RESEARCH PAPER

Hyaluronic acid-modified PLGA nanoparticles encapsulating METTL14 siRNA enhance sunitinib sensitivity in drug-resistant renal cell carcinoma

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ABSTRACT

Objective(s): Sunitinib resistance remains a major obstacle in the treatment of renal cell carcinoma (RCC). This study sought to construct a targeted nanoparticle-based delivery system for silencing methyltransferase-like 14 (METTL14), with the aim of restoring drug responsiveness in resistant RCC.

Methods: Hyaluronic acid-functionalized poly (lactic-co-glycolic acid) nanoparticles (HA-PLGA-NPs) were engineered to encapsulate METTL14 siRNA. Their physicochemical characteristics, targeting capability toward CD44-positive sunitinib-resistant RCC cells (786-O-SUR and ACHN-SUR), and therapeutic performance were systematically evaluated in vitro. Transcriptomic analysis was conducted to investigate underlying mechanisms. Antitumor efficacy and biosafety were further examined in a xenograft mouse model.

Results: The fabricated nanoparticles displayed uniform morphology, appropriate particle size, and high siRNA encapsulation efficiency (>88%), along with favorable stability. HA modification significantly improved cellular uptake in CD44-positive resistant cells compared with non-targeted nanoparticles. Delivery of METTL14 siRNA via HA-PLGA-NPs markedly reduced the IC50 of sunitinib, increased apoptotic cell death, and effectively reversed drug resistance. In vivo, treatment with HA-PLGA (METTL14 siRNA)-NPs led to substantial tumor growth inhibition. RNA sequencing indicated that METTL14 silencing was associated with pathways involved in apoptosis, cell cycle regulation, and immune-related processes. No obvious systemic toxicity was observed.

Conclusion: HA-PLGA nanoparticles provide an effective and selective platform for METTL14 siRNA delivery, enabling reversal of sunitinib resistance in RCC models. This approach offers a potential therapeutic strategy for overcoming drug resistance in renal cell carcinoma.

Keywords: *Renal Cell Carcinoma; Drug Resistance; Nanoparticles; RNA, Small Interfering; Methyltransferases*

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INTRODUCTION

Renal cell carcinoma (RCC) represents the predominant histological subtype of kidney cancer and arises mainly from renal tubular epithelial cells, accounting for nearly 80–90% of all renal malignancies worldwide (1). Although improvements in diagnostic imaging have increased the detection of early-stage tumors, a substantial number of patients still progress to metastatic disease or experience recurrence

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after surgery, which continues to limit long-term survival outcomes (2). Moreover, RCC exhibits intrinsic resistance to conventional radiotherapy and cytotoxic chemotherapy, creating persistent challenges in the treatment of advanced disease (3, 4).

Sunitinib has been extensively used as a standard targeted therapy for patients with advanced, recurrent, or unresectable RCC because of its inhibitory effects on multiple receptor tyrosine kinases (5). However, the clinical benefit of sunitinib is often temporary, as many patients eventually develop acquired resistance during treatment. Previous studies have shown that resistance may involve multiple biological processes, including adaptive angiogenesis, epigenetic alterations, activation of compensatory signaling pathways, drug transport mechanisms, cancer stemness, and autophagy-related responses (6). Identifying effective strategies to overcome this resistance therefore remains an important research priority.

Recent studies have highlighted the role of epitranscriptomic regulation in cancer progression. Among RNA modifications, N6-methyladenosine (m6A) is recognized as the most abundant internal modification in messenger RNA (7). METTL14 functions as a critical catalytic component of the m6A methyltransferase complex and has been reported to exert either tumor-promoting or tumor-suppressive effects depending on the biological context (8). In RCC, METTL14-mediated m6A regulation has been implicated in the development of sunitinib resistance through stabilization of resistance-associated transcripts such as TRAF1 (9). These findings suggest that METTL14 may serve as a potential therapeutic target for sensitizing resistant tumors.

Nanotechnology-based delivery platforms have provided new opportunities for improving the therapeutic application of siRNA molecules (10). PLGA nanoparticles are particularly attractive because of their biodegradability, biosafety, and drug-loading capacity. To further improve tumor selectivity, hyaluronic acid (HA) can be introduced onto nanoparticle surfaces to exploit its affinity for CD44, a receptor frequently upregulated in RCC cells (11, 12). This design may enhance siRNA stability during circulation while improving selective uptake by tumor cells (13).

In this study, we established an HA-functionalized PLGA nanoparticle system for METTL14 siRNA delivery and investigated its ability to restore sunitinib responsiveness in resistant RCC models. The physicochemical properties, tumor-targeting capacity, therapeutic efficacy, and biosafety of this platform were systematically evaluated in both cellular and animal experiments. Our results support the feasibility of combining RNA interference with targeted nanomedicine for overcoming therapeutic resistance in RCC.

MATERIALS AND METHODS

Preparation of siRNA-loaded PLGA nanoparticles

PLGA-based nanoparticles containing siRNA were generated using a double emulsion solvent evaporation approach (water/oil/water). In brief, siRNA solution (160 μg, 4 OD) was first dispersed in the internal aqueous phase. This phase was then mixed with dichloromethane containing 60 mg PLGA and subjected to probe sonication under ice-bath conditions to obtain a primary emulsion.

The resulting emulsion was subsequently transferred into an aqueous phase containing 2% PVA and homogenized to form a secondary emulsion. Organic solvent removal was achieved by continuous stirring at room temperature overnight. Nanoparticles were recovered through centrifugation and repeatedly washed with distilled water.

For surface modification, the purified particles were incubated with dilute HA solution (0.1%) under gentle stirring for several hours. After coating, nanoparticles were collected by centrifugation and finally dispersed in PBS.

Physicochemical characterization

Particle diameter and surface charge were analyzed by dynamic light scattering. Morphology was observed using transmission electron microscopy after sample preparation.

For release profiling, nanoparticles were suspended in PBS (pH 7.4) and incubated at physiological temperature under agitation. At selected time points, supernatants were collected and replaced with fresh buffer. Released siRNA content was quantified using UV-based measurement.

Serum stability was tested by incubating free siRNA and nanoparticle-encapsulated siRNA in 50% fetal bovine serum at 37°C. Samples were analyzed on agarose gel to evaluate nucleic acid integrity.

Encapsulation efficiency analysis

siRNA loading was quantified using ion-pair reversed-phase HPLC. Nanoparticles were first

dissolved in DMSO to release entrapped siRNA, followed by centrifugation and filtration.

Chromatographic separation was performed on a C18 column using TEAA buffer and acetonitrile as mobile phases under gradient elution. Detection was carried out at 260 nm. Encapsulation efficiency and loading capacity were calculated based on calibration curves.

Cell culture

Human RCC cell lines 786-O and ACHN were maintained in standard culture media (RPMI-1640 or DMEM) supplemented with 10% fetal bovine serum. All cell lines were obtained from ATCC and cultured under humidified conditions at 37°C with 5% CO_2.

Generation of sunitinib-resistant cells

Drug-resistant variants (786-O-SUR and ACHN-SUR) were established by repeated exposure to sunitinib. Cells were intermittently treated with 40 μM drug-containing medium for two-week cycles, alternated with drug-free culture periods. This process was repeated multiple times until stable resistance was achieved.

siRNA transfection

Fluorescently labeled and control siRNAs were synthesized commercially. Transfection into RCC cells was performed using a lipid-based reagent following the manufacturer's protocol. The METTL14 targeting sequence was GCAGCACCUCGAUCAUUUATT, while control siRNA had a scrambled sequence (UUCUCCGAACGUGUCACGUTT).

Cell viability assay

Cells were seeded into 96-well plates and allowed to adhere. After treatment with different formulations and sunitinib, cell viability was assessed using CCK-8 reagent according to standard procedures. Absorbance was measured using a microplate reader.

Apoptosis detection

After treatment, cells were collected, washed, and stained with Annexin V-FITC and propidium iodide. Flow cytometric analysis was performed to quantify apoptotic populations.

Animal experiments

A total of 42 NSG mice (6-8 weeks old) were purchased from SHANG HAI MODEL ORGANISMS (Shanghai, China). The mice were randomly allocated into 7 treatment groups. All animal experiments were approved by Institutional Animal Ethics Committee at Anhui University of Science and Technology (Permit Number: LW2022-016). NSG mice were randomly assigned to experimental groups. RCC cells were injected under the renal capsule to establish orthotopic tumors. Treatments were administered via tail vein at scheduled intervals. Tumor progression was monitored using in vivo imaging, and animals were sacrificed at endpoint for analysis.

Immunofluorescence

For immunofluorescence analysis, specimens underwent fixation and permeabilization prior to blocking treatment. Primary antibody incubation was performed overnight at 4°C, after which fluorophore-conjugated secondary antibodies were introduced. Nuclear staining was achieved using DAPI, and images were acquired with a fluorescence imaging system.

Statistical analysis

Data analysis was performed using GraphPad Prism. Differences between groups were evaluated using t-tests or one-way ANOVA. Results are presented as mean ± SEM, and statistical significance was defined as $P < 0.05$.

RESULTS

Characterization and biological evaluation of HA-coated PLGA nanoparticles loaded with siRNA

Because CD44 is frequently elevated in malignant cells, hyaluronic acid has been extensively used as a ligand to improve nanoparticle selectivity. HA is a naturally derived polysaccharide composed of repeating disaccharide structures and has been implicated in multiple biological activities, including cell adhesion, proliferation, and migration (14, 15). Based on these characteristics, we employed PLGA as the nanoparticle core and introduced HA surface modification to construct a METTL14 siRNA delivery platform.

Four formulations, including PLGA-NPs, PLGA(siRNA)-NPs, HA-PLGA-NPs, and HA-PLGA(siRNA)-NPs, were analyzed for their physicochemical characteristics. Particle diameter and zeta potential measurements are shown in Figure 1A–B. HPLC quantification demonstrated efficient siRNA incorporation in both nanoparticle systems, with encapsulation efficiencies of 88.0% for PLGA-NPs and 88.9%

for HA-PLGA-NPs (Figure 1C). Transmission electron microscopy further confirmed that the prepared nanoparticles displayed regular spherical architecture with relatively homogeneous particle distribution (Figure 1D). A summary of nanoparticle parameters is provided in Figure 1E.

The intrinsic safety of the carrier material was subsequently examined in 786-O-SUR and ACHN-SUR cells. Exposure to blank nanoparticles did not significantly alter cell viability at any tested concentration, suggesting limited carrier-associated toxicity (Figure 2A). We next examined whether nanoparticle encapsulation could improve siRNA stability in serum-containing conditions. Gel electrophoresis showed rapid degradation of free siRNA, whereas nanoparticle-loaded siRNA remained substantially preserved after serum exposure (Figure 2B), indicating that encapsulation effectively protected siRNA from degradation.

