



Dual-targeting by rotating magnetic field-driven superparamagnetic bionic nanorobots for enhanced triple-negative breast cancer therapy

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Abstract

Triple-negative breast cancer (TNBC) is a highly aggressive subtype of breast cancer with limited treatment options and poor prognosis due to the absence of estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 (HER2). Doxorubicin (DOX)-based chemotherapy remains the standard of care, yet dose-limiting cardiotoxicity and rapid chemoresistance compromise efficacy. To overcome these hurdles, we engineered rotating magnetic field-driven nanorobots (MFDNs) comprising DOX-loaded hollow mesoporous iron oxide nanoparticles cloaked with 4T1 cancer cell membranes. Under a rotating magnetic field (RMF; 5 Hz, 100 mT), MFDNs self-assemble into dynamic chains, evading the aggregation that plagues static magnetic field approaches and enabling deep intratumoral penetration. This dual-targeting mechanism, passive homing via membrane recognition and active navigation via RMF, delivers a three-fold higher intracellular DOX concentration than uncoated carriers. Mechanistically, MFDNs depleted intracellular glutathione by 70%, suppressed glutathione peroxidase-4 (GPX4), and elevated Fe^{2+} , reactive oxygen species (ROS), and lipid peroxidation, thereby triggering robust ferroptosis. In 4T1 tumor-bearing mice, intravenous MFDNs plus RMF shrank tumors by 90% compared with 45% for free DOX, without systemic toxicity or weight loss. Histopathology confirmed extensive necrosis, abundant ferroptosis markers, and negligible off-target accumulation. Collectively, the seamless integration of dynamic RMF guidance with biomimetic membrane cloaking positions MFDNs as a clinically translatable nanoplatform that overcomes chemoresistance and markedly improves therapeutic outcomes for TNBC.

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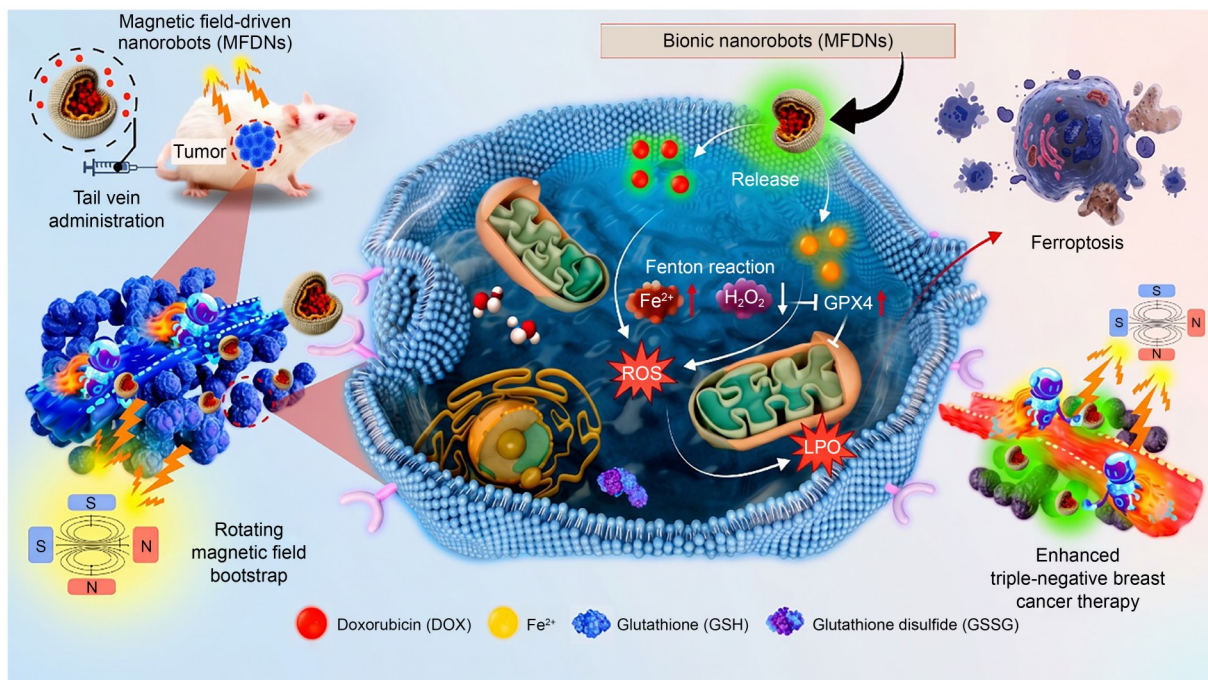
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Graphical abstract



Keywords Biomimetic membrane · Magnetic bionic nanorobots · Ferroptosis · Magnetic guidance · Triple-negative breast cancer

1 Introduction

Breast cancer is the most frequently diagnosed malignancy among women and the leading cause of cancer-related mortality, accounting for 23% of all cancer cases and 14% of cancer deaths globally [1, 2]. Among the various subtypes of breast cancer, triple-negative breast cancer (TNBC) is particularly aggressive and metastatic, with a notably poor prognosis [3]. TNBC is characterized by the absence of expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). This lack of receptor expression limits the availability of targeted therapies, rendering endocrine and HER2-targeted therapies largely ineffective. Consequently, chemotherapy remains the primary treatment modality for TNBC. Doxorubicin (DOX) is a cornerstone chemotherapeutic agent used in TNBC treatment, demonstrating significant efficacy [4, 5]. However, its use is often associated with severe systemic adverse effects, including cardiotoxicity, nephrotoxicity, and myelosuppression, which necessitate close monitoring [6, 7]. These limitations highlight the urgent need for innovative therapeutic strategies that enhance the efficacy of chemotherapeutic agents while minimizing their toxicity to healthy tissues. Developing such approaches is a critical challenge in the ongoing quest to improve TNBC management and

patient outcomes. Ferroptosis is a form of regulated necrosis characterized by iron-dependent lipid peroxidation and distinct from apoptosis. It is driven mainly by an imbalance between oxidative stress and cellular antioxidant defenses. Key features of ferroptosis include the accumulation of iron ions, elevated levels of reactive oxygen species (ROS), depletion of glutathione (GSH), and increased lipid peroxide (LPO) levels [8, 9]. These molecular changes disrupt cellular homeostasis, leading to membrane damage and cell death. Ferroptosis has emerged as a critical pathway in tumorigenesis, tumor progression, and cancer therapy [10, 11]. Recent studies have shown that nanomaterials can induce ferroptosis by providing exogenous iron, enhancing the Fenton reaction, and promoting lipid peroxidation in tumor cells [12–14]. Iron oxide nanoparticles (IONPs), rich in iron ions, have become a focal point in ferroptosis-related research due to their potential to augment intracellular iron levels and induce ferroptosis [15, 16]. Moreover, some superparamagnetic iron oxide nanoparticles (SPIONs) have already been applied in biomedical fields such as drug delivery, magnetic resonance imaging, and gene delivery, demonstrating promising potential [17–19]. In particular, SPIONs are often used in tumor treatment because they can be targeted to tumors using a magnetic field and remain in the tumor area [20, 21]. Static magnetic fields (SMFs) are commonly used to target

SPIONs for tumor therapy [22, 23]. An SMF induces magnetic dipole–dipole attraction between SPIONs, causing them to aggregate into long chain-like structures that can extend indefinitely [24]. This aggregation effect can affect drug release at the tumor site and reduce therapeutic efficacy. In this context, the role of rotating magnetic fields (RMFs) in magnetic targeting biomedical delivery systems is becoming increasingly prominent. Several researchers have shown that RMFs inhibit the aggregation of SPIONs, thereby achieving better therapeutic effects than SMFs [25, 26]. The reason is that when SPIONs are in an RMF, the competition between magnetic and viscous forces in the fluid causes the chains to rotate, thereby limiting their aggregation length [25]. In addition, unmodified hollow iron oxide nanoparticles (HIONs) are prone to adsorption by plasma proteins, leading to rapid recognition and clearance by the mononuclear phagocyte system (MPS), which results in a short circulation time and poor tumor accumulation efficiency [27, 28]. Moreover, they cannot actively recognize tumor cells and rely solely on passive enrichment via the enhanced permeability and retention (EPR) effect, which is often limited and uneven. Due to their non-selective biodistribution, unmodified HIONs are extensively taken up by normal tissues such as the liver and kidneys, potentially causing oxidative damage and iron overload in non-target organs, thereby posing biosafety risks [29, 30]. To enhance nanoparticle stability, prolong circulation time, and achieve precise targeting, various surface modification strategies have been developed. However, traditional coatings have inherent limitations in facilitating complex biological interactions. For instance, polyethylene glycol (PEG)ylation can extend circulation time but may inhibit cellular uptake and trigger immune responses, a phenomenon known as the “PEG dilemma” [31]. Cationic polymers such as polyethyleneimine (PEI) promote endocytosis but often exhibit high cytotoxicity [32]. Even widely used natural polysaccharide coatings like dextran have been associated with metabolic interference, organ-specific cytotoxicity, and DNA damage risks [33]. Bionanotechnology offers a promising alternative to address these limitations. By leveraging the unique properties of biological cell membranes including those derived from red blood cells, platelets, leukocytes, and cancer cells, these coatings inherit the long-circulating characteristics (e.g., the “self-marking” feature of red blood cell membranes) or active targeting capabilities (e.g., the homotypic targeting property of cancer cell membranes) of their source cells [34–37]. Furthermore, through complex surface protein groups such as cluster of differentiation 47 (CD47), integrins, and adhesion molecules, these biomimetic coatings enable precise, low-immunogenicity integration with biological systems [38]. Cancer cell membranes are particularly effective coatings for nanoparticle encapsulation among these biological membranes. They provide a stealth effect against immune clearance

and confer specific targeting capabilities to tumors [37, 39]. This dual functionality significantly improves nanoparticle accumulation at tumor sites, thereby enhancing the delivery of therapeutic agents to cancer cells while minimizing off-target effects.

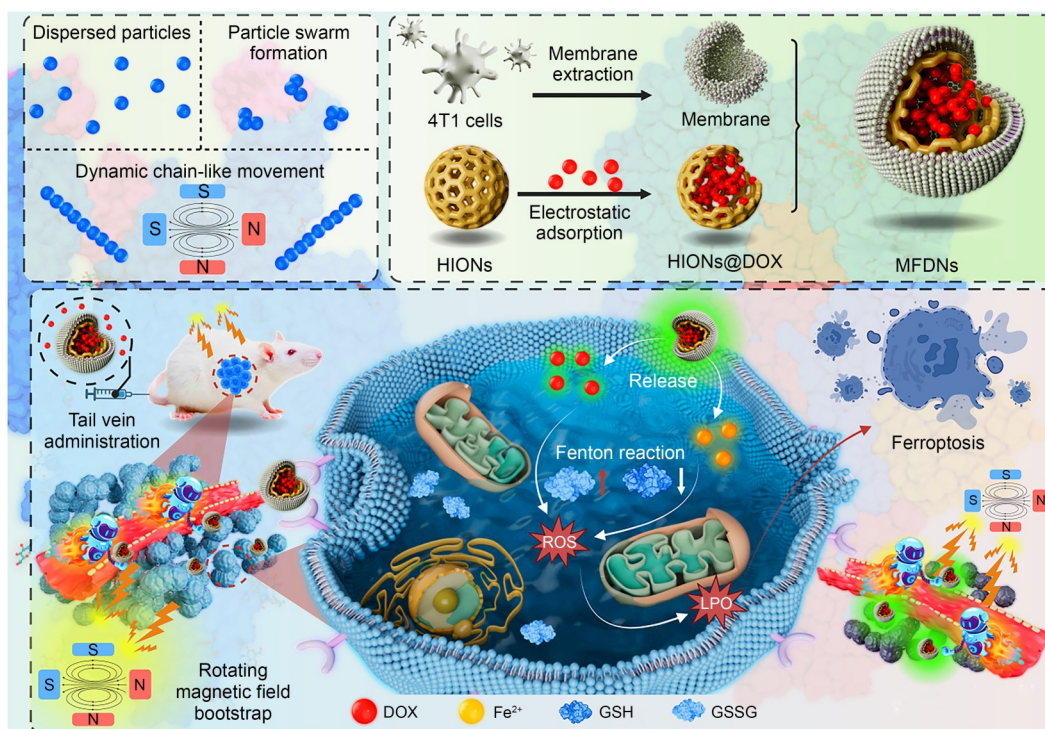
Therefore, to enhance the therapeutic effect on TNBC, we developed rotating magnetic field-driven nanorobots (MFDNs) composed of TNBC cell membrane-encapsulated DOX-loaded hollow mesoporous iron oxide nanoparticles, which exhibit a rotating, chain-like movement when subjected to an RMF. The TNBC cell membrane coating prolonged the nanoparticles' circulation time and conferred homologous passive targeting, facilitating selective accumulation in TNBC tumors. Additionally, the intrinsic magnetic properties of MFDNs enabled their active targeting under an external magnetic field, thereby improving site-specific DOX delivery (Scheme 1). In vitro studies demonstrated that MFDNs significantly enhanced the cytotoxic effects of DOX against TNBC cells. Significantly, the acidic tumor microenvironment facilitated iron ion release from the nanoparticles [40], disrupting intracellular iron metabolism and markedly increasing ROS and LPO accumulation. This cascade effectively induced ferroptosis in tumor cells, as evidenced by elevated oxidative stress markers. In vivo experiments further confirmed that MFDNs, under the guidance of an RMF, substantially inhibited 4T1 tumor growth in a murine model. These results highlight the dual-targeting and ferroptosis-inducing capabilities of MFDNs, underscoring their strong potential as a promising nanotherapeutic platform for TNBC treatment.

2 Materials and methods

2.1 Materials

2.1.1 Experimental chemicals and reagents

Doxorubicin hydrochloride $C_{27}H_{29}NO_{11} \cdot HCl$ (DOX) was purchased from Innochem Technology Co., Ltd. (Beijing, China) and ferric chloride hexahydrate ($FeCl_3 \cdot 6H_2O$), sodium citrate, and urea from the Shanghai Aladdin Biochemical Technology Co. (Shanghai, China). Polyacrylamide (PAM) was obtained from the Sinopharm Chemical Reagent Co. (Shanghai, China). Lipid oxidation (malondialdehyde (MDA)) and terminal deoxynucleotidyl transferase-mediated dUTP nick-end labeling (TUNEL) apoptosis assay kits were purchased from Beyotime Biotechnology (Shanghai, China). 1,1'-Diocetadecyl-3,3,3',3'-tetramethylindotricarbocyanine iodide (DIR) and CellROX Green fluorescent reagent were procured from Thermo Fisher Scientific (MA, USA). Calcein acetoxymethyl ester (Calcein-AM)/propidium iodide (PI) live/dead cell kits and FerroOrange fluorescent probe assay kits were



Scheme 1 Schematic representation of magnetic field-driven nanorobot (MFDN) preparation, magnetic field-driven targeting, tumor-specific delivery, and intracellular Fenton reaction-triggered ferroptosis for enhanced triple-negative breast cancer (TNBC) treatment

sourced from the Dojindo Laboratories (Kumamoto, Japan). Phosphate-buffered saline (PBS) and C11-BODIPY581/591 were purchased from Gibco (NY, USA). Mouse TNBC cell line 4T1 was obtained from the Cell Bank of the Chinese Academy of Sciences. These cells were incubated in Roswell Park Memorial Institute (RPMI) 1640 medium containing 10% fetal bovine serum and 1% penicillin–streptomycin (Gibco). The cells were incubated at 37 °C in 5% CO₂.

2.1.2 Experimental instruments

Nanoparticles (HIONs) were synthesized using a high-pressure reaction vessel (Xi'an Yichuang Instrument and Equipment Co., Xi'an, China) and a DGG-9070B forced-air drying oven (Shanghai Senxin Experimental Instruments Co., Shanghai, China). The morphology of the nanoparticles and MFDNs was characterized using transmission electron microscopy (TEM; Tecnai G2 F20 S-TWIN, FEI Company, OR, USA). The magnetic properties were assessed using a quantum vibrational sample magnetometer (VSM; Quantum Design, CA, USA) at 300 K. The crystalline structure was analyzed by X-ray diffraction (XRD) using a D8 Advance diffractometer (Bruker Corporation, MA, USA). Ultraviolet–visible (UV–Vis) absorption spectra were recorded using a UV-4802 spectrophotometer (Shanghai Unocal Instruments Co., Shanghai, China). Microfluorescence images were captured using an inverted fluorescence microscope (EVOS M5000; Thermo Fisher Scientific) and cell absorbance was

measured using a Multiskan FC microplate spectrophotometer (Thermo Fisher Scientific). The elemental composition and distribution of the samples were analyzed using a Genesis XM series X-ray energy-dispersive spectrometer (EDS; EDAX Inc., NJ, USA).

2.2 Preparation of HIONs

Superparamagnetic Fe₃O₄ hollow microspheres were synthesized using a modified hydrothermal method [41]. First, 2 mmol of FeCl₃·6H₂O, 4 mmol of sodium citrate, and 6 mmol of urea were dissolved in 40 mL of deionized water. Subsequently, 0.3 g of PAM was added to the solution under continuous stirring until all reagents were completely dissolved. The obtained mixture was transferred to a 50-mL stainless steel high-pressure reactor with a polytetrafluoroethylene (PTFE) inner liner and sealed. The sealed reactor was placed in a forced-air drying oven, and the temperature was increased at a rate of 5 °C/min to 200 °C, where it was maintained for 12 h to carry out the hydrothermal reaction. After the reaction was completed, the oven was turned off, and the oven and reactor were allowed to cool naturally to room temperature (about 8–10 h). Following cooling, the reactor was opened, and the black product was collected using a magnet. The product was magnetically separated and washed three times with deionized water and three times with ethanol, and then placed in a vacuum drying oven at 60 °C for 6 h to obtain HION powder for subsequent experiments.

2.3 Fabrication of MFDNs

To prepare MFDNs, the synthesized HIONs were first conjugated with DOX via electrostatic adsorption and coordination interactions, yielding the HIONs@DOX complex [42, 43]. Briefly, HIONs (2.5 mg) and DOX (0.5 mg) were dispersed in 10 mL of ultrapure water and stirred for 12 h at room temperature in the dark. The negatively charged hollow mesoporous structure of HIONs facilitates DOX loading through electrostatic attraction, while coordination bonds between iron ions and DOX functional groups (hydroxyl/carbonyl groups) stabilize the complex. The resulting HIONs@DOX was collected by centrifugation, washed, and used for subsequent membrane coating. Moreover, the drug loading (η_{DL}) and encapsulation efficiency (η_{EE}) were determined by quantifying unloaded DOX in the supernatant using UV spectrophotometry, with the following formulas:

$$\eta_{DL} = \frac{m_{Total1} - m_{Free}}{m_{Total2} + (m_{Total1} - m_{Free})} \times 100\%,$$

$$\eta_{EE} = \frac{m_{Total1} - m_{Free}}{m_{Total1}} \times 100\%,$$

where m_{Total1} is the weight of total drug, m_{Total2} is the weight of total carrier, and m_{Free} is the weight of free drug.

For membrane coating, the prepared HIONs@DOX was mixed with extracted 4T1 cancer cell membranes at a predetermined ratio. The mixture was sonicated for 10 min, and then sequentially extruded through polycarbonate membranes of decreasing pore size (800, 400, and 200 nm), with 10 passes through each membrane. The final extrusion was performed through a 200-nm membrane, and the resulting MFDNs were stored at 4 °C for further use.

2.4 In vitro drug release profile of MFDNs

To evaluate the drug (DOX) release kinetics of MFDNs, we conducted in vitro release experiments under simulated physiological and tumor microenvironment conditions. PBS at pH 7.4 was used to simulate the physiological body fluid environment [44]. PBS at pH 6.8 and 5.4 was used to mimic the acidic extracellular and intracellular tumor microenvironments, respectively [45]. Specifically, 2.5 mg of MFDNs were accurately weighed and placed into a dialysis bag, which was then submerged in 30 mL of PBS with different pH values (7.4, 6.8, and 5.4) in separate triangular flasks. The ends of the dialysis bag were tightly sealed to prevent leakage. The flasks were placed in a water bath maintained at 37 °C with continuous mechanical stirring to ensure uniform conditions. DOX release was monitored over time by periodically removing 1 mL of the external solution at multiple time points. The absorbance of the removed solution was measured using a UV spectrophotometer to quantify the

amount of released DOX. After each removal, the same volume of PBS at the corresponding pH value was added back to maintain a constant 30 mL volume outside the dialysis bag. The release experiment for free DOX followed the same procedure. An Fe^{2+} detection kit (Solarbio, Beijing, China) was used to test for the release of Fe. Excess sodium hydroxylamine powder was added to the supernatant to reduce Fe^{3+} to Fe^{2+} , while all other steps remained unchanged. This procedure enabled assessment of the drug and Fe release behavior of MFDNs under conditions mimicking the physiological environment (pH 7.4) and the acidic tumor microenvironment (pH 6.8 and 5.4).

2.5 Magnetic field-driven motion dynamics and velocity profiles of MFDNs

The self-assembly ability of MFDNs was evaluated by observing their chain formation under an RMF at a frequency of 5 Hz for 60 s. The RMF was generated using a customized multi-coil magnetic field controller, enabling precise control of the magnetic field's intensity and direction. The movement ability of MFDNs was assessed by tracking their trajectories under various RMF frequencies (1, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, and 60 Hz). The movement of MFDNs was captured using an inverted fluorescence microscope (Nikon, Nikon Corporation, Tokyo, Japan) equipped with a scientific complementary metal-oxide-semiconductor (sCMOS) high-speed camera, recording videos at 10 frames/s for 20 s. The trajectories of MFDNs were manually tracked using ImageJ, and their coordinates were recorded. The average speed of the MFDNs was calculated using ImageJ software (version 1.52a) and its plugin MTrackJ, which processed the recorded coordinates to determine the velocity profiles. To quantify the diffusion behavior of MFDNs, the mean square displacement (MSD) was calculated using the following formula:

$$MSD = (x_{\Delta t} - x_0)^2 + (y_{\Delta t} - y_0)^2,$$

where $x_{\Delta t}$ and $y_{\Delta t}$ are the spatial position coordinates at time Δt , x_0 and y_0 are the initial coordinates at time $t=0$, and Δt is the time interval.

2.6 Cytotoxicity assessment

The cytotoxicity of various nanoformulations on 4T1 cells was evaluated by seeding 1×10^4 4T1 cells per well in a 96-well plate. The cells were treated with various nanoformulations at a DOX concentration of 5 $\mu\text{g/mL}$, including control (no treatment), HIONs, DOX, HIONs@DOX, MFDNs, and MFDNs+RMF (5 Hz, 30 min). Later, cells were incubated with these formulations for 24 h. After incubation, the culture medium was aspirated, and the cells were washed with PBS. Subsequently, the cells were incubated with 100 μL

of cell counting kit-8 (CCK-8) solution for 24 h. The 96-well plate was then incubated in a cell incubator for 1 h. The absorbance at 450 nm was measured using a microplate reader to assess cell viability. Further, a Calcein-AM/PI live/dead cell kit was used to determine cell viability and death. 4T1 cells were seeded into 12-well plates and treated with the respective formulations according to the experimental groups. After 24 h of incubation, the culture medium was aspirated, and the supernatant containing dead cells was collected. The remaining live cells were trypsinized and combined with the collected dead cells. The mixed cell suspension was then reseeded into the 12-well plates. Next, 1 mL of the Calcein-AM/PI staining solution from the kit was added to each well. The 12-well plate was incubated in a cell incubator at 37 °C, protected from light, for 30 min. Following incubation, the staining solution was aspirated, and the cells were washed three times with PBS. Fluorescence microscopy (20× objective) was used to randomly capture at least three non-overlapping fields per sample, and images were acquired in the Calcein-AM (excitation/emission wavelength: 494 nm/517 nm) and PI (excitation/emission wavelength: 535 nm/617 nm) channels. Using ImageJ software, a validated fluorescence intensity threshold (based on negative controls) was applied to each channel to quantify live cells (green) and dead cells (red). Live and dead cell counts per field were determined under single-blind conditions and expressed as percentages relative to the total cell count per field. Final data for each group represent the average of these percentages across multiple independent experiments.

2.7 In vitro ROS generation assay

ROS production in 4T1 cells following treatment was detected using the CellROX Green fluorescence kit. 4T1 cells were seeded into 12-well plates and exposed to the designated formulations according to the experimental groups. After a 24-h incubation, the culture medium was removed, and the cells were washed three times with PBS. A 2',7'-dichlorodihydrofluorescein diacetate (DCFH-DA) staining solution was prepared according to the kit instructions, and 1 mL was added to each well. The 12-well plate was then incubated in a cell culture incubator for 15 min, protected from light. After incubation, the staining solution was removed, and the cells were washed three times with PBS. The cells were then imaged using the green fluorescence channel of an inverted fluorescence microscope.

2.8 Assessment of the markers related to ferroptosis

Ferroptosis induction in 4T1 cells was evaluated by measuring several key markers. The 4T1 cells were grown in 12-well plates and treated with the corresponding formulations in

tandem with the experimental groups. After 24 h of incubation, intracellular ferrous iron (Fe^{2+}) levels were quantified using the FerroOrange Intracellular Ferrous Ion Fluorescent Probe Detection Kit (Dojindo Laboratories). LPO was assessed using the C11-BODIPY581/591 probe. GSH and glutathione disulfide (GSSG) levels were determined using GSH and GSSG assay kits. MDA, a marker of lipid peroxidation, was measured using an MDA assay kit. These assays collectively provided insights into the ferroptosis-related changes in the treated 4T1 cells.

2.9 Western blot (WB) analysis of ferroptosis-related proteins

The effects of nanoformulations on the expression of ferroptosis-related proteins were investigated using western blotting. The 4T1 cells were seeded into 6-well plates and treated with control, HIONs, DOX, HIONs@DOX, and MFDNs (DOX concentration of 5 $\mu\text{g/mL}$) for 24 h. The cells were washed three times with PBS, lysed with cell lysis buffer supplemented with phenylmethylsulfonyl fluoride (PMSF) on ice, and centrifuged at 12,000 r/min for 15 min at 4 °C. The protein concentration in the supernatants was measured using a bicinchoninic acid (BCA) protein quantification kit. After being placed onto a polyacrylamide gel for electrophoresis, protein samples were transferred to a polyvinylidene difluoride (PVDF) membrane. With a 1:1000 dilution of an anti-glutathione peroxidase 4 (GPX4) primary antibody, the membrane was blocked and incubated overnight at 4 °C. After three washes with Tris-buffered saline containing Tween-20 (TBST), the membrane was incubated with the appropriate secondary antibody (diluted 1:5000 in TBST) for 1 h at room temperature. Later, protein bands were identified using an enhanced chemiluminescence system.

2.10 In vivo anti-tumor efficacy of MFDNs

Female BALB/c mice (6–8 weeks, SBF Biotechnology, Beijing, China) were kept in specific-pathogen-free conditions ((22 ± 1) °C, (50 ± 10)% humidity, 12 h light/dark cycle) with unrestricted access to food and water. 4T1 cells (1×10^6 in 100 μL PBS) were inoculated subcutaneously into the right flank. Tumor size was measured with digital calipers, and volume was calculated as $V = 0.5 \times L \times W^2$ (L , the longest diameter; W , the perpendicular width). When tumors reached 100–150 mm^3 , mice were randomly assigned to six groups ($n=4$): Control (saline), HIONs, DOX, HIONs@DOX, MFDNs, and MFDNs+RMF. The MFDNs+RMF group received MFDNs via tail vein injection while an RMF was applied at the tumor site. Formulations were administered via tail vein injection at 5 mg DOX per kg body weight every 48 h. For group 6, an RMF at 5 Hz and 100 mT was locally applied for 15 min immediately after each injection. Body

weight and tumor dimensions were recorded every 3 d. On Day 18, mice were euthanized; tumors and major organs (heart, liver, spleen, lungs, and kidneys) were harvested, weighed, and imaged. Tumor sections were processed for hematoxylin and eosin (H&E) staining, immunohistochemistry (IHC), immunofluorescence (IF), TUNEL, Prussian blue staining, and LPO staining. The major organs were also collected and analyzed using H&E staining.

2.11 In vivo distribution and biosafety of MFDNs

To track the in vivo distribution of MFDNs, we replaced DOX with 20 µg/mL of the imaging dye DIR during the preparation process, yielding MFDNs@DIR and MFDNs@DIR+RMF. The DIR emits near-infrared fluorescence that can penetrate tissues and skin and be detected by an in vivo imaging system. The mice were anesthetized using isoflurane inhalation and administered MFDNs@DIR via tail vein injection with and without an RMF (MFDNs@DIR and MFDNs@DIR+RMF). Then, at 2, 6, 12, 24, and 48 h post-injection, the mice were imaged using an AniView100 multimodal animal live-imaging system (Boluteng Biotechnology Co., Ltd., Guangzhou, China). At 48 h post-injection, the mice were euthanized, and their major organs (heart, liver, spleen, lungs, and kidneys) and tumor tissues were isolated and photographed ex vivo. For the MFDNs@DIR+RMF group, the incubation period was prolonged to 72 h, and all other procedural parameters were held constant. This approach permitted time-resolved evaluation of MFDN distribution and accumulation across various tissues in the mouse model.

2.12 Statistical analysis

All data are expressed as mean±standard deviation. Statistical significance was determined using one-way and two-way analysis of variance (ANOVA). In all analyses, $p < 0.05$ was considered statistically significant (95% confidence interval).

3 Results

3.1 Preparation and characterization of MFDNs

The nanoparticles (HIONs@DOX) and bionic nanorobots (MFDNs) were successfully fabricated. The TEM image in Fig. 1a reveals that the synthesized HIONs@DOX nanoparticles exhibit a uniform spherical hollow structure loaded with DOX. The hollow structure makes them suitable as drug carriers. Figure 1b shows that the surface of these HIONs@DOX nanoparticles is covered with translucent cell membranes (termed MFDNs). EDS analysis (Fig. 1c) was performed to

determine the chemical composition and elemental distribution in MFDNs. The results showed that the nanorobots are composed mainly of iron (Fe) and oxygen (O), with nitrogen (N) and phosphorus (P) present on the surface. The sodium dodecyl sulfate–polyacrylamide gel electrophoresis (SDS-PAGE) result of MFDNs revealed a protein fingerprint identical to that of native 4T1 cell membranes, confirming quantitative membrane transfer and retention of surface antigens (Fig. 1d). Dynamic light scattering showed a monodisperse size progression from (213.1 ± 1.7) nm (HIONs) to (227.0 ± 4.2) nm (HIONs@DOX) and (260.4 ± 4.1) nm (MFDNs), consistent with sequential DOX loading and membrane cloaking (Fig. 1e). Surface charge shifted from (22.4 ± 0.6) mV (HIONs@DOX) to (-29.0 ± 0.4) mV (MFDNs), mirroring the zeta potential of isolated 4T1 membranes (-37.0 ± 1.7) mV and corroborating complete membrane envelopment (Fig. 1f). Powder X-ray diffractograms showed reflections at $2\theta = 30.1^\circ, 35.5^\circ, 43.1^\circ, 57.0^\circ$, and 62.6° , indexing exclusively to the cubic spinel phase of magnetite (Fe_3O_4 , PDF#19-0629) with no impurity peaks (Fig. 1g). Vibrating-sample magnetometry revealed superparamagnetic behavior at 300 K, with a saturation magnetization (M_s) of 329.05 emu/g at 3 kOe ($1 \text{ emu/g} = 1000 \text{ A/m}$; $1 \text{ kOe} = 79.58 \text{ kA/m}$; Fig. 1h), indicating that the magnetization of HIONs@DOX approaches saturation at this field strength. These results indicate that the magnetic induction intensity of HIONs@DOX is proportional to the applied magnetic field intensity. This confirms that the synthesized MFDNs exhibit strong superparamagnetism, providing a theoretical basis for subsequent experiments involving active magnetic-field targeting. The MFDN's comparative figure after magnetic field adsorption is shown in Fig. S1 (supplementary information). The in vitro DOX release profiles of free DOX and MFDNs at different pH levels are shown in Fig. S2 (supplementary information). Free DOX exhibited pH-independent release, with nearly overlapping release curves at pH 7.4 and 5.4. The cumulative release exceeded 65% within 8 h and approached 90% after 48 h, indicating that the diffusion behavior of free DOX is not affected by pH. In contrast, MFDNs demonstrated significant pH-responsive release. Under acidic conditions (pH 6.8 and 5.4), DOX release was markedly accelerated, with final release rates exceeding 60% after 72 h. Under physiological pH (7.4), release was substantially slower, with only about 40% released over the same period. These results confirm that MFDNs achieve pH-triggered controlled release: slow release under normal physiological conditions, thereby minimizing systemic toxicity, and accelerated release in the acidic tumor microenvironment, enabling targeted drug delivery. Free DOX lacks this pH selectivity and cannot achieve such controlled release. Furthermore, the Fe release studies (Fig. 1i) showed a similar pH-responsive pattern, which was slow and limited release under physiological conditions (pH 7.4), ensuring circulatory stability, and accelerated release under acidic

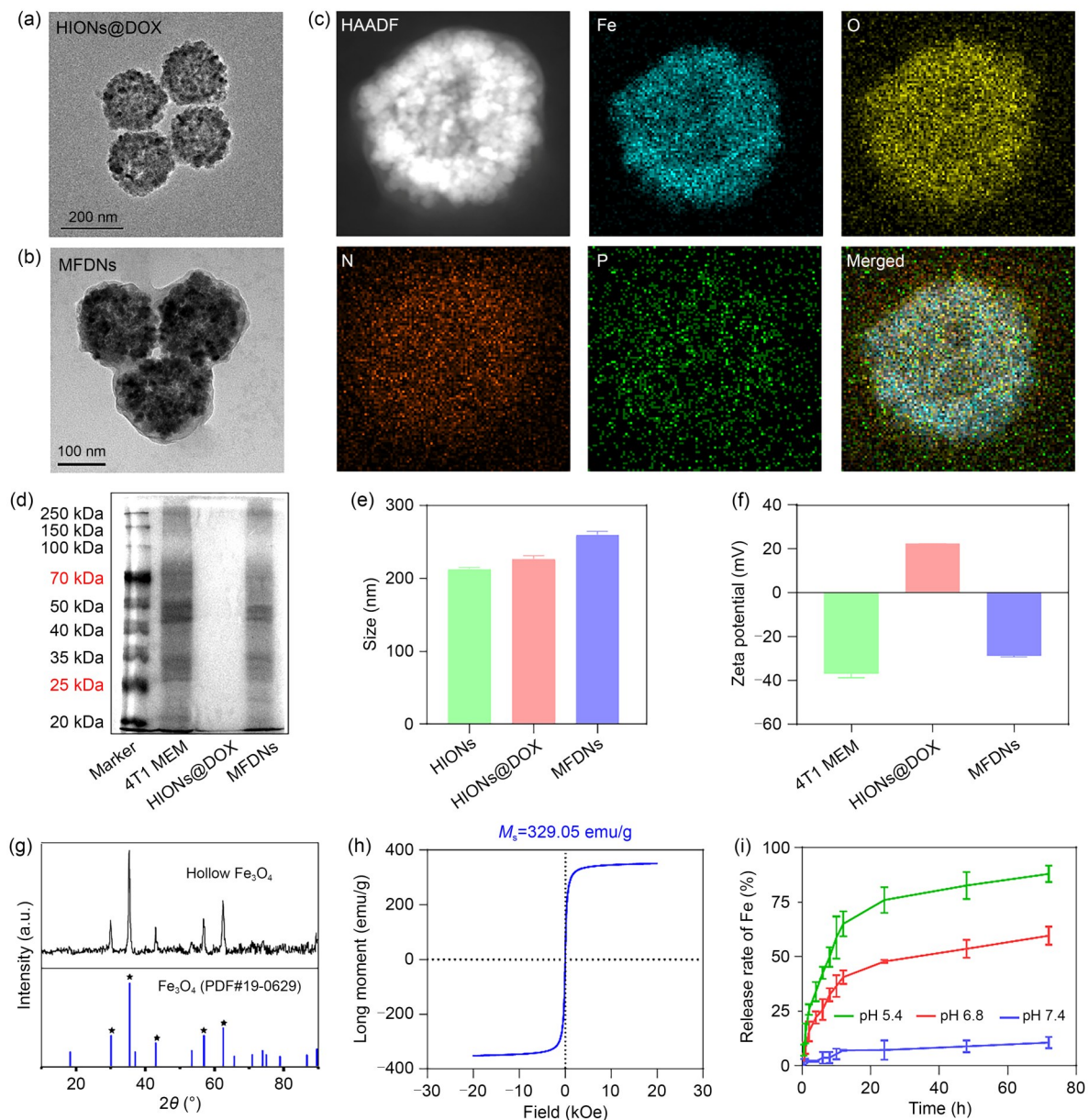


Fig. 1 Synthesis and characterization of magnetic field-driven nanorobots (MFDNs). (a) The transmission electron microscopy (TEM) image of HIONs@DOX. (b) TEM image of MFDNs. (c) High-angle annular dark-field (HAADF) image and elemental mapping images of MFDNs. (d) Sodium dodecyl sulfate–polyacrylamide gel electrophoresis (SDS–PAGE) analysis of 4T1 tumor cell membrane (4T1 MEM), HIONs@DOX, and MFDNs. (e) Hydrodynamic size distribution profiles of various nanoformulations. (f) Zeta potential measurements of 4T1 MEM and various nanoformulations (HIONs@DOX and MFDNs). (g) X-ray diffraction (XRD) of HIONs@DOX. (h) Hysteresis loop of HIONs@DOX (1 emu/g=1000 A/m; 1 kOe=79.58 kA/m). (i) Fe release profiles from MFDNs under different pH conditions (5.4, 6.8, and 7.4). Data in (e, f, i) are expressed as mean±standard deviation ($n=3$)

tumor conditions facilitating iron-mediated ferroptosis. This pH-responsive characteristic provides a crucial foundation for MFDNs to specifically induce ferroptosis at the tumor site.

3.2 Magnetic field-driven motion dynamics and velocity profiles of MFDNs

Following the successful synthesis of MFDNs, we constructed a customized multi-coil magnetic field controller to

generate an RMF that transforms MFDNs into chain-like nanorobots. The magnetic field controller comprised two pairs of orthogonal electromagnetic coils and a solenoid [46] (Fig. 2a; Fig. S3 in the supplementary information). These orthogonal coils could be individually controlled to generate RMFs of varying intensities and directions, thereby facilitating the assembly and propulsion of MFDNs. Upon application of the RMF, the superparamagnetic MFDNs induce a magnetic

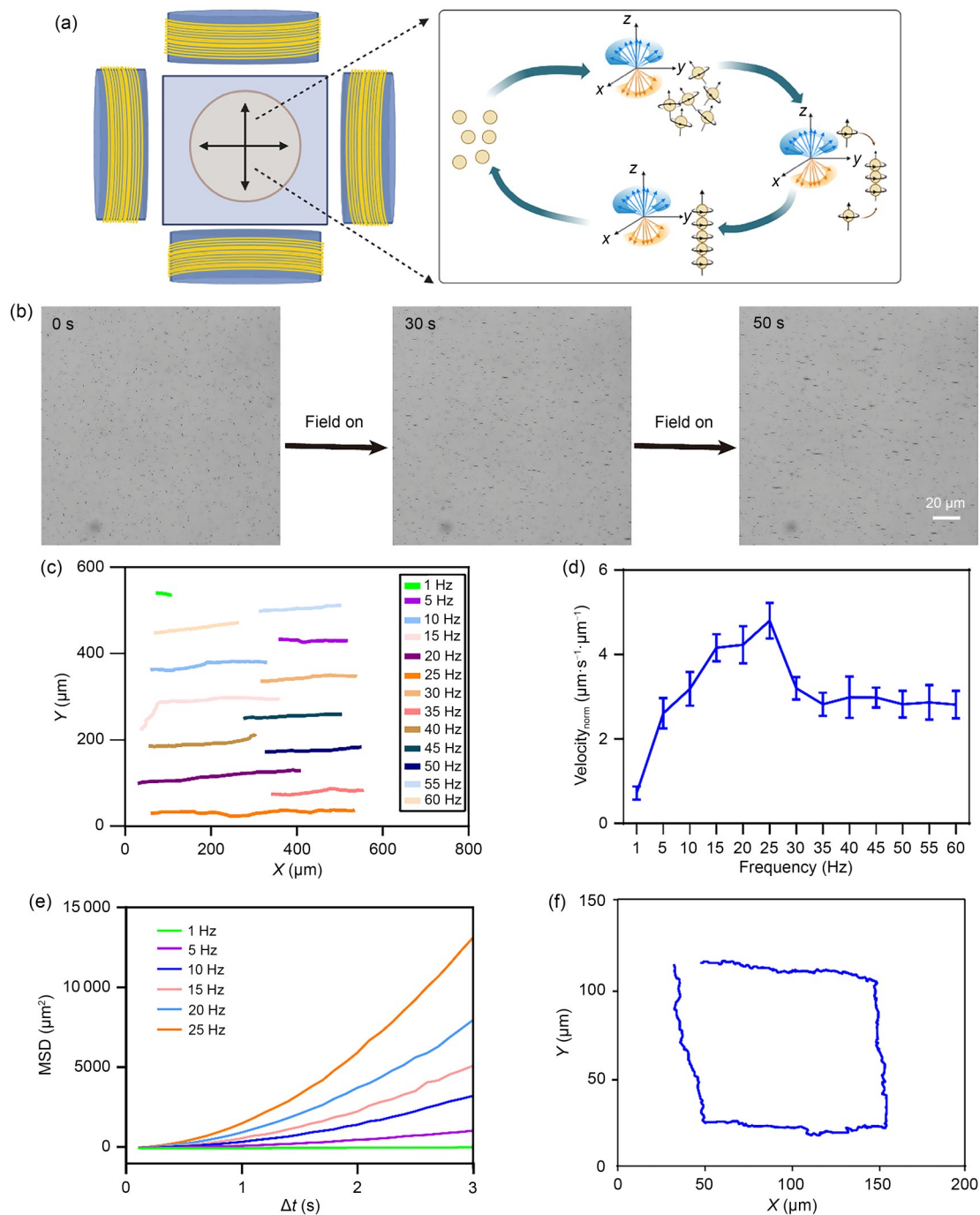


Fig. 2 Magnetic-driven motion dynamics and velocity of magnetic field-driven nanorobots (MFDNs). (a) Schematic diagram of the chain formation process under a rotating magnetic field (RMF). (b) Microscopic images of the MFDN self-assembly process under the action of a magnetic field ($n=15$). (c) Optical tracking trajectories of MFDNs at different frequencies ($n=15$). (d) Normalized velocities of MFDNs at different frequencies in phosphate-buffered saline ($n=15$, mean±standard deviation). (e) Mean square displacement (MSD) curves of MFDNs at multiple frequencies ($n=15$). (f) The drawing of a rectangular trajectory by adjusting the magnetic field ($n=3$)

dipole moment that aligns with the angular velocity provided by the magnetic torque [47]. This alignment causes the particles to dynamically self-assemble into chains, forming micron-level MFDNs (Fig. 2b; Video S1 in the supplementary information). In our design, the chain length is governed by the dynamic equilibrium among magnetic field strength,

field frequency, fluid viscosity, and the hydrodynamic torque generated by chain rotation. As chains elongate, the hydrodynamic torque increases proportionally, establishing a physical limit on further chain growth. Under our experimental conditions (5 Hz RMF), the chain length remained within the submicron-to-micrometer range, with an average

length of about 3 μm (Fig. 2b). This upper limit prevents excessive aggregation and mitigates the risk of embolus formation, keeping chain lengths below the typical threshold for clinically significant vascular emboli [48]. Furthermore, to investigate the motion behavior of MFDNs under different magnetic field intensities [49], we varied the RMF frequency from 1 to 60 Hz and recorded their trajectories (Fig. 2c). To eliminate chain length as a confounding factor, we normalized the measured velocity of each chain by its corresponding length. Analysis of this length-normalized velocity revealed that the intrinsic motion efficiency of MFDNs peaked at 25 Hz ($4.80 \mu\text{m}\cdot\text{s}^{-1}\cdot\mu\text{m}^{-1}$) and then decreased with increasing frequency and eventually stabilized at about $2.80 \mu\text{m}\cdot\text{s}^{-1}\cdot\mu\text{m}^{-1}$ (Fig. 2d; Video S2 in the supplementary information). This behavior is attributed to the balance between magnetic torque and hydrodynamic resistance. When the magnetic torque exceeds the hydrodynamic resistance, particles rotate synchronously with the magnetic field. However, as the angular velocity induced by the magnetic torque exceeds the particle's critical value, hydrodynamic resistance dominates, limiting particle rotation and reducing the rotational speed. This critical frequency, known as the step-out frequency, was determined to be 25 Hz in our experiments [50]. This finding aligns with observations from other studies on spiral micro-robots [46], indicating that the cell membrane coating on MFDNs does not impede their motility under an RMF. To quantify the diffusion behavior of MFDNs at different magnetic field frequencies, we calculated the MSD from their motion trajectory coordinates (Fig. 2e). The resulting fitting curves showed that MFDNs exhibit directional motion, with the curves' slopes correlating with the observed frequency–velocity relationship [51]. For individual MFDNs, we adjusted the phase of the coil-axis ($x/y/z$) that controls the RMF to change the precession axis direction, thereby directing the movement of the MFDNs. We designed an approximate motion route for a single MFDN. Under our control, the MFDNs traveled along a predetermined path (Video S3 in the supplementary information) and followed a motion trajectory resembling a rectangle (Fig. 2f; Fig. S4 in the supplementary information).

In summary, we have developed a self-assembling chain-like nanorobot that can be remotely manipulated and encapsulated in cancer cell membranes. This approach differs from traditional magnetic tumor-targeting methods that use SMFs, which often result in local particle aggregation [25]. In contrast, we investigated the diffusive motion of MFDNs under an RMF. Unlike static magnetic fields that induce uncontrolled aggregation, the rotational drive generates a “drilling” effect that enables MFDNs to penetrate dense extracellular matrices and tumor stroma. This enhanced diffusion facilitates deeper tumor penetration, while the dynamic nature of the chains allows for reversible assembly, promoting uniform intratumoral distribution and preventing local over-aggregation.

3.3 Cellular uptake and cytotoxicity assay of MFDNs

To exert therapeutic effects, tumor cells must internalize nanoparticles to facilitate intracellular drug release and subsequent tumor cell death. Therefore, we first evaluated the cellular uptake of HIONs@DOX and MFDNs by 4T1 breast cancer cells (Fig. 3a). Fluorescence microscopy and quantitative analysis revealed that both nanoformulations were effectively internalized. Notably, the average fluorescence intensity of MFDNs in 4T1 cells was 2.39-fold higher than that of HIONs@DOX ($p<0.001$), indicating enhanced cellular uptake efficiency (Fig. 3c). To investigate homologous targeting specificity, we compared the uptake of HIONs@DOX and MFDNs by L929 fibroblasts (Fig. 3b). Quantitative analysis confirmed the selectivity of cellular uptake: MFDNs exhibited 1.48-fold higher uptake in 4T1 cells than in L929 cells ($p<0.05$), confirming the selective targeting capability conferred by the cancer cell membrane coating (Fig. 3c). This difference can be attributed to the “protective effect” provided by the cancer cell membrane coating, which reduces the interaction of MFDNs with non-homologous cells. These findings confirm that MFDNs exhibit strong homologous targeting ability, minimizing off-target effects and potential in vivo cytotoxicity to normal cells. The in vitro cytotoxicity of the nanoparticles and nanorobots was evaluated using the CCK-8 assay. First, the biocompatibility of HIONs and MFDNs with normal cells was assessed using L929 cells. Even at a high concentration of 80 $\mu\text{g/mL}$, the viability of L929 cells decreased only slightly (Fig. 3d), indicating that both HIONs and MFDNs exhibit good biocompatibility with normal cells. Furthermore, the CCK-8 results (Fig. 3e) showed that free DOX exhibited significant cytotoxicity, confirming its chemotherapeutic efficacy. HIONs@DOX showed superior cytotoxicity compared to free DOX, attributed to enhanced intracellular drug accumulation. Notably, cell viability was significantly lower in the MFDNs group than in the HIONs@DOX group ($p<0.001$) and further reduced in the MFDNs+RMF group ($p<0.001$), indicating that biomimetic membrane modification enhances tumor targeting and RMF active navigation further improves therapeutic efficacy. Calcein-AM/PI staining also confirmed these findings (Figs. 3f and 3g). The MFDNs+RMF group exhibited the highest percentage of dead cells ($(78.05\pm1.41)\%$) and the lowest percentage of live cells, with significant differences compared to the control group ($p<0.001$, Fig. 3f). Fluorescence images (Fig. 3g) visually demonstrated the strongest red fluorescence (dead cells) and weakest green fluorescence (live cells) in the MFDNs+RMF group. Collectively, these results demonstrate that HIONs@DOX exerts anti-tumor effects through chemotherapy, MFDNs achieve enhanced targeting via biomimetic membrane modification, and RMF actively drives and potentiates therapeutic efficacy.

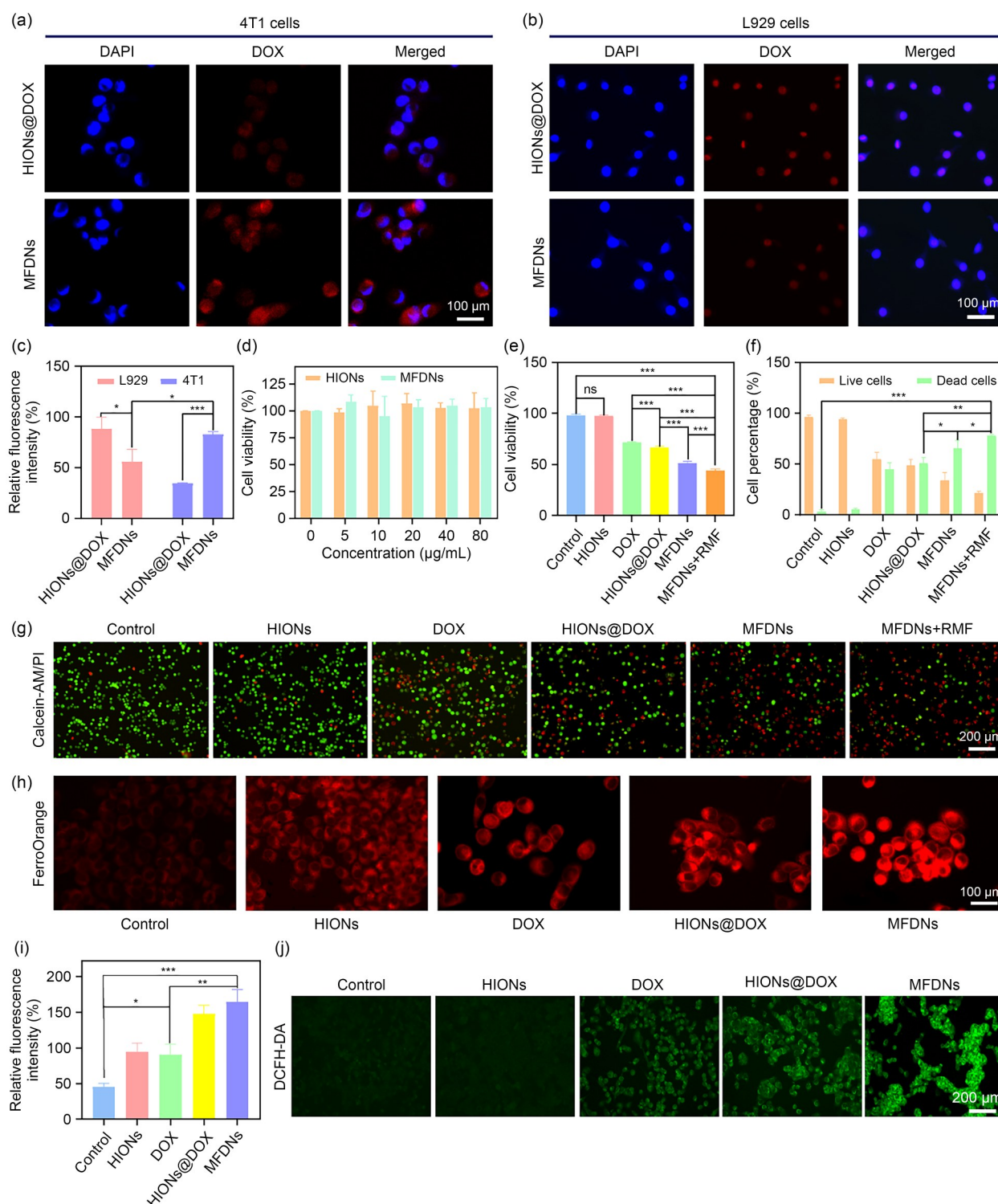


Fig. 3 In vitro evaluation of cellular uptake, cytotoxicity, and ferroptosis-inducing capability of magnetic field-driven nanorobots (MFDNs). (a) Cellular uptake of HIONs@DOX and MFDNs by 4T1 cells. (b) Cellular uptake of HIONs@DOX and MFDNs by L929 cells. (c) Semi-quantitative analysis of fluorescence intensity in 4T1 cells and L929 cells. (d) Survival rate of L929 cells after incubation with different concentrations of HIONs and MFDNs for 24 h. (e) Survival rate of 4T1 cells after incubation with various groups of treatment for 24 h. (f) Percentages of live and dead cells in each group after calcein acetoxymethyl ester (Calcein-AM)/propidium iodide (PI) staining. (g) Images of 4T1 cells stained with Calcein-AM/PI after treatment with different nanoformulations. (h) Fluorescence microscope images of 4T1 cells stained with FerroOrange after various therapies. (i) Quantitative analysis of fluorescence intensity of FerroOrange staining. (j) Reactive oxygen species (ROS) plots of 4T1 cells treated with multiple groups. Data in (c–f, i) are expressed as mean $\pm$ standard deviation ