis. YZ and XY designed the project and acquired funding. YZ, RL and XY confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The animal experiments were permitted by the institutional animal ethics committee of Kunming Medical University (approval no. kmmu20241355; Kunming, China). All clinical procedures were conducted in accordance with the relevant provisions of the Declaration of Helsinki. The studies were conducted in accordance with the local legislation and institutional requirements.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Hendriks LEL, Remon J, Faivre-Finn C, Garassino MC, Heymach JV, Kerr KM, Tan DSW, Veronesi G and Reck M: Non-small-cell lung cancer. Nat Rev Dis Primers 10: 71, 2024.
2. Travis WD, Brambilla E and Riely GJ: New pathologic classification of lung cancer: Relevance for clinical practice and clinical trials. J Clin Oncol 31: 992-1001, 2013.
3. Barta JA, Powell CA and Wisnivesky JP: Global epidemiology of lung cancer. Ann Glob Health 85: 8, 2019.
4. Araghi M, Mannani R, Heidarnejad Maleki A, Hamidi A, Rostami S, Safa H, Faramarzi F, Khorasani S, Alimohammadi M, Tahmasebi S and Akhavan-Sigari R: Recent advances in non-small cell lung cancer targeted therapy; an update review. Cancer Cell Int 23: 162, 2023.
5. Howington JA, Blum MG, Chang AC, Balekian AA and Murthy SC: Treatment of stage I and II non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 143 (Suppl 5): e278S-e313S, 2013.
6. Zhao YS, Guo SP, Deng J, Shen J, Du FK, Wu X, Chen Y, Li MX, Chen MJ, Li XB, *et al*: VEGF/VEGFR-targeted therapy and immunotherapy in non-small cell lung cancer: Targeting the tumor microenvironment. Int J Biol Sci 18: 3845-3858, 2022.
7. Lind JSW and Smit EF: Angiogenesis inhibitors in the treatment of non-small cell lung cancer. Ther Adv Med Oncol 1: 95-107, 2009.
8. Le XN, Nilsson M, Goldman J, Reck M, Nakagawa K, Kato T, Ares LP, Frimodt-Moller B, Wolff K, Visseren-Grul C, *et al*: Dual EGFR-VEGF pathway inhibition: A promising strategy for patients with EGFR-mutant NSCLC. J Thorac Oncol 16: 205-215, 2021.
9. Fu K, Xie FC, Wang F and Fu LW: Therapeutic strategies for EGFR-mutated non-small cell lung cancer patients with osimertinib resistance. J Hematol Oncol 15: 173, 2022.
10. Passaro A, Mok T, Peters S, Popat S, Ahn MJ and Marinis FD: Recent advances on the role of EGFR tyrosine kinase inhibitors in the management of NSCLC with uncommon, non exon 20 insertions, EGFR mutations. J Thorac Oncol 16: 764-773, 2021.
11. Ellis PA, Smith IE, Hardy JR, Nicolson MC, Talbot DC, Ashley SE and Priest K: Symptom relief with MVP (mitomycin C, vinblastine and cisplatin) chemotherapy in advanced non-small-cell lung cancer. Br J Cancer 71: 366-370, 1995.
12. Cosaert J and Quoix E: Platinum drugs in the treatment of non-small-cell lung cancer. Br J Cancer 87: 825-833, 2002.
13. Goffin J, Lacchetti C, Ellis PM, Ung YC and Evans WK; Lung Cancer Disease Site Group of Cancer Care Ontario's Program in Evidence-Based Care: First-line systemic chemotherapy in the treatment of advanced non-small cell lung cancer: A systematic review. J Thorac Oncol 5: 260-274, 2010.

14. Fennell DA, Summers Y, Cadranel J, Benepal T, Christoph DC, Lal R, Das M, Maxwell F, Visseren-Grul C and Ferry D: Cisplatin in the modern era: The backbone of first-line chemotherapy for non-small cell lung cancer. Cancer Treat. Rev 44: 42-50, 2016.
15. Yao YF, Fareed R, Zafar A, Saleem K, Huang T, Duan YT and Rehman MU: State-of-the-art combination treatment strategies for advanced stage non-small cell lung cancer. Front Oncol 12: 958505, 2022.