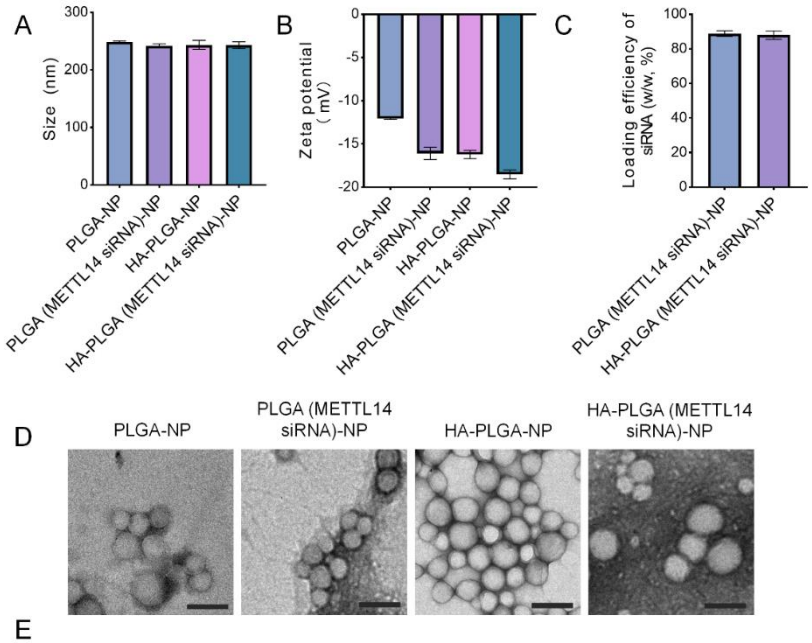
Compared with other reported carriers such as chitosan nanoparticles or antibody-based delivery systems, PLGA nanoparticles provide broader loading flexibility and favorable biosafety profiles, supporting their suitability for therapeutic applications (16-18).

HA modification improves nanoparticle uptake in CD44-expressing RCC cells

To verify whether HA functionalization could enhance tumor targeting, CD44 expression was first examined in two sunitinib-resistant RCC cell lines. Flow cytometry confirmed clear membrane expression of CD44 in both 786-O-SUR and ACHN-SUR cells (Figure 3A and B).

We next compared intracellular delivery efficiency between HA-modified nanoparticles and non-modified nanoparticles using Cy5-labeled siRNA. Fluorescence imaging demonstrated substantially stronger intracellular signals in cells treated with HA-coated nanoparticles than in those receiving conventional PLGA nanoparticles (Figure 3C & D).

These observations suggest that HA surface decoration improves nanoparticle uptake efficiency in CD44-positive resistant RCC cells and enhances intracellular siRNA delivery.



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Formulation	Mean diameter ± SD	Zeta potential ± SD	Loading efficiency of siRNA (w/w, %)	Polydispersity index
PLGA-NP	248.9±2.0	-12.1±0.2	-	0.202
PLGA (METTL14 siRNA)-NP	240.9±5.9	-16.4±1.1	88.9	0.164
HA-PLGA-NP	241.5±13.2	-16.05±0.8	-	0.105
HA-PLGA (METTL14 siRNA)-NP	241.4±10.3	-18.7±0.9	88.0	0.110

Fig. 1. Characterization of PLGA-based nanoparticles under different formulations. (A) Particle size distribution profiles. (B) Surface charge (zeta potential) measurements. (C) Encapsulation efficiency of METTL14 siRNA in nanoparticle formulations. (D) Representative TEM images showing nanoparticle morphology. (E) Summary of key physicochemical parameters. Scale bar = 200 nm.

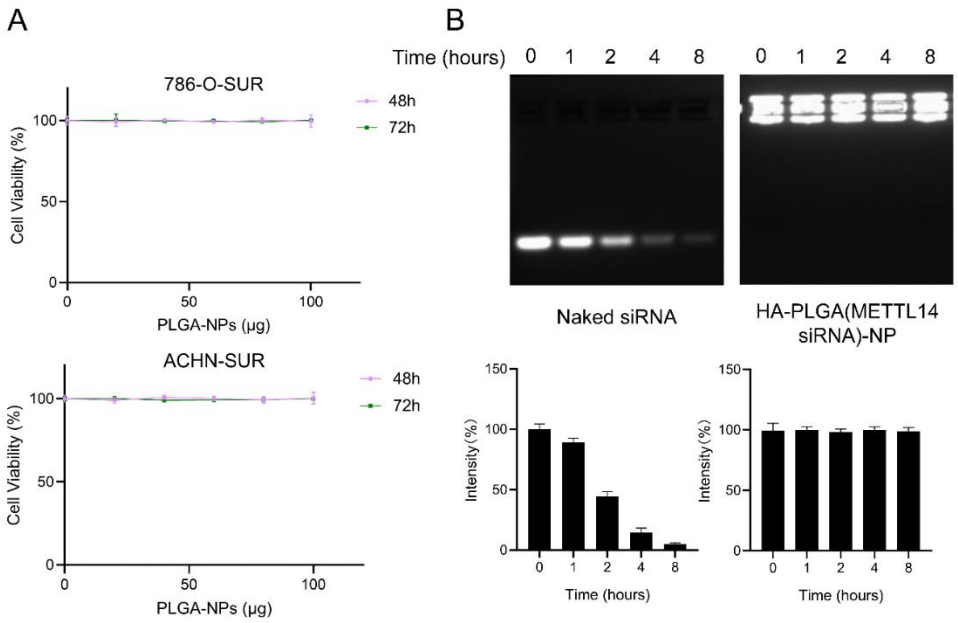

Fig. 2. Evaluation of biological properties of siRNA-loaded PLGA nanoparticles.
(A) Cell viability of RCC cells treated with HA-PLGA nanoparticles assessed using CCK-8 assay. (B) Agarose gel analysis of siRNA stability following incubation in serum-containing conditions at 37°C. (C) Electrophoretic profiles of free siRNA and nanoparticle-associated siRNA collected at indicated time points. Data are presented as mean ± SD from independent experiments.

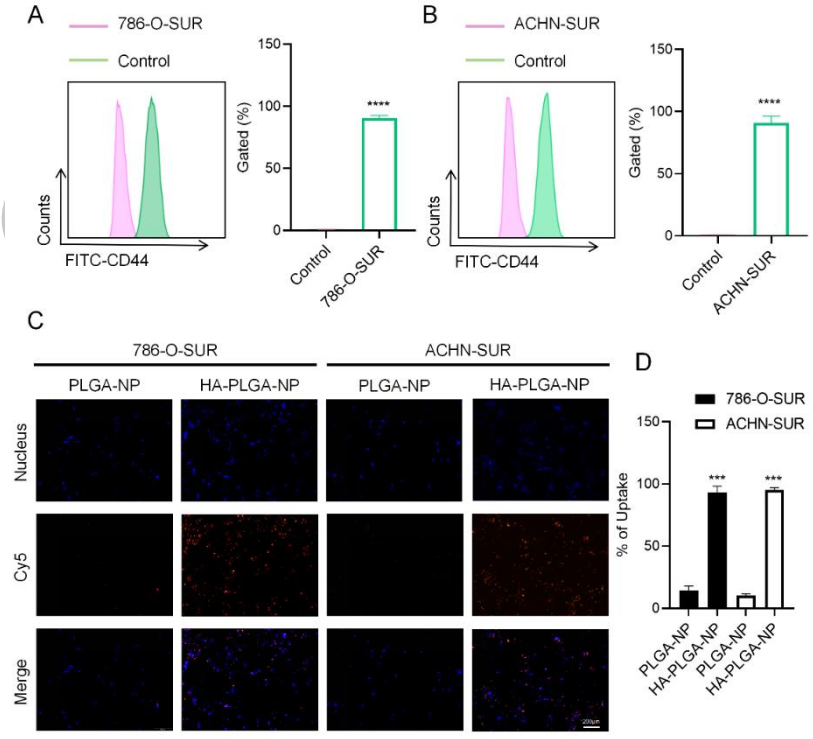

Fig. 3. Targeted delivery performance of HA-functionalized nanoparticles in CD44-enriched RCC cells. (A, B) Surface expression of CD44 in 786-O-SUR and ACHN-SUR cells was quantified by flow cytometry. (C, D) Cellular uptake of Cy5-labeled siRNA delivered by PLGA-based nanoparticles, with or without HA modification, was visualized using fluorescence microscopy. Nuclear staining is shown in blue (DAPI). Quantitative data are expressed as mean ± SD, with statistical analysis performed using one-way ANOVA (***$P < 0.001$).

METTL14 silencing restores sunitinib responsiveness in resistant RCC cells

To determine whether METTL14 inhibition could reverse drug resistance, resistant RCC cells were treated with different nanoparticle formulations followed by sunitinib exposure. Cell viability analysis showed that delivery of METTL14 siRNA through HA-PLGA nanoparticles significantly lowered the IC50 value of sunitinib compared with control nanoparticles lacking siRNA cargo (Figure 4A–B).

Apoptotic responses were further analyzed by flow cytometry. Cells treated with HA-PLGA(METTL14 siRNA)-NPs exhibited markedly higher apoptotic rates than those receiving free METTL14 siRNA alone (Figure 4C–D), indicating improved functional delivery efficiency.

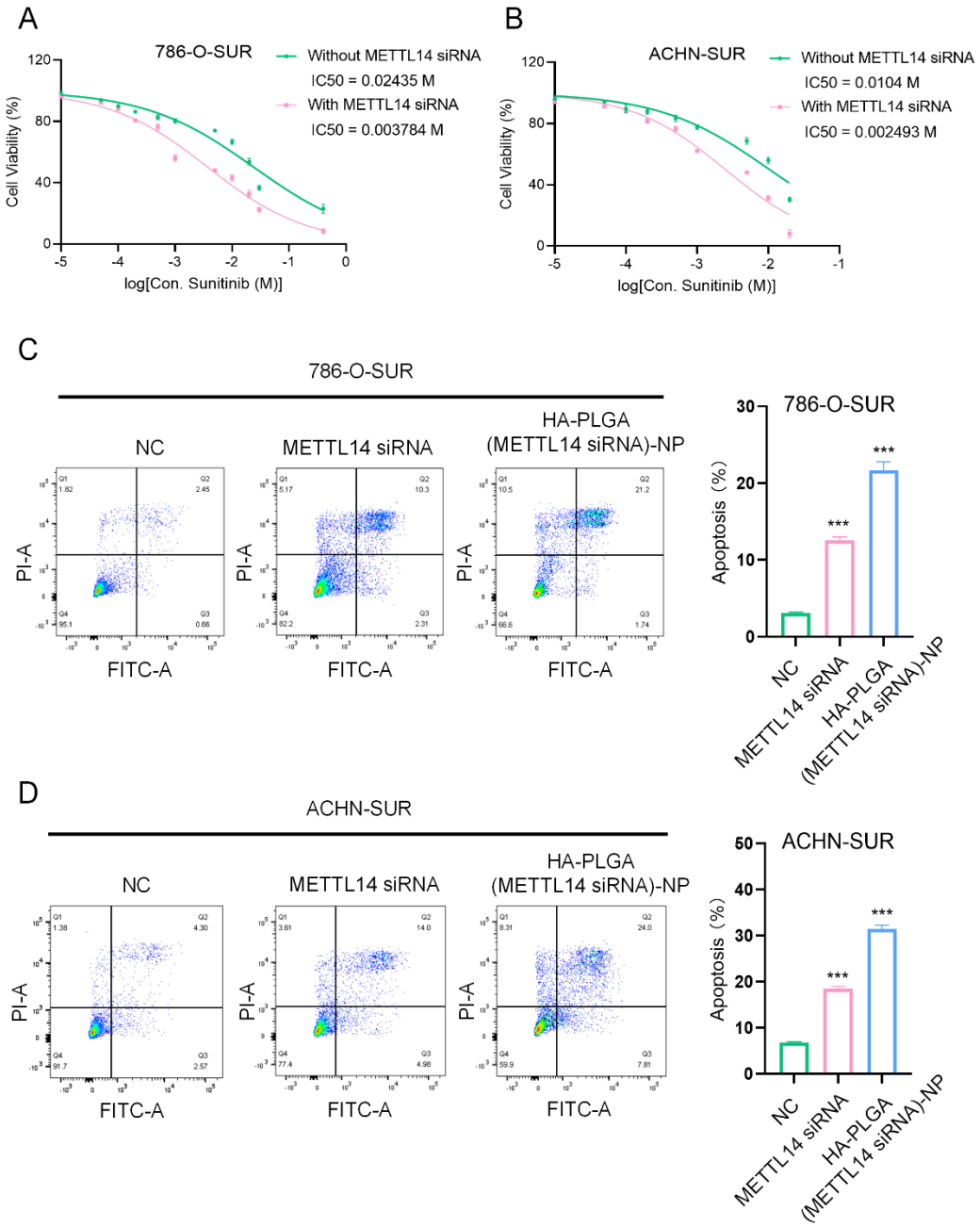

Fig. 4. Effects of METTL14 silencing on sunitinib sensitivity in resistant RCC cells.
(A, B) Determination of IC50 values using CCK-8 assay following different treatments. (C, D) Flow cytometry-based assessment of apoptosis after exposure to METTL14 siRNA or nanoparticle formulations. Results are shown as mean ± SD. Statistical significance was evaluated using one-way ANOVA (***$P < 0.001$).

METTL14 is an important regulator of m6A-mediated RNA modification and influences multiple downstream transcriptional programs (8, 19, 20). To investigate the molecular basis of resistance reversal, RNA sequencing was performed after METTL14 depletion in 786-O-SUR cells. Transcriptomic profiling identified 1,054 downregulated genes and 470 upregulated genes based on |log2FC| ≥1 and p <0.05 (Figure 5A).

Pathway enrichment analysis showed significant alterations in apoptosis-related pathways, cell cycle regulation, and senescence-associated pathways (Figure 5B–E). GO analysis additionally revealed enrichment in pathways related to immune activation and chemotactic signaling (Figure 5F).

These findings indicate that METTL14 suppression may influence both intrinsic tumor survival mechanisms and microenvironment-related pathways.

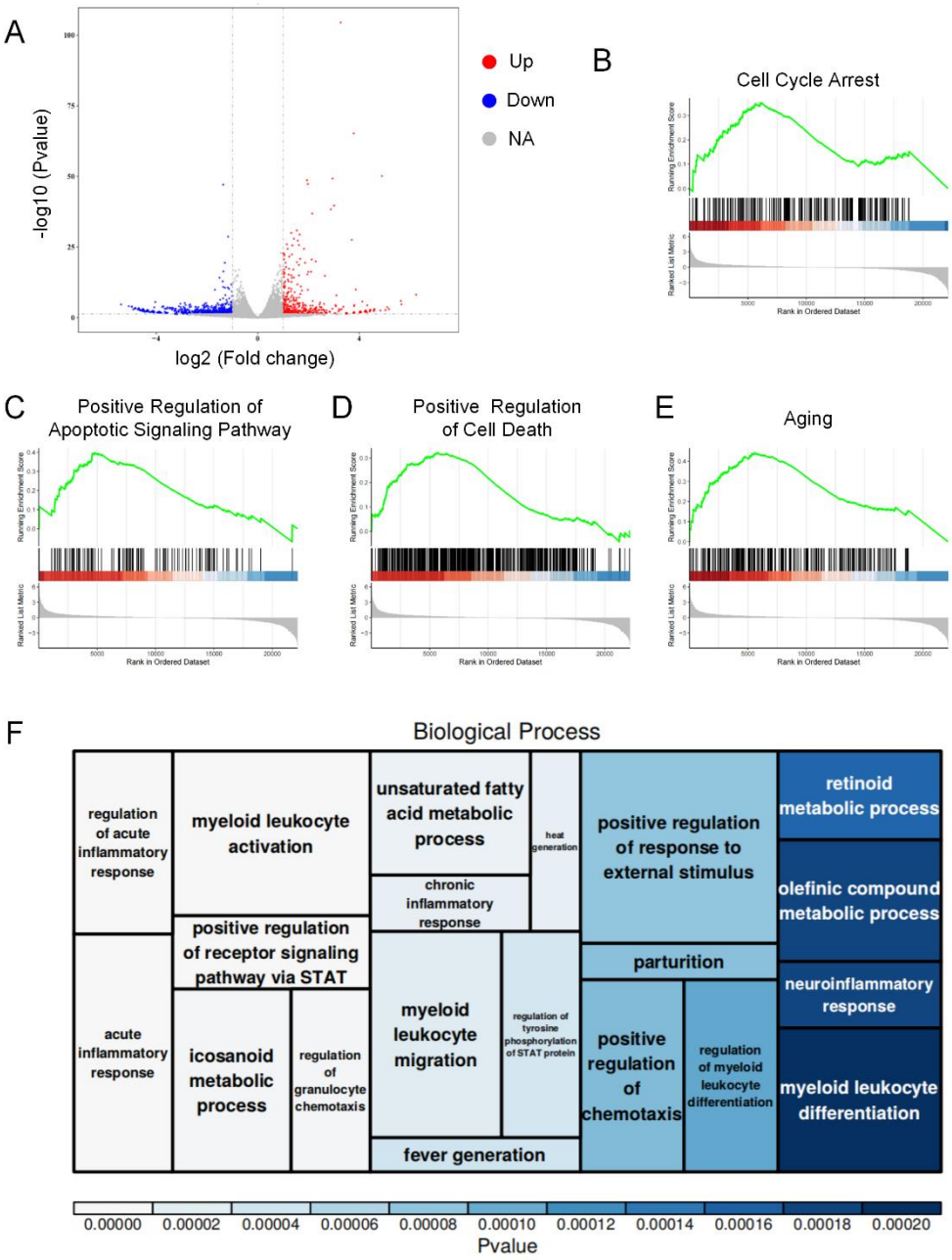

Fig. 5. Transcriptomic alterations induced by METTL14 knockdown.
(A) Volcano plot showing differentially expressed genes identified by RNA-seq analysis. (B–E) Gene set enrichment analysis highlighting significantly affected pathways. (F) Gene Ontology classification of altered genes, with bar plots indicating enrichment significance.

Antitumor activity of HA-PLGA(METTL14 siRNA)-NPs in vivo

The therapeutic potential of this platform was further evaluated using orthotopic RCC mouse models. Equal numbers of 786-O-SUR or ACHN-SUR cells were implanted beneath the renal capsule of NSG mice to establish tumors. After tumor formation, animals received systemic treatment with either HA-PLGA nanoparticles plus sunitinib or METTL14 siRNA-loaded HA-PLGA nanoparticles combined with sunitinib.

Serial *in vivo* imaging showed weaker tumor-associated fluorescence signals in mice treated with METTL14 siRNA-loaded nanoparticles, indicating slower tumor progression (Figure 6A). Consistently, tumors collected at the study endpoint were significantly smaller and lighter in this treatment group (Figure 6B).

These results support the ability of HA-PLGA(METTL14 siRNA)-NPs to enhance therapeutic responses to sunitinib under *in vivo* conditions.

Biosafety and in vivo distribution of HA-PLGA nanoparticles

To assess systemic safety, mice were administered PBS, HA-PLGA-NPs, or HA-To evaluate systemic tolerance, mice were intravenously injected with PBS, blank HA-PLGA nanoparticles, or METTL14 siRNA-loaded HA-PLGA nanoparticles.

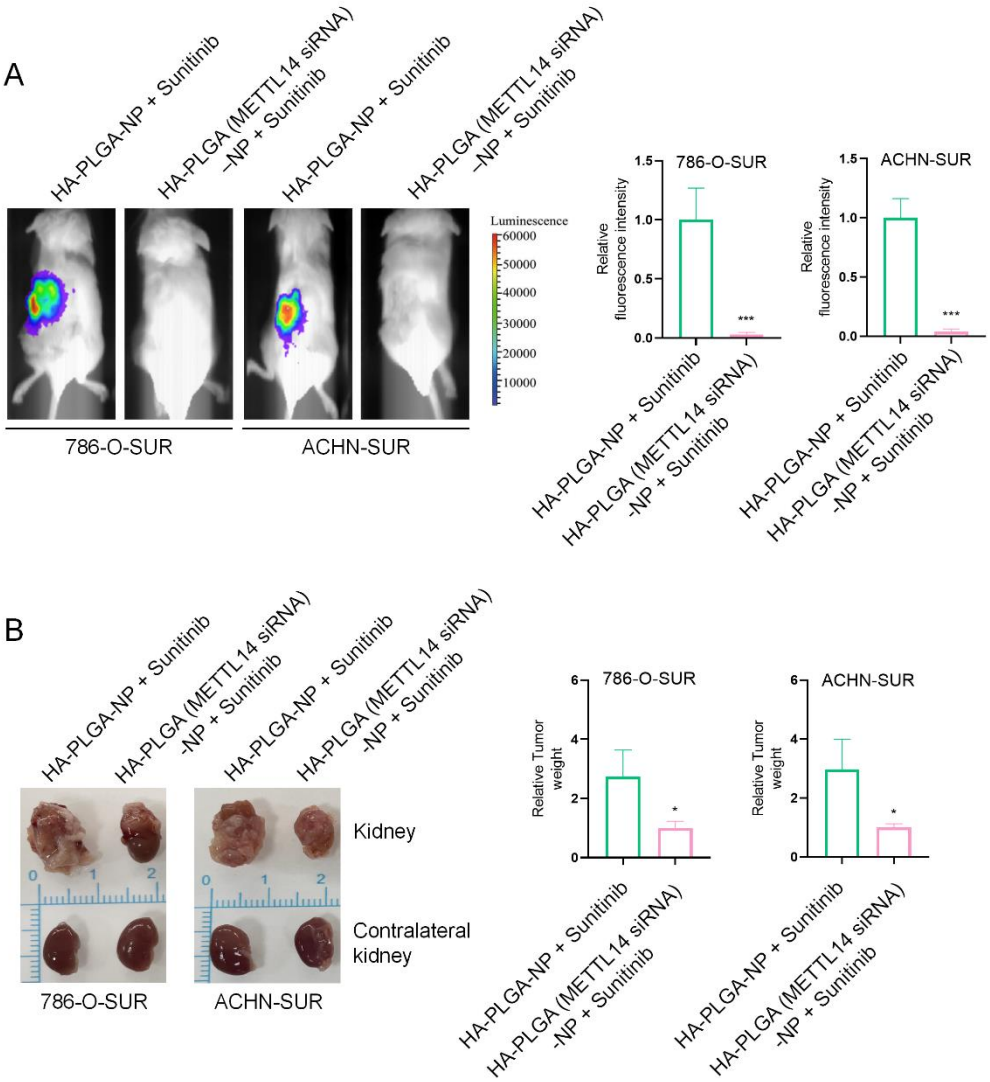

Fig. 6. *In vivo* therapeutic efficacy of HA-PLGA(METTL14 siRNA)-NPs.
(A) Representative in vivo imaging of tumor-bearing mice under different treatment conditions, with corresponding fluorescence quantification. (B) Tumor weights measured at the experimental endpoint. Data are expressed as mean ± SD, and statistical comparisons were performed using one-way ANOVA (**P* < 0.05, ****P* < 0.001).

Serum biochemical measurements showed no significant differences in creatinine, ALT, or AST levels among groups (Figure 7A–C), suggesting minimal hepatic or renal toxicity.

Tumor-targeting behavior was further assessed using Cy5-labeled nanoparticles in orthotopic RCC-bearing mice. Fluorescence analysis combined with CD44 staining demonstrated preferential accumulation of nanoparticles in tumor-bearing kidneys, whereas only weak signals were detected in normal organs, including the contralateral kidney, liver, lung, and pancreas (Figure 7D).

These data indicate that the nanoparticle system possesses acceptable biosafety and demonstrates selective tumor localization *in vivo*.

DISCUSSION

This study established an HA-functionalized PLGA delivery platform capable of transporting METTL14 siRNA into resistant RCC cells and improving responsiveness to sunitinib treatment. Although METTL14 has been reported to play divergent roles across tumor types, our findings support its contribution to resistance maintenance in RCC, which is consistent with previous reports (9). Increased apoptosis and disrupted survival signaling following METTL14 depletion further support this conclusion.

RNA interference has attracted substantial attention as a therapeutic strategy because of its ability to selectively suppress disease-associated genes (21-23). Clinical approval of Patisiran has further demonstrated the therapeutic feasibility of RNA-based approaches (24).

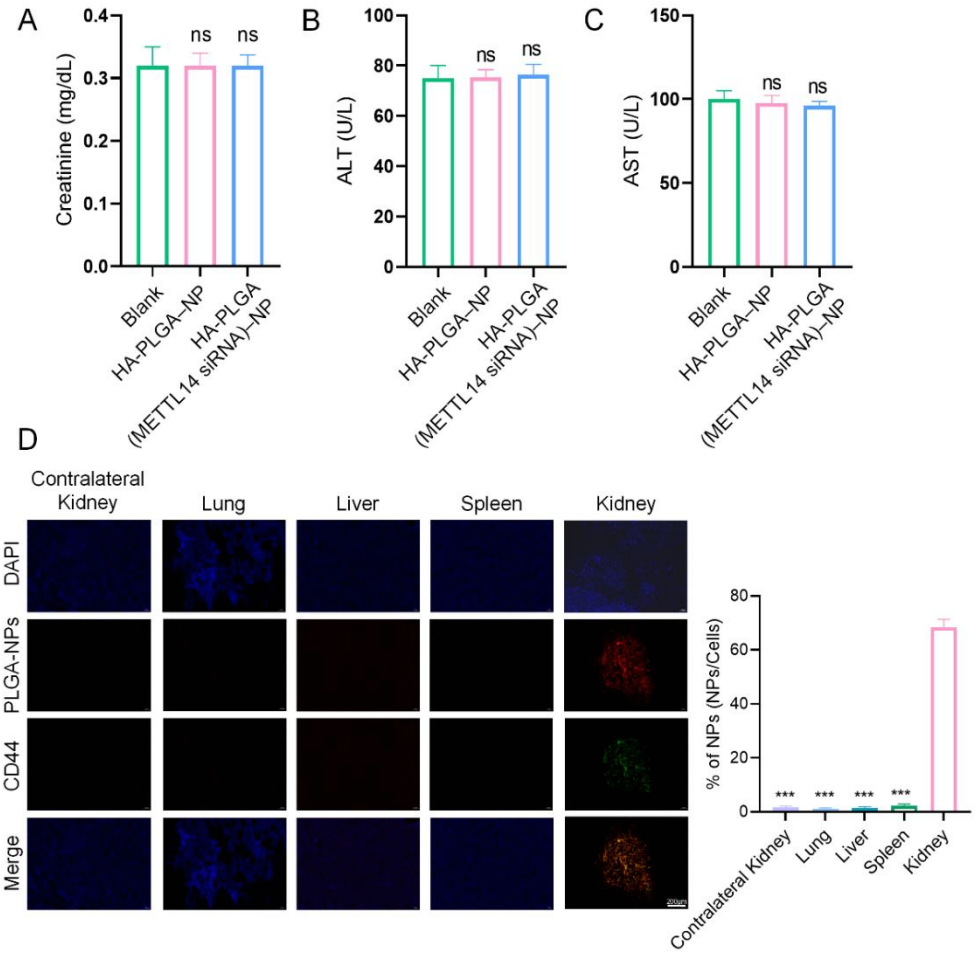

Fig. 7. Safety assessment and in vivo targeting performance of HA-PLGA nanoparticles.
(A–C) Serum biochemical parameters (creatinine, ALT and AST) following treatment. (D) Immunofluorescence analysis showing colocalization of Cy5-labeled nanoparticles (red) with CD44 (green) in tumor and major organs. Quantification data are presented as mean ± SD with statistical analysis by one-way ANOVA (***$P < 0.001$).

Nevertheless, instability in circulation and inefficient intracellular delivery remain major barriers for siRNA therapeutics. Multiple delivery systems have therefore been developed to improve pharmacological performance, including lipid carriers, viral systems, and synthetic polymers (25-28).

Among these strategies, HA-mediated targeting offers a practical method for improving tumor selectivity. CD44 serves as an important receptor for HA and is involved in tumor migration, adhesion, and progression (29, 30). Since CD44 expression was confirmed in resistant RCC cells in our study, HA coating provided an effective approach for enhancing nanoparticle uptake.

Drug resistance in RCC involves numerous signaling pathways and cannot be fully explained by a single molecular target (31-33). Although METTL14 silencing produced encouraging results in this study, future work may investigate co-delivery strategies, multi-target approaches, or combination regimens to further improve therapeutic efficacy (34, 35).

Transcriptomic analysis also suggested possible immune-related effects following METTL14 inhibition. The enrichment of chemotaxis- and immune-associated pathways raises the possibility that METTL14 may influence tumor-immune interactions in addition to regulating intrinsic survival pathways. This hypothesis requires further mechanistic validation.

Several limitations should also be noted. Potential off-target effects of siRNA remain possible, long-term toxicity studies were not performed, and cell-line xenograft models may not fully replicate clinical heterogeneity. Additional validation in patient-derived models will be necessary.

Despite these limitations, our findings provide preliminary evidence supporting nanoparticle-mediated METTL14 targeting as a potential strategy for overcoming sunitinib resistance in RCC.

CONCLUSION

This work establishes a HA-decorated PLGA nanoparticle system as an effective carrier for METTL14 siRNA delivery in renal cell carcinoma. The engineered nanoparticles exhibited stable physicochemical properties, including uniform morphology and efficient siRNA loading, while maintaining negligible intrinsic cytotoxicity.

Functional assays demonstrated that the HA modification enhanced selective interaction with CD44-expressing RCC cells, leading to improved intracellular delivery of siRNA. As a consequence, METTL14 suppression significantly increased the responsiveness of resistant cells to sunitinib, both in vitro and in vivo.

In animal models, treatment with HA-PLGA(METTL14 siRNA)-NPs resulted in a pronounced reduction in tumor burden without detectable impairment of liver or kidney function. Furthermore, fluorescence tracking confirmed preferential accumulation of nanoparticles within tumor tissues, indicating effective targeting capability.

Taken together, these findings support the potential of HA-PLGA-based siRNA delivery systems as a viable approach to overcome therapeutic resistance in RCC. This platform may provide a basis for further development of precision nanomedicine strategies targeting drug-resistant tumors.

CONFLICTS OF INTEREST

There is no conflict of interest

AUTHOR CONTRIBUTION

Yue Gao and Lei Cui were responsible for the investigation, methodology, data curation, and writing of the original draft. Xuelian Wang, Fang Wang and Baobao Fu were responsible for nanoparticle synthesis, characterization, cell culture and animal model construction. Chenchen Wang and Qianqian Jia performed the characterization of the image and data analyses, provided methodology and project administration. Yong Wang, Jin Wang and Hongjiang Zhang performed the conceptualization, supervision, and project administration of this work. All the authors reviewed the manuscript.

ETHICAL APPROVAL

All animal experiments were approved by Institutional Animal Ethics Committee at Anhui University of Science and Technology (Permit Number: LW2022-016).

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DECLARATION

We have not used any AI tools or technologies to prepare this manuscript.

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