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ORIGINAL ARTICLE

***KRAS* mutant colon cancer-targeted induction of ferroptosis *via* photocatalytic activation of BiVO₄-embedded silica nano with cascading downregulation of GPX4/xCT axis**



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CD44 targeting peptide

Abstract Kirsten rat sarcoma virus (*KRAS*) is a common oncogene in human cancers. Approximately 40% of the patients diagnosed with colorectal cancer (CRC) have *KRAS* mutations that exhibit strong resistance to targeted molecular therapy and EGFR antibody treatment. In this study, we present photocatalytic silica nanoparticles (A6-FS/BiVO₄ DMSNs) for targeted therapy of *KRAS* mutant CRC with the induction of cascading ferroptosis events. Dendritic mesoporous silica nanoparticles (DMSNs) were impregnated with photocatalytic BiVO₄, loaded with ferroptotic agents (benzoyl ferrocene: B and sorafenib: S), and encoded with CD44-targeting A6 peptides. For the targeting design, we observed CD44 overexpression in *KRAS* mutant CRC cells using CPTAC data analysis. Upon laser irradiation, A6-FS/BiVO₄ DMSNs generate electron–hole pairs (e[−]/h⁺), which produce hydroxyl radical (OH[•]) and superoxide anions (O₂^{•−}). Laser irradiation simultaneously initiates the dissociation of iron (Fe²⁺) from benzoyl ferrocene and the release of sorafenib. This cascade induces ferroptosis in *KRAS* mutant CRC cells, especially under conditional inhibition of redox-regulating proteins (cystine/glutamate antiporter and glutathione peroxidase 4), and significantly inhibits tumor growth in a *KRAS* mutant CRC xenograft animal model.

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1. Introduction

Colorectal cancer (CRC) accounted for approximately 1.9 million new cases and 0.9 million deaths worldwide in 2020. The global incidence of new CRC cases is expected to rise to 3.2 million by 2040¹. The increase in CRC incidence can be primarily attributed to intensified exposure to environmental risk factors, a consequence of evolving lifestyles and dietary patterns shifting towards westernization².

In terms of genetic aspects, approximately 40% of CRC cases are associated with *Kirsten rat sarcoma (KRAS)* viral oncogene homolog mutations³. *KRAS*, which encodes its associated protein (KRAS GTPase), is a well-known oncogene found in approximately 14% of all cancer cases^{4–6}. KRAS GTPase functions as an on-off switch that regulates cellular proliferation, such as cell growth, differentiation, migration, and lipid vesicle trafficking, by converting the nucleotide guanosine triphosphate (GTP) into guanosine diphosphate (GDP)^{7–9}. However, *KRAS* mutations result in the hyperactivation of the KRAS protein, keeping it in the “on” state, and leading to uncontrolled cell growth¹⁰. Patients with *KRAS* mutations exhibit strong resistance to chemotherapy and have poorer relapse-free survival rates than those with the *KRAS* wild-type¹¹.

Despite well-established studies on the tumorigenicity of *KRAS* mutations, numerous efforts to develop targeted cancer therapies for *KRAS*-mutant cancers have faced significant challenges and have largely proven unsuccessful. Sotorasib (Lumakras®, Amgen Inc., CA) was approved by the US Food and Drug Administration for non-small cell lung cancer with *KRAS* G12C mutation. However, restricted therapeutic indications have prompted researchers to explore alternative therapeutic modalities for *pan-KRAS* mutations.

The intrinsic characteristic of KRAS protein, characterized by the absence of a drug-binding pocket, makes the inhibition of KRAS protein a formidable challenge¹². Shaw et al.¹³ reported promising results demonstrating that tolperisone-like drugs (TLDs) can selectively induce apoptosis in *KRAS* mutant cells by generating high levels of reactive oxygen species (ROS). Researchers found that TLDs showed 2 to 3 times higher selective cytotoxicity against *KRAS* mutant cells than that against wild-type cells. *KRAS* mutant cells under the treatment of TLDs exhibited a significantly higher surge in ROS levels than wild-type cells and could not scavenge ROS in the specific metabolic environment of *KRAS* mutant cells.

Currently, there is considerable interest in utilizing metal oxide-based photocatalytic agents, as opposed to organic photosensitizers, for phototherapeutic cancer treatment. Metal oxides such as zinc oxide (ZnO), titanium oxide (TiO₂), and tungsten oxide (WO₃) possess potent photocatalytic functions and are widely used for the decomposition of organic pollutants, elimination of odors, and inactivation of pathogens in aqueous systems^{14,15}. For biological approaches, researchers are interested in developing super-oxidative photocatalysts for bactericides and, more recently, for ROS-mediated cancer therapy, because photocatalysts can generate cytotoxic free radicals in sufficient yields to induce cancer cell death¹⁶. Among various metal oxide

photocatalysts, bismuth vanadate (BiVO₄) stands out for its excellent photocatalytic activity, relatively narrow band gap of 2.4–2.5 eV, high chemical stability, and efficient energy conversion rate^{17–19}. However, applications of BiVO₄ have primarily been explored in bacterial disinfection, organic pollutant decomposition, and solar cell development^{20–22}. Its potential in biomedical applications, particularly as a photocatalytic agent for cancer therapy, remains largely unexplored.

Ferroptosis is a type of iron-related programmed cell death caused by the interaction of abnormally increased cellular iron with ROS^{23,24}. Ferroptosis was first observed in *KRAS* mutant cancer cells. Stockwell and co-workers found that the ferroptotic agents, erastin and RSL3, selectively killed *KRAS*-mutant cells^{25,26}. They demonstrated that apoptosis of *KRAS* mutant cells was mediated by increased cellular ROS and iron content. These findings suggest that ferroptosis could be a potential approach to *pan-KRAS* mutant cancer therapy, and that further investigation is highly attractive. Excessive cellular ROS serve as important initiators of ferroptosis²³. Therefore, cascading downregulation of the ROS scavenging system, that is, systemic disruption of the glutathione (GSH)-dependent antioxidant system involving CD44, glutathione peroxidase 4 (GPX4) and the cystine/glutamate antiporter SLC7A11 (xCT), is a good target for ferroptosis-based cancer therapy^{27,28}.

In this study, we present a novel approach for the targeted therapy of *KRAS* mutant CRC using BiVO₄-embedded dendritic mesoporous silica nanoparticles (A6-FS/BiVO₄ DMSNs) loaded with multiple ferroptotic agents. To achieve this, we embedded photocatalytic *m*-BiVO₄ into dendritic mesoporous silica nanoparticles (DMSNs) functionalized with a CD44-targeting A6 peptide and loaded them with a ferroptotic iron donor (benzoyl ferrocene: F) and an xCT inhibitor (sorafenib: S)^{29–32}. The resulting A6-FS/BiVO₄ DMSNs were shown to induce a photo-triggered cascading chain reaction of ferroptosis, characterized by photocatalytic ROS generation, photo-triggered ferroptotic iron release, downregulation of cellular reduction-oxidation (redox) proteins, and cellular lipid peroxidation in *KRAS* G13D mutant CRC cells. We evaluated the therapeutic effects of A6-FS/BiVO₄ DMSNs on *KRAS* mutant CRC cells. Finally, we tested the tumor growth inhibition efficacy of the A6-FS/BiVO₄ DMSNs in *KRAS* mutant CRC cell-xenografted mouse models.

2. Materials and methods

2.1. Clinical implications of *KRAS* mutation in patients with CRC

2.1.1. TCGA data analysis

The Cancer Genome Atlas Colon Adenocarcinoma (TCGA-COAD) dataset was downloaded from FireBrowse (<http://firebrowse.org/>), an R client of the Broad Institute's RESTful Firehose Pipeline. This dataset was used to explore the clinical relevance of *KRAS* mutations in patients with COAD. Kaplan–Meier survival analysis was performed on a subset of the TCGA-COAD dataset (154 COAD patients) to assess the

difference in overall survival between patients with *KRAS* mutant and wild-type tumors.

In this study, we used *KRAS* wild-type (*KRAS* WT) and *KRAS* mutant (*KRAS* MT) DLD-1 human colorectal adenocarcinoma cell lines provided by the Translational Research Center for Protein Function Control (Yonsei University, Seoul, Korea). Specifically, *KRAS* MT cells harbor the G13D mutation^{33,34} which is associated with poor survival in patients with resected stage III colon cancer³⁵. To further understand the clinical implications of *KRAS* G13D mutation in patients with CRC, the frequency of *KRAS* G13D mutation in CRC was analyzed using the Genomic Data Commons (GDC)-TCGA dataset (<https://portal.gdc.cancer.gov/>).

2.1.2. Resistance of *KRAS* MT cells to ROS-induced oxidative stress

KRAS mutation-driven neoplasia aberrantly increases ROS levels and consequently upregulates antioxidant proteins¹³. In this study, we examined the resistance of *KRAS* MT cells to ROS-induced oxidative stress. *KRAS* WT and MT cells were seeded in a 96-well plate at 1000 cells per well in McCoy's 5A medium and incubated for 12 h at 37 °C. Cells were subsequently treated with varying concentrations of H₂O₂ (0, 1, 5, 10, 25, 50, and 100 µmol/L) for 48 h, and cell viability was determined using the CCK-8 assay (Thermo Fisher Scientific Inc., Waltham, MA). A colony formation assay was also performed on each cell line treated with H₂O₂ (0 and 80 µmol/L) for 4 h, followed by plating in 6-well plates (2000 cells/well) in fresh medium. After two weeks of incubation, colonies were fixed, stained with crystal violet, and counted. Additionally, Western blotting was performed to assess *KRAS* and antioxidant proteins (CD44, xCT, Nrf2, and GPX4) in *KRAS* WT and MT cells before and after H₂O₂ treatment.

2.1.3. CD44 expression of *KRAS* MT cells

KRAS MT cells highly express cancer stem cell markers such as CD44, CD133, and CD166. CD44 is a compelling marker for cancer stem cells and plays an important role in the development of chemoresistance and CD44 has been widely explored as a biomarker for target therapy of nanomedicine³⁶. In this study, we observed the frequency of CD44 gene expression in colon adenocarcinoma (COAD) tissues using the Gene Expression Profiling Interactive Analysis (GEPIA) dataset (<http://gepia.cancer-pku.cn/>) and performed CD44 Western blot analysis on *KRAS* WT and MT CRC cells.

2.2. Design, synthesis, and characterization of A6-FS/BiVO₄ DMSNs

BiVO₄ DMSNs were prepared following previously reported methods^{37,38}. Initially, DMSNs were prepared using a micro-emulsion system that included water, cyclohexane, and cetyltrimethylammonium chloride (CTAC) with triethanolamine (TEA) as a surfactant. This microemulsion approach facilitates the formation of well-defined mesoporous silica structures suitable for subsequent BiVO₄ doping. Doping of BiVO₄ was achieved through the incipient wetness impregnation method, utilizing bismuth (III) nitrate pentahydrate and ammonium metavanadate in a 3 mol/L HCl solution. The resulting BiVO₄-embedded DMSNs were heat-treated at 400°C for 6 h to form the monoclinic crystals of bismuth vanadate (m-BiVO₄). The acquired BiVO₄-DMSNs were further processed for introduction of redox-responsive chemistry, conjugation of CD44-targeting A6 peptide, and

loading of benzoylferrocene and sorafenib. The detailed steps are provided in the Supporting Information

Based on our investigation of GEPIA data, which suggested the specific overexpression of CD44 in *KRAS* mutant CRC, the CD44-targeting A6 peptide (KPSSPPEE) was conjugated to BiVO₄ DMSNs *via* a thiol–maleimide reaction, followed by surface modification of the DMSNs (Supporting Information)³⁹. Subsequently, we uploaded ferroptosis-inducing drugs (benzoyl ferrocene as a ferrous ion donor and sorafenib as an xCT inhibitor) into the BiVO₄-DMSNs *via* the wet absorption method and finally acquired A6-FS/BiVO₄ DMSNs. The surface morphology of the BiVO₄ DMSNs was observed on field-emission transmission electron microscopy (FE-TEM; JEM-2100F, JEOL Co., Tokyo, Japan). The crystal structure of the prepared particles was examined using an X-ray diffractometer. Raman spectroscopy, Fourier transform infrared spectrometry (FT-IR Spectrometer, Spectrum-2000, PerkinElmer, Waltham, MA), and UV–vis spectrophotometry (SpectraMax M5 microplate reader, Molecular Devices, San Jose, CA) were used to identify the chemical bonds and surface chemical compositions of the A6-BiVO₄ DMSNs.

2.3. Observation of A6-FS/BiVO₄ DMSN-induced cell death

Cancer cell death induced *via* the photocatalytic activation of A6-FS/BiVO₄ DMSNs was evaluated *via* multiple assays, including the CCK-8 cell viability assay, colony formation assay, and Live and Dead cell staining assays. *KRAS* WT and MT cells were treated with sorafenib (4.86 µg/mL) + benzoyl ferrocene (2.9 µg/mL), A6-BiVO₄ DMSNs (200 µg/mL), and A6-FS/BiVO₄ DMSNs (sorafenib: 24.3 mg/g and benzoyl ferrocene: 12.45 mg/g), incubated for 48 h, and introduced to CCK-8 cell viability assay and colony formation assay. Live and dead cell staining was conducted using an assay kit (LIVE/DEAD™ Viability/Cytotoxicity Kit, Thermo Fisher Scientific Inc., Waltham, MA) (Please refer to Supporting Information).

2.4. Identification of cell death mechanism

2.4.1. Cellular iron accumulation

The cellular disposition of iron was confirmed by Prussian blue staining⁴⁰. *KRAS* WT and MT cells were treated with A6-FS/BiVO₄ DMSNs at a concentration of 300 µg/mL, with or without laser irradiation. Following treatment, the cells were stained with Prussian blue solution composed of 4% potassium ferrocyanide and 4% hydrochloric acid, then fixed and examined under a microscope.

2.4.2. Downregulation of cellular antioxidant proteins

Western blot analysis was conducted to estimate the cellular levels of antioxidant proteins (CD44, *KRAS*, xCT, Nrf2, and GPX4) in *KRAS* WT and MT cells after treatment with A6-BiVO₄ DMSNs and A6-FS/BiVO₄ DMSNs.

2.4.3. Lipid peroxidation

BODIPY™ 581/591 C11 dye (Thermo Fisher Scientific Inc., Waltham, MA, USA) was used to assess the extent of cellular lipid peroxidation as an indicator of ferroptosis⁴¹. Cells (100,000 cells per well) were cultured in fresh McCoy's 5A medium and treated with sorafenib + benzoyl ferrocene, A6-BiVO₄ DMSNs, A6-FS/BiVO₄ DMSNs (–) DFO, and A6-FS/BiVO₄ DMSNs (+) DFO for 4 h. Subsequently, the cells were exposed to laser irradiation (47.2 J/cm²), incubated for 4 h, and stained with McCoy's 5A

medium containing 5 $\mu\text{mol/L}$ of BODIPYTM 581/591 C11 dye (Thermo Fisher Scientific Inc., Waltham, MA) at 37 °C for 1 h in the dark. The extent of cellular lipid peroxidation was visualized using fluorescence microscopy.

2.5. *In vivo* tumor growth inhibition study

All animal experiments were conducted in accordance with the guidelines of the Institutional Animal Care and Use Committee (IACUC) of Inha University (Protocol No. INHA-200309-690) and complied with the regulations set by the Korean Food and Drug Administration (KFDA). Xenografting of colorectal tumors was performed by subcutaneous injection of *KRAS* MT cells (5×10^6) suspended in 30% MatrigelTM solution into BALB/c-nude mice (5 mice per group). Once the tumor volume reached approximately 100 mm³, which typically occurs 10 days after injection, the mice were randomly divided into four groups. These groups were subjected to different treatments: sorafenib + benzoyl ferrocene, A6-BiVO₄ DMSNs, A6-FS/BiVO₄ DMSNs (–) L, or A6-FS/BiVO₄ DMSNs (+) L. The injection dose of A6-FS/BiVO₄ DMSNs was adjusted to 1.3 mg/kg of sorafenib and 0.77 mg/kg of benzoyl ferrocene. After 12 h of injection, the tumors were exposed to a laser (94.4 J/cm²). Tumor

size and body weight were measured every other day, and tumor volume was calculated using Eq. (1):