16. Fitzgerald AA and Weiner LM: The role of fibroblast activation protein in health and malignancy. Cancer Metast Rev 39: 783-803, 2020.
17. Lee HH and Al-Ogaili Z: Fibroblast activation protein and the tumour microenvironment: Challenges and therapeutic opportunities. Oncol Rev 19: 1617487, 2025.
18. Wang Q, Song C, Zhao CY, Wei XY, Li DL, Wu QT, Li J and Yang XM: Decoding tumors from fibroblast activation protein: A review of the latest diagnostic and therapeutic prospects. Int J Biol Macromol 318: 145006, 2025.
19. Eberhardt J, Santos-Martins D, Tillack AF and Forli S: AutoDock Vina 1.2.0: New docking methods, expanded force field, and python bindings. J Chem Inf Model 61: 3891-3898, 2021.
20. DeLano WL: PyMOL: An open-source molecular graphics tool. CCP4 Newsletter on Protein Crystallography 40: 82-92, 2002. https://www.scirp.org/reference/ReferencesPapers?ReferenceID=2323923
21. Laskowski RA and Swindells MB: LigPlot+: Multiple ligand-protein interaction diagrams for drug discovery. J Chem Inf Model 51: 2778-2786, 2011.
22. Kurokawa M, Ise N, Omi K, Goishi K and Higashiyama S: Cisplatin influences acquisition of resistance to molecular-targeted agents through epithelial-mesenchymal transition-like changes. Cancer Sci 104: 904-911, 2013.
23. Skowron MA, Oing C, Bremmer F, Ströbel P, Murray MJ, Coleman N, Amatruda JF, Honecker F, Bokemeyer C, Albers P and Nettersheim D: The developmental origin of cancers defines basic principles of cisplatin resistance. Cancer Lett 519: 199-210, 2021.
24. Liu SX, Yang PS, Wang L, Zou XF, Zhang DD, Chen WY, Hu C, Xiao DQ, Ren HZ, Zhang H and Cai SW: Targeting PAK4 reverses cisplatin resistance in NSCLC by modulating ER stress. Cell Death Discov 10: 36, 2024.
25. Crinò L, Scagliotti G, Marangolo M, Figoli F, Clerici M, Marinis FD, Salvati F, Cruciani G, Dogliotti L, Pucci F, *et al*: Cisplatin-gemcitabine combination in advanced non-small-cell lung cancer: A phase II study. J Clin Oncol 15: 297-303, 1997.
26. Ardizzoni A, Antonelli G, Grossi F, Tixi L, Cafferata M and Rosso R: The combination of etoposide and cisplatin in non-small-cell lung cancer (NSCLC). Ann Oncol 10 (Suppl 5): S13-S17, 1999.
27. Zhao CC, Yan HF, Pang WT, Wu T, Kong XB, Li XJ, Liu HG, Zhao LL, Liang F and Jia YJ: Lentinan combined with cisplatin for the treatment of non-small cell lung cancer. Medicine (Baltimore) 100: e25220, 2021.
28. Xi ZC, Dai RC, Ze YF, Jiang X, Liu MF and Xu HX: Traditional Chinese medicine in lung cancer treatment. Mol Cancer 24: 57, 2025.
29. Fan XL, Wang T, Ji ZY, Li QP, Shen HY and Wang J: Synergistic combination therapy of lung cancer using lipid-layered cisplatin and oridonin co-encapsulated nanoparticles. Biomed Pharmacother 141: 111830, 2021.
30. Zhong GC, Chang XY, Xie WL and Zhou XX: Targeted protein degradation: Advances in drug discovery and clinical practice. Signal Transduct Target Ther 9: 308, 2024.
31. Martín-Acosta P and Xiao XS: PROTACs to address the challenges facing small molecule inhibitors. Eur J Med Chem 210: 112993, 2021.
32. Cho JM, Yang EH, Quan WY, Nam EH and Cheon HG: Discovery of a novel fibroblast activation protein (FAP) inhibitor, BR103354, with anti-diabetic and anti-steatotic effects. Sci Rep 10: 21280, 2020.

Copyright © 2026 Zhou et al. This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) License.