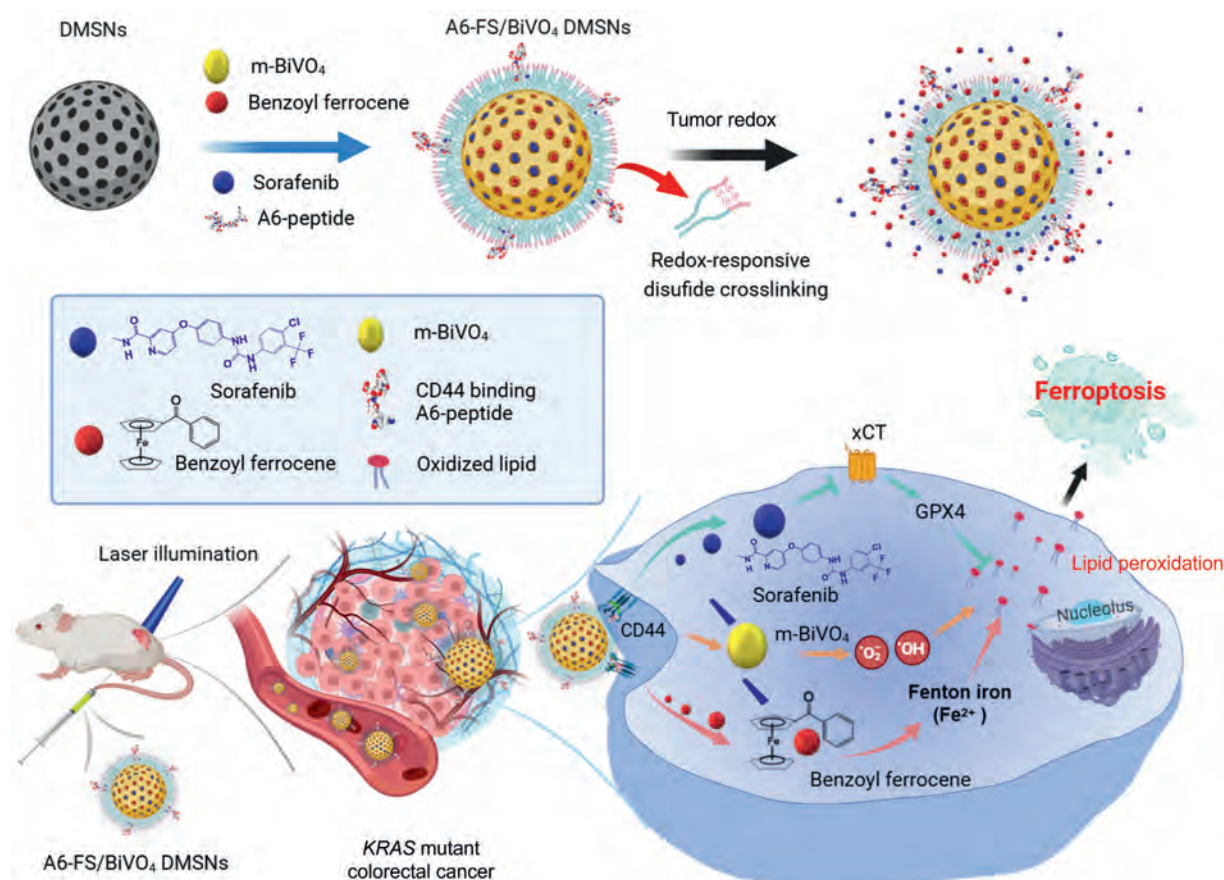
$$\text{Tumor volume} = (1/2 \times L \times W \times H) \quad (1)$$

For further histological analysis, the major organs (lungs, kidneys, hearts, livers, and spleens) and tumors were harvested, fixed in 10% formalin, and subjected to subsequent histological observations.

3. Results and discussion

3.1. Physicochemical characteristics of A6-FS/BiVO₄ DMSNs

A6-BiVO₄ DMSNs were synthesized following the procedure illustrated in the schematic diagram (Scheme 1 and Fig. 1A). The A6-BiVO₄ DMSNs exhibited a mesoporous spherical structure with specifically designed surface chemistry (Supporting Information Scheme S1 and Supporting Information Fig. S1–S5). Electron microscopy (JEM-2100F, JEOL Co., Tokyo, Japan) analysis revealed a particle size of 85.22 ± 13.39 nm (Fig. 1B and Supporting Information Fig. S6). However, hydrodynamic size observed by dynamic light scattering method showed mean particle size of 120 nm (Fig. 1C and Supporting Information Fig. S7).



Scheme 1 Induction of ferroptosis through the photocatalytic activation of A6-FS/BiVO₄ DMSNs and cascading control of antioxidant pathway (GPX4/xCT axis) for target therapy of *KRAS* mutant colorectal cancer. The cascading induction ferroptosis; CD44-specific *KRAS* mutant CRC targeting via A6-peptide, Photocatalytic activation of A6-FS/BiVO₄ DMSNs and ROS generation, Photo-responsive release of ferrous iron from benzoyl ferrocene (F), ROS-responsive release of sorafenib (S) and downregulation of cellular antioxidant enzymes (xCT and GPX4), Fenton reaction-associated ferroptosis of *KRAS* mutant CRC cells.

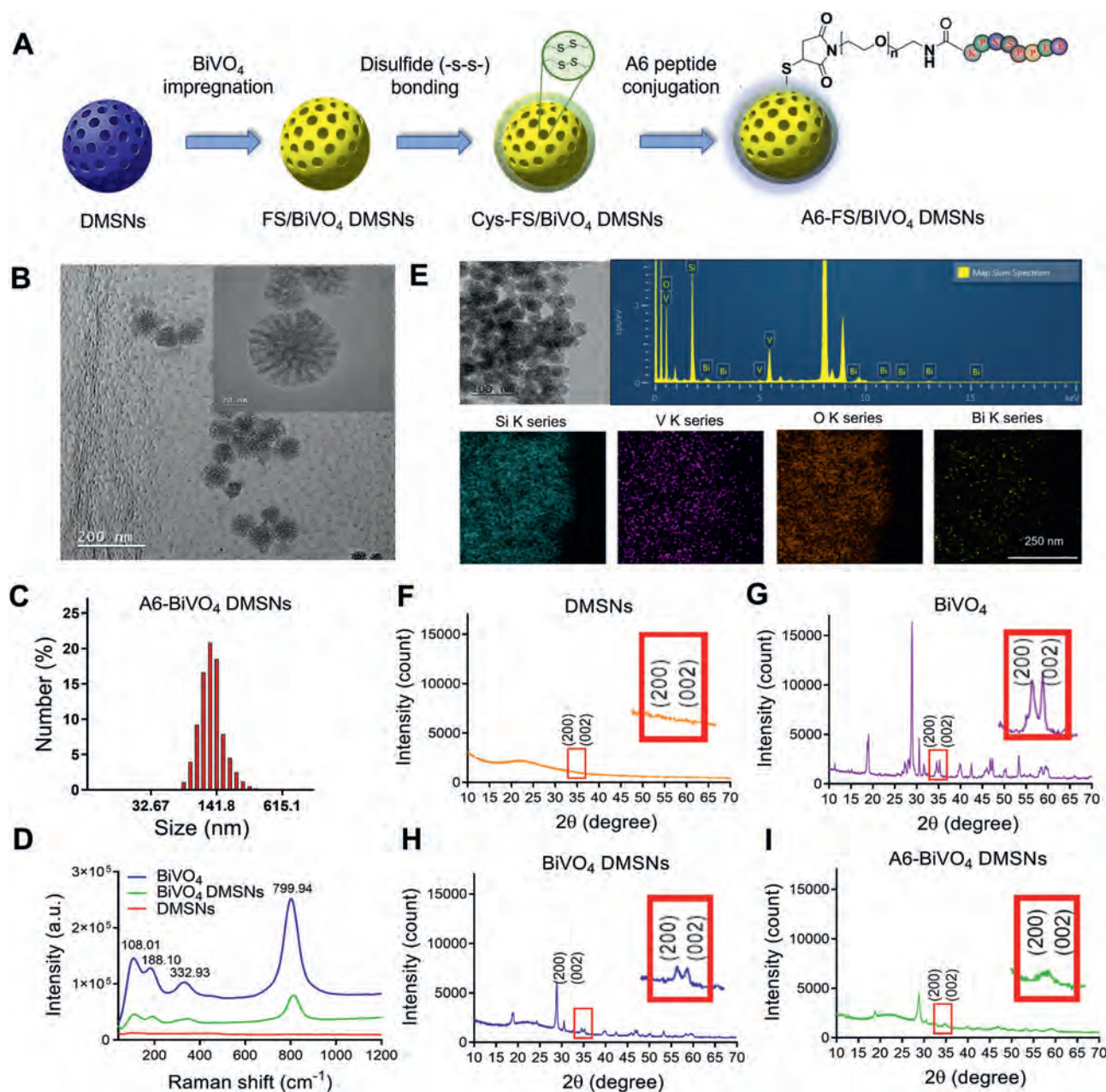


Figure 1 Physicochemical characteristics of A6-BiVO₄ DMSNs. (A) Schematic illustration of the fabrication of A6-BiVO₄ DMSNs. (B) Transmission electron microscope (TEM) image displays particle size and morphological structure of A6-BiVO₄ DMSNs (scale bar: 200 nm). (C) Particle size distribution, determined by dynamic light scattering method. (D) Raman spectra for BiVO₄, DMSNs, and BiVO₄ DMSNs. (E) EDS elemental mapping and spectra obtained from TEM image analysis. (F–I). XRD patterns for DMSNs, BiVO₄, BiVO₄ DMSNs, and A6-BiVO₄ DMSNs.

Our particles maintained excellent dispersion stability without aggregation in the medium for over 72 h (Fig. S7).

Energy dispersive spectroscopy (EDS) and elemental mapping confirmed the presence of Si, O, Bi, and V on the surface of DMSNs (Fig. 1E), implying the successful integration of the BiVO₄ component. Further characterization using Raman spectroscopy and Powder X-ray Diffraction confirmed the impregnation of BiVO₄ onto the DMSNs (Fig. 1D and F–I)⁴².

BiVO₄, a versatile metal oxide semiconductor, has gained attention as a promising photocatalyst and photoanode for oxygen

(O₂) production. It exists in three crystalline forms: monoclinic scheelite (m-BiVO₄), tetragonal scheelite (t-BiVO₄), and tetragonal zircon (tz-BiVO₄), each with unique structural and photocatalytic characteristics^{43,44}. Among these, m-BiVO₄ is notable for its relatively low bandgap, which makes it highly photoactive and efficient for many applications involving light-driven chemical reactions^{45,46}. Our BiVO₄ DMSNs exhibited a standard diffraction pattern for m-BiVO₄ (JCPDS 00-14-688), confirming the successful crystallographic formation of m-BiVO₄ within the DMSNs (Supporting Information Fig. S8). These data support the

strong potential of BiVO₄ DMSNs for high-yield photocatalytic ROS generation and for successfully triggering the cascading events of ferroptosis in KRAS mutant CRC cells^{42,47}.

3.2. Clinical implication of KRAS mutation in patients with CRC

KRAS mutations are recognized as predictive biomarkers in CRC, particularly for determining resistance to anti-EGFR therapies, such as cetuximab and panitumumab⁴⁸. However, the prognostic value of KRAS mutations, particularly in metastatic CRC, remains controversial⁴⁹. Therefore, we examined the clinical implications of KRAS mutations in CRC using genomic data from the GDAC FireBrowse (<https://gdac.broadinstitute.org/#>). First, KRAS mutations were detected in 43.5% (174/400) of colon adenocarcinomas (COAD), 41.61% (57/137) of rectal adenocarcinomas (READ), and 75.27% (137/182) of pancreatic adenocarcinomas (PAAD) (Supporting Information Fig. S9). We also observed that patients with KRAS mutant COAD exhibited poor overall survival, particularly when diagnosed at stage II or higher (Fig. 2A). Notably, no significant correlation was observed between KRAS mutations and survival in patients with stage I disease, implying that KRAS mutations may exert a greater impact as the disease progresses⁵⁰. KRAS mutations are commonly grouped into specific variants, such as G12D, G12V, G12C, and G13D⁵¹, and we selected KRAS G13D-mutant CRC cells for the study. KRAS G13D mutation is the second most common KRAS variant in CRC and has been linked to an elevated risk of anastomotic recurrence in patients with CRC⁵². Our analysis revealed that the KRAS

G13D mutation was present in 7.26% (31/427) of the cases across 14 distinct projects (Supporting Information Fig. S10) and accounted for 17.82% of KRAS mutant CRC cells (Fig. 2B).

3.3. Proliferation and migration properties of KRAS MT CRC cells

In accordance with clinical data, we examined the proliferation and migration properties of KRAS WT and MT cells under normal culture conditions. KRAS MT cells demonstrated rapid, exponential growth, with a significantly faster doubling time of 9.46 ± 0.17 h ($P < 0.01$) compared to KRAS WT cells, which had a doubling time of 10.79 ± 0.42 (Fig. 2E). Moreover, the migration rate of KRAS MT cells was substantially higher than that of KRAS WT cells (Fig. 2C). Following a 12-h incubation period, the wound healing assay exhibited a residual wound area of $39.43 \pm 1.05\%$ for KRAS MT cells, in contrast to $83.00 \pm 2.95\%$ for KRAS WT cells (Fig. 2D, $P < 0.001$), indicating an enhanced migratory capability in KRAS MT cells.

3.4. Strong expression of antioxidant Nrf2/GPX4/xCT proteins in KRAS MT CRC cells

In the present study, we observed that KRAS MT cells developed a strong antioxidant system involving Nrf2, GPX4, and xCT. The estimated IC₅₀ of H₂O₂ was 22.68 μ M/L for KRAS WT cells and 30.01 μ M/L for KRAS MT cells (Fig. 3B and C, $P < 0.001$). Interestingly, KRAS MT cells demonstrated a more robust induction of antioxidant proteins in the Nrf2/GPX4/xCT axis when

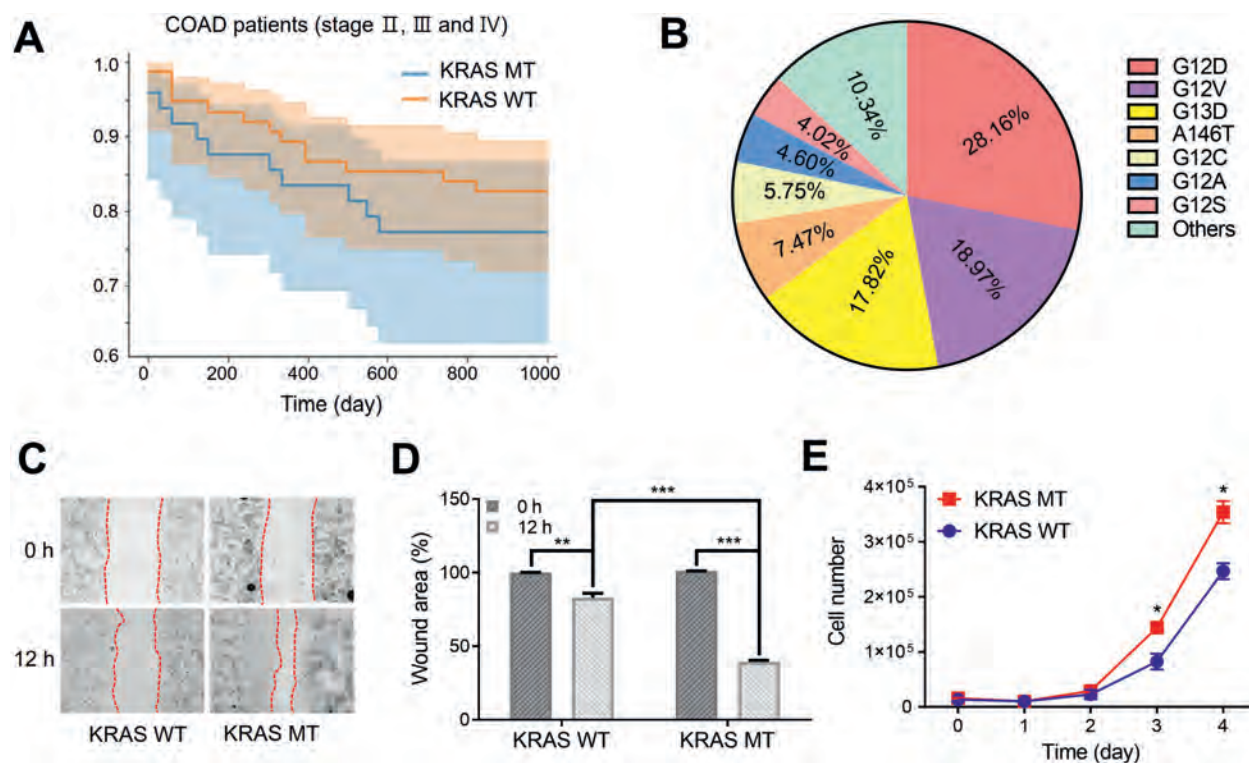


Figure 2 Poor overall survival of patients with KRAS mutant COAD, and higher cell proliferation rate and migration power of KRAS mutant CRC cells. (A) Kaplan–Meier survival curve for CRC patients with KRAS mutation, acquired from GDC data portal. (B) Subpopulation of KRAS mutants in CRC observed from GDC-TCGA dataset. (C, D) Higher migration property of KRAS MT cells, determined by wound healing assay. (E) *In vitro* proliferation properties of KRAS WT and MT cells. All experiments were repeated in triplicate and data are expressed as means $\pm$ SD ($n = 3$). Statistical significance was calculated by an unpaired *t*-test (* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$).

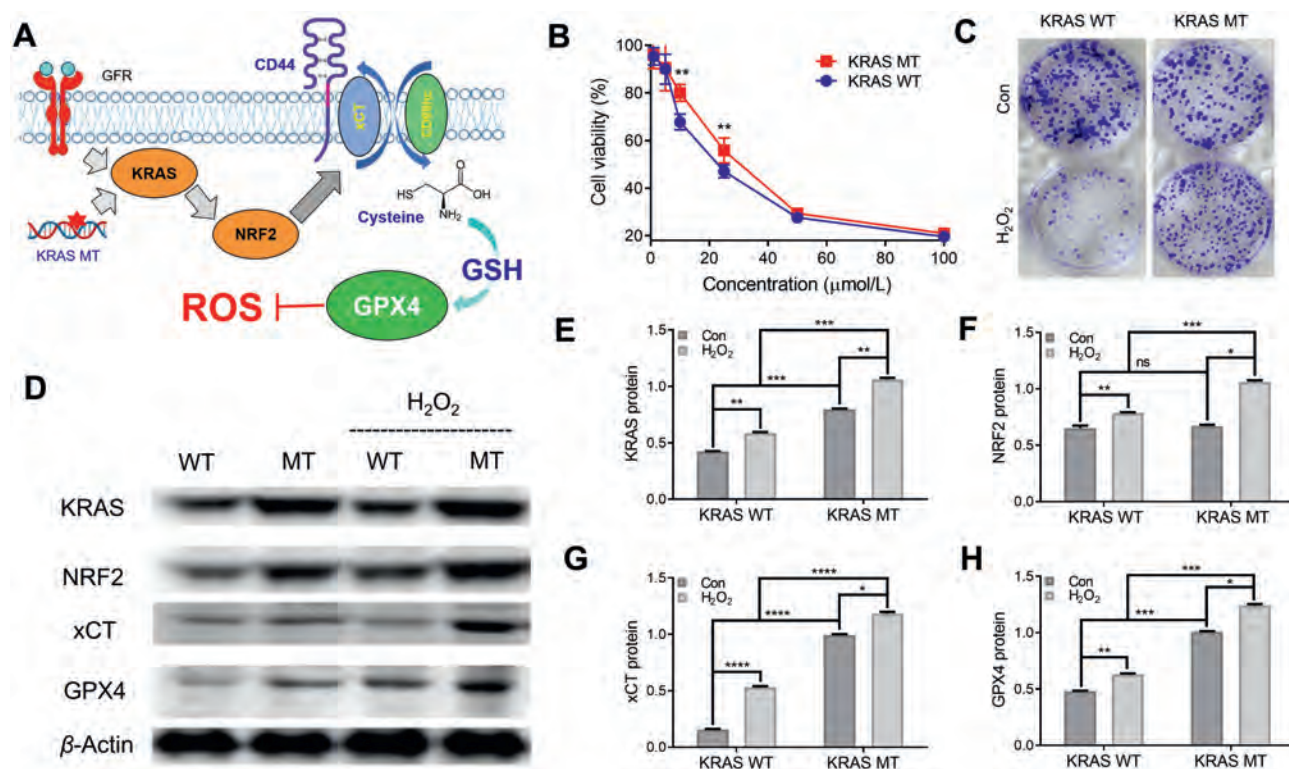


Figure 3 Strong redox regulatory power of KRAS mutant CRC cells. (A) Schematic illustration showing that KRAS and Nrf2 effectively regulate ROS homeostasis. (B, C) Colony forming assay and CCK-8 assay of KRAS WT and MT CRC cells after treatment with H₂O₂. (D) Western blot analysis for KRAS, Nrf2, xCT, and GPX4 proteins in KRAS WT and MT CRC cells after treatment with H₂O₂. (E–H) Histograms of expression levels for KRAS (E), Nrf2 (F), xCT (G), and GPX4 (H). All experiments were repeated in triplicate and data are expressed as means ± SD ($n = 3$). Statistical significance was calculated using an unpaired t -test (* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$).

exposed to ROS-induced oxidative stress (Fig. 3D)⁵³. Constitutive activation of Nrf2 may lead to the overexpression of xCT and GPX4, particularly in KRAS MT cells (Fig. 3E–H, $P < 0.05$)^{54,55}. During CRC progression, elevated ROS levels induced by oncogenic KRAS must be tightly regulated by the cellular antioxidant system to prevent ROS levels from exceeding a threshold that could lead to cell death (Fig. 3A)^{13,56}.

3.5. Photocatalytic activation of A6-FS/BiVO₄ DMSNs and ferroptosis

Many studies have suggested that KRAS mutant cancer cells are more resistant to ROS-induced cellular stress¹³. And our studies also proved that KRAS MT CRC cells showed higher IC₅₀ values than KRAS WT CRC cells for H₂O₂ treatment and more strongly induced antioxidant proteins under H₂O₂ treatment⁵⁵. In this study, we testified that our designed A6-FS/BiVO₄ DMSNs effectively trigger ferroptosis of KRAS MT cells.

3.5.1. Photocatalytic ROS generation

Fig. 4A illustrates the proposed mechanism for generation of hydroxyl radical (OH[•]) and superoxide anions (O₂^{•-}) through the photocatalytic activation of A6-BiVO₄ DMSNs. The photocatalytic activation of BiVO₄ DMSNs generated electrons, which were then transferred to the surrounding oxygen molecules to produce ROS. Fig. 4B demonstrates that the BiVO₄ DMSNs generated cyclic photocurrent transients, characterized by a smooth rise and rapid decay, under laser irradiation (78.6 mW/cm²). The estimated

intensity of the photocurrent obtained from 1 mg/mL A6-BiVO₄ DMSNs reached 0.53 μA. This is further demonstrated in Fig. 4C, where the energy absorption of 9,10-dimethylanthracene (DMA) gradually decreased with increasing irradiation time, confirming ROS generation. The production of singlet oxygen was also validated using Singlet Oxygen Sensor Green (SOSG) dye (Thermo Fisher Scientific Co., Waltham, MA), where fluorescence green peaked after 10 min of A6-BiVO₄ DMSNs treatment. Cellular photocatalytic ROS generation of BiVO₄ DMSNs was assessed using HCT116 human colon cancer cells (Fig. 4D)⁵⁷. HCT116 cells were incubated with A6-BiVO₄ DMSNs for 2 h, followed by photocatalytic activation and staining with SOSG and DCF-DA (2',7'-dichlorofluorescein diacetate). The results revealed that BiVO₄ DMSNs specifically generated ROS in the cytosol of HCT116 cells (Fig. 4E). These findings suggest that BiVO₄ DMSNs possess sufficient photocatalytic activity to generate sufficient ROS to trigger cascading ferroptosis, even in cellular environments.

3.5.2. CD44-targeting specificity of A6-BiVO₄ DMSNs for KRAS mutant CRC cells

First, we investigated the gene expression levels of CD44 in CRC tissues using the Gene Expression Profiling Interactive Analysis (GEPIA) tool (<http://gepia.cancer-pku.cn/>). Our results revealed that COAD tissues exhibited significantly higher CD44 expression than normal tissues (Fig. 5A). Western blot analysis confirmed the overexpression of CD44 in KRAS MT cells (Fig. 5B). Notably, the expression of CD44 was 1.18-fold higher in KRAS MT cells than in KRAS WT cells ($P < 0.01$)⁵⁸. Consequently, we evaluated

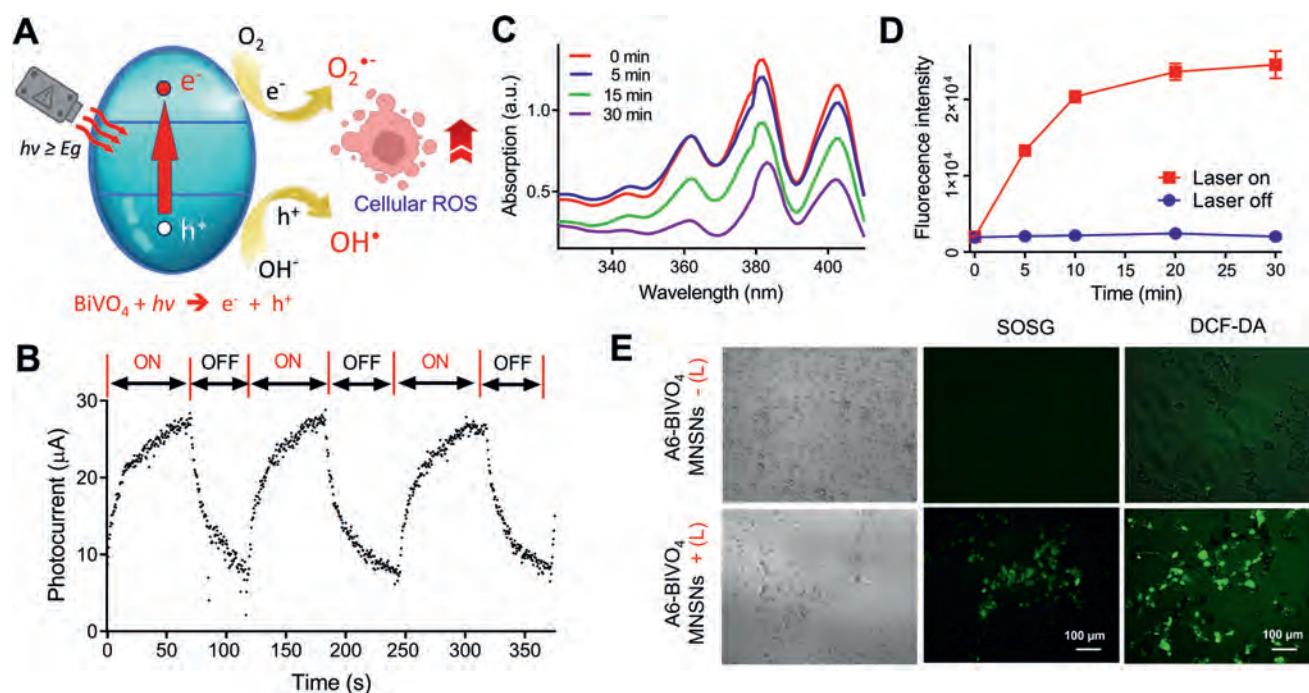


Figure 4 Generation of electric current and subsequent ROS under photocatalytic activation of A6-BiVO₄ DMSNs. (A) Schematic illustration for photocatalytic ROS generation of A6-BiVO₄ DMSNs under laser irradiation. (B) Generation of electric current under on/off cyclic laser irradiation of A6-BiVO₄ DMSNs. (C) ROS-driven degradation of 10-dimethylanthracene (DMA) under laser irradiation of A6-BiVO₄ DMSNs. (D) Singlet oxygen generation detected by SOSG dye under laser irradiation of A6-BiVO₄ DMSNs. Data are expressed as means $\pm$ SD ($n = 3$). (E) Microscopic observation of cellular ROS measured by SOSG and DCFH-DA in HCT 116 colon cancer cells after uptake of A6-BiVO₄ DMSNs and laser irradiation (scale bar: 100 μm).

the CD44-targeting specificity of A6-BiVO₄ DMSNs using *in vitro* and *in vivo* animal models. Fig. 5C strongly suggests A6-BiVO₄ DMSNs exhibited higher cellular uptake efficiency in *KRAS* MT cells than in *KRAS* WT cells. Blocking CD44 with A6-peptide pretreatment (50 $\mu\text{g}/\text{mL}$) further confirmed CD44-targeting specificity of A6-BiVO₄ DMSNs. Additionally, the *in vivo* organ distribution study conducted with a *KRAS* mutant CRC xenograft mouse model strongly supported the CD44-targeting specificity of A6-BiVO₄ DMSNs (Fig. 5D and Supporting Information Fig. S11).

3.5.3. Triggered release of iron and sorafenib

Previous experiments demonstrated that A6-BiVO₄ DMSNs effectively generated photocatalytic ROS, sufficient to induce ferroptosis of *KRAS* MT cells. To achieve cascading control of ferroptosis, we strategically loaded ferroptotic agents (benzoyl ferrocene as an iron donor and sorafenib as an xCT inhibitor) into the A6-BiVO₄ DMSNs and evaluated the drug loading content and release characteristics. The dendritic mesoporous structure of the DMSNs facilitated efficient drug loading of benzoylferrocene and sorafenib, achieving payloads of $12.5 \pm 2.1\%$ and $24.3 \pm 1.4\%$ with 20.8% and 24.3% of loading efficiency, respectively. To enable the controlled release of the ferroptotic agents, our DMSNs were end-capped using disulfide oxidation of cysteine, which ensured that the release was responsive to the cellular redox environment (Supporting Information Fig. S12).

The photo-triggered dissociation of iron from benzoyl ferrocene was successfully demonstrated under UV irradiation. As illustrated in Fig. 6A, there was a notable increase in the absorption maximum (λ_{max}) at 350 nm, accompanied by the disappearance of the absorption peak at 482 nm. These spectral changes

confirmed that laser irradiation effectively induced the degradation of benzoyl ferrocene, leading to the release of ferrous iron. This observation is consistent with those of previous reports^{32,59}.

Redox-responsive release of sorafenib from A6-FS/BiVO₄ DMSNs was quantitatively assessed using an Ultra Performance Liquid Chromatography (UPLC) system (ACQUITY® H-Class, Waters Co., Milford, MA). Upon treatment with dithiothreitol (DTT), A6-FS/BiVO₄ DMSNs rapidly released around 50.0–60.0% of the loaded sorafenib (Supporting Information Fig. S13).

3.5.4. Downregulation of GPX4/xCT axis

Fig. 6A and Fig. S12 demonstrated that A6-FS/BiVO₄ DMSNs efficiently released both iron and sorafenib through a triggered drug release mechanism, ensuring effective loading of the ferroptotic agents to the *KRAS* MT cells. Fig. 6C and D demonstrate that sorafenib released from A6-FS/BiVO₄ DMSNs significantly downregulated the expression of xCT and GPX4 in both *KRAS* WT and MT cells compared to that in A6-BiVO₄ DMSNs. Remarkably, sorafenib is classified as a class I inducer of ferroptosis; it blocks xCT-mediated cystine influx, thereby disrupting the cellular ROS scavenging system, specifically the GPX4/xCT axis. We expected this action coordinately precipitate the ferroptosis when combined with benzoyl ferrocene⁶⁰.

3.5.5. Induction of the Fenton reaction

Cellular iron accumulation and lipid peroxidation are regarded as evidence of the Fenton reaction and markers of ferroptosis. In accordance with the drug release data (Fig. 6A and B) shows that the released iron accumulated in the cytoplasm of CRC cells following the uptake and photocatalytic activation of A6-FS/BiVO₄

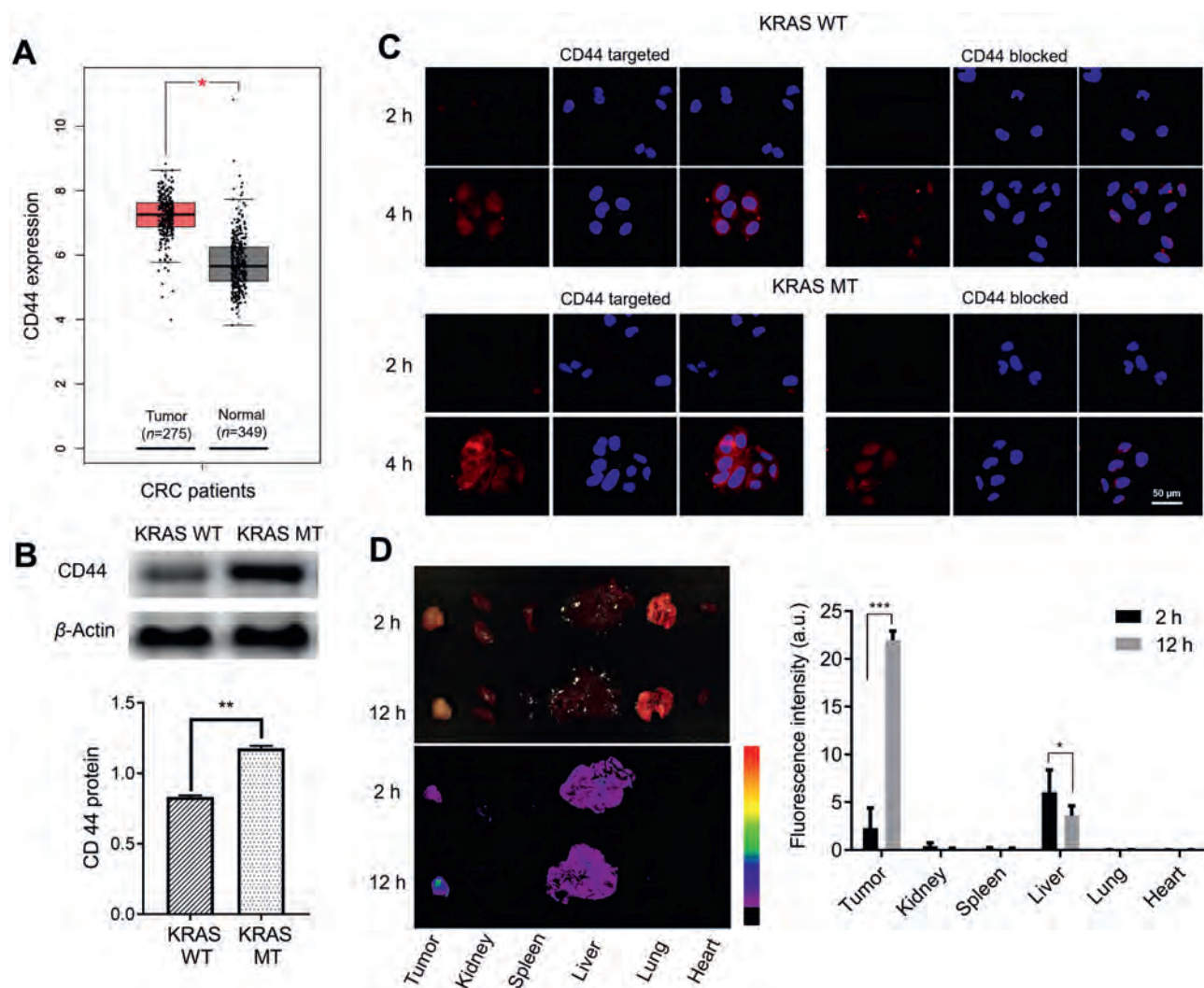


Figure 5 CD44-targeting specificity of A6-BiVO₄ DMSNs for KRAS mutant CRC cells. (A) The expression of CD44 gene in COAD and normal tissue. Data were acquired from GEPIA datasets (<http://gepia.cancer-pku.cn/>). (B) Western blot analysis of CD44 protein in KRAS WT and MT CRC cells. (C) CD44-specific uptake of A6-Nile red/BiVO₄ DMSNs. KRAS WT and MT CRC cells were treated with A6-Nile red/BiVO₄ DMSNs (100 μ g/mL) for 2 h and observed on a fluorescence microscope (scale bar: 50 μ m). For CD44-blocking study, cells were pre-treated with A6-peptide (50 μ g/mL). (D) Ex-vivo fluorescence images of dissected organs obtained from KRAS MT cell-xenografted nude mouse. Mouse were sacrificed at 2, 12, 48 and 72 h after an injection of A6-FITC/BiVO₄ DMSNs (90 μ g per mice). All experiments were repeated in triplicate and data are expressed as means $\pm$ SD, $n = 3$. Statistical significance was calculated using an unpaired t -test (* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$).

DMSNs (300 μ g/mL). And the lipid peroxidation in CRC cells was assessed using a lipid peroxidation sensor dye (BODIPYTM 581/591 C11, Thermo Fisher Scientific Co., Waltham, MA). The shift in fluorescence emission from red to green, particularly in the photocatalytic A6-FS/BiVO₄ DMSNs treatment groups of KRAS WT and MT cells, signified lipid peroxidation associated with ferroptosis (Fig. 6E and F). In contrast, KRAS WT and MT cells that were pretreated with DFO (an iron chelator) and Fer-1 (a ferroptosis inhibitor) exhibited red fluorescence, indicating that ferroptosis inhibition effectively prevented lipid peroxidation.

3.5.6. Ferroptosis-associated cell death for KRAS MT CRC cells
Based on the observed cell death mechanism (Fig. 6E and F), we evaluated the ferroptosis-associated cell death for KRAS MT CRC cells after treatment with A6-FS/BiVO₄ DMSNs. We first confirmed that laser irradiation (up to 47.2 J/cm²) did not

negatively impact cell viability (Supporting Information Fig. S14), and A6-BiVO₄ DMSNs alone (Supporting Information Fig. S15). However, A6-FS/BiVO₄ DMSNs with laser irradiation demonstrated a significantly stronger cytotoxic effect than all other treatments (Supporting Information Figs. S16–S19). Live/dead cell staining further confirmed that the ferroptotic agents (F and S) enhanced the cytotoxicity of the A6-FS/BiVO₄ DMSNs (Supporting Information Figs. S20 and S21). Co-treatment with Fer-1 effectively rescued CRC cell death (Supporting Information Figs. S20–S22), indicating that ferroptosis was a major contributor to the observed cell death. Additionally, we noted significant cellular accumulation of ROS in CRC cells following the photocatalytic activation of A6-FS/BiVO₄ DMSNs (Supporting Information Fig. S23). These findings suggest that the KRAS MT cell-specific death induced by A6-FS/BiVO₄ DMSNs is primarily attributed to ROS generation through the photocatalytic

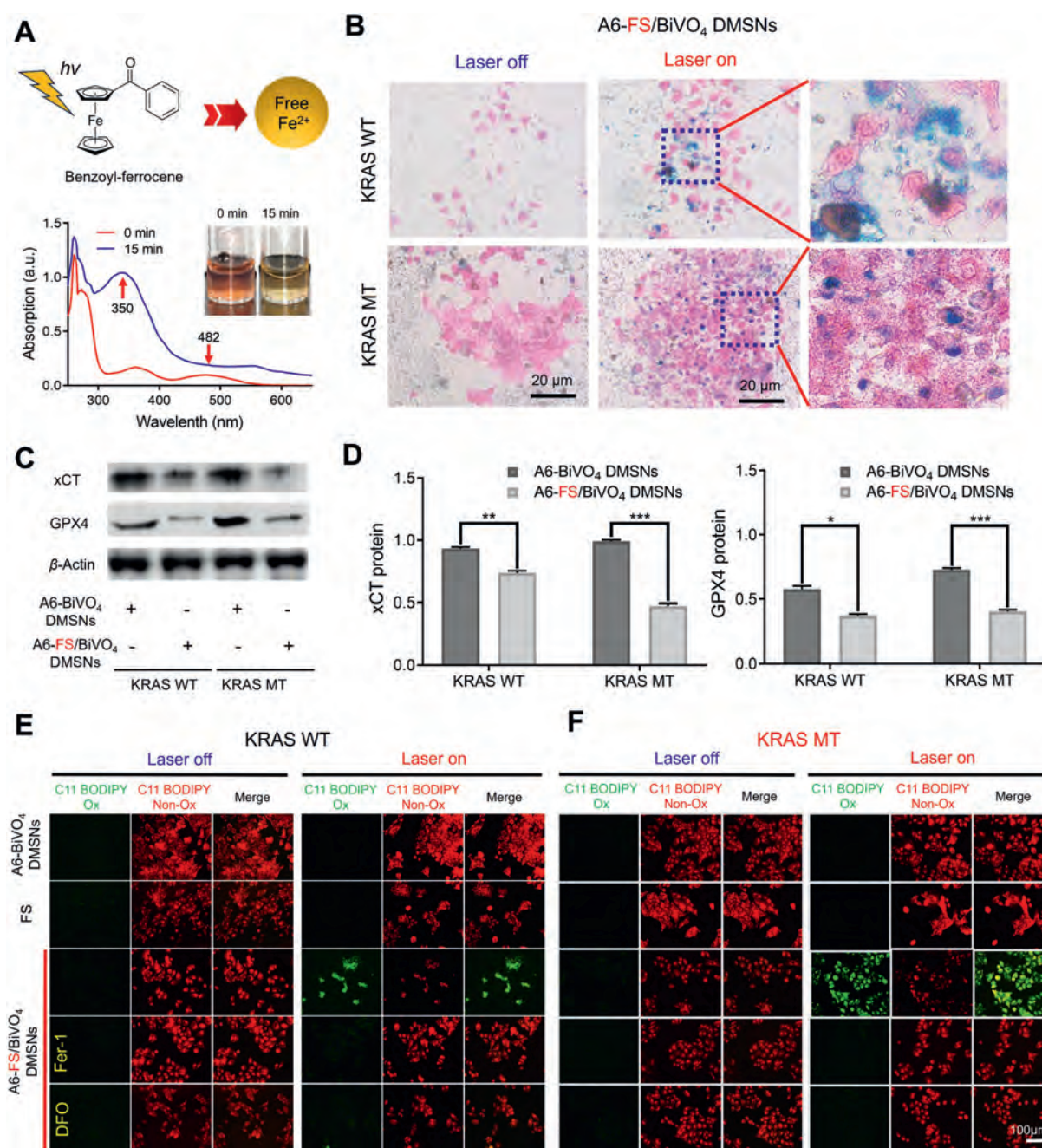


Figure 6 Cascade induction of ferroptosis triggered by photocatalytic activation of A6-FS/BiVO₄ DMSNs and the resulting cellular lipid-peroxidation of KRAS WT and MT CRC cells. (A) Dissociation of ferrous ions from benzoyl ferrocene under laser irradiation. The increased UV absorption suggests the release of ferrous ions. (B) Cellular accumulation of iron assessed through Prussian blue staining (scale bar: 20 μm). (C, D) Downregulation of xCT and GPX4 proteins from the released sorafenib (class I inducer of ferroptosis). (E, F) Lipid peroxidation of KRAS WT (E) and MT (F) CRC cells after treatment with A6-FS/BiVO₄ DMSNs and laser irradiation (Green fluorescence of BODIPYTM 581/591 C11 suggests oxidation of cellular lipid and induction of ferroptosis) (scale bar: 100 μm). All experiments were repeated in triplicate and data are expressed as means $\pm$ SD ($n = 3$). Statistical significance was calculated by an unpaired t -test (* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$).

mechanism, coupled with CD44-specific targeting, subsequent iron accumulation and the downregulation of the GPX4/xCT axis.

3.6. In vivo antitumor efficacy of A6-FS/BiVO₄ DMSNs

In vivo tumor growth inhibition by A6-FS/BiVO₄ DMSNs was evaluated in a KRAS MT CRC cell xenograft animal model.

Initially, we observed the target specificity of A6-FS/BiVO₄ DMSNs in KRAS MT tumor tissue (Fig. 5D and Fig. S11). For the tumor growth inhibition study, the first injection of A6-FS/BiVO₄ DMSNs was administered when the tumor size reached 100 mm³, followed by laser treatment at a dose of 94.32 J/cm², according to the established schedule (Fig. 7A). Over the course of the 21-day treatment period, we noted a significant reduction in tumor growth

in the A6-FS/BiVO₄ DMSNs (+) L group compared to that in the other treatment groups (Fig. 7B–E). Histological analysis of the tumor tissues provided strong evidence that A6-FS/BiVO₄ DMSNs (+) L effectively induced ferroptosis. This was indicated by the observed disruption of the tumor stroma and the presence of abnormally large lipid droplets (Fig. 7F)⁶¹. Additionally, lipid peroxide staining confirmed the accumulation of lipid peroxides in tumor tissues treated with A6-FS/BiVO₄ DMSNs (+) L (Supporting Information Fig. S24). The general toxicity of A6-FS/BiVO₄ was evaluated by monitoring body weight changes during the treatment period, and no significant weight loss was observed

(Fig. 7G), indicating A6-FS/BiVO₄ is non-toxic. Importantly, H&E staining of other organs revealed no signs of toxic injury or inflammation throughout the duration of A6-FS/BiVO₄ DMSNs treatment (Supporting Information Fig. S25). Blood biochemical analysis data of AST, ALT, BUN and creatinine levels after the multiple injections of BiVO₄ DMSNs at a dose of 5 mg/mL/kg also proved A6-FS/BiVO₄ DMSNs treatment did not affect the hepatic and kidney functions in mouse model (Supporting Information Fig. S26). Overall, these findings suggest that the A6-FS/BiVO₄ DMSNs hold promise as an effective therapeutic option for inhibiting tumor growth.

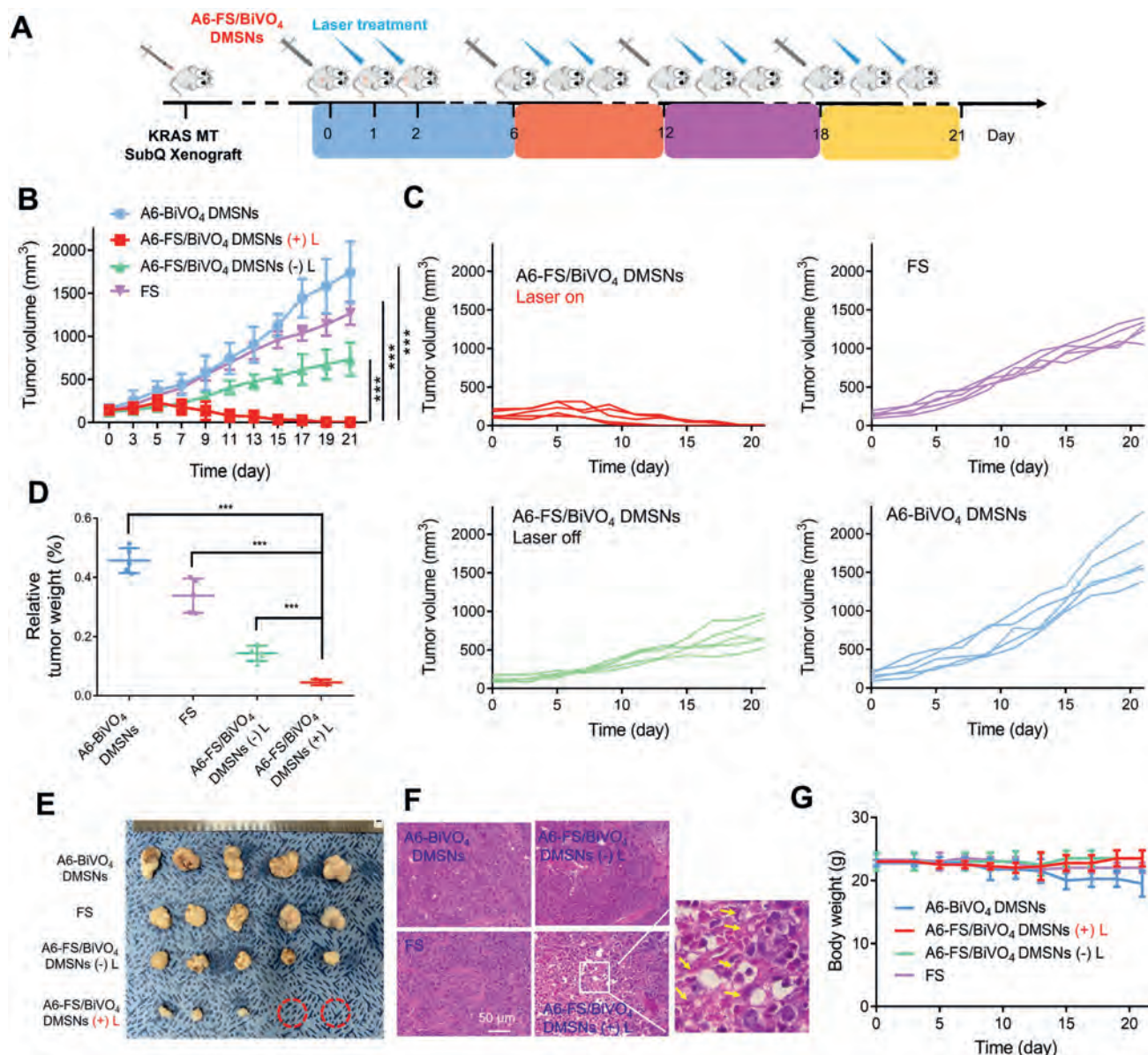


Figure 7 Tumor growth inhibition of photocatalytic A6-FS/BiVO₄ DMSNs in a KRAS MT CRC xenograft model. (A) Treatment protocol for tumor-growth inhibition study. (B) Averaged tumor growth curve of KRAS MT xenograft CRC mouse models under each treatment ($n = 5$). (C) Relative tumor weight (%) of the resected tumors after 21 days of treatment. (D) Tumor growth curves of KRAS MT xenograft CRC mouse models after treatment with A6-BiVO₄ DMSNs, FS, A6-FS/BiVO₄ DMSNs (-) L, and A6-FS/BiVO₄ DMSNs (+) L ($n = 5$). (E) Photo images of the resected tumors after 21 days of treatment. The red circle indicates complete remission of tumors. (F) Representative microscopic photo images of H&E-stained tumor tissues for each treatment. The yellow arrow indicates lipid droplets formed from ferroptosis. (G) Averaged body weight changes in each treatment. Data are expressed as means $\pm$ SD ($n = 5$). Statistical significance was calculated using an unpaired t -test (* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$).

4. Conclusions

We successfully developed a photocatalytic A6-FS/BiVO₄ DMSN capable of triggering ferroptosis chain reactions under laser irradiation to overcome the therapeutic hurdles in KRAS mutant cancer treatment. Our results demonstrated that A6-FS/BiVO₄ DMSNs, when excited by photo-laser, produced an electron hole pair (h⁺ and e⁻) and generated ROS (OH[•] and O₂^{•-}). This photocatalytic activation initiates the ferroptosis cascade, as evidenced by studies on CD44-related KRAS mutant CRC targeting, the release of ferroptotic agents (Fe²⁺ and sorafenib), cellular iron accumulation and ROS generation, the downregulation of xCT, and lipid peroxidation. The A6-FS/BiVO₄ DMSNs system induced ferroptosis in KRAS mutant CRC cells and significantly inhibited tumor growth in KRAS MT cell-xenografted animal models. Our *in vitro* and *in vivo* results demonstrate that the combined design of photocatalytic BiVO₄ and ferroptotic drugs delivered by DMSNs offers reliable therapeutic efficacy against KRAS mutant cancer models and holds great promise for clinical applications.

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Author contributions

Yixin Jiang: Methodology, Result analysis, and writing the original draft. Ratchapol Jenjob: Results analysis, Writing, and Conceptualization. Dahee Ryu: Methodology, Result analysis, and writing for the revision. Zheyu Shen: Result analysis, Conceptualization. Su-Geun Yang: Resources, Supervision, Writing, review and editing, funding acquisition.

Conflicts of interest

The authors declare no conflicts of interest.

Appendix A. Supporting information

Supporting information to this article can be found online at <https://doi.org/10.1016/j.apsb.2025.06.024>.

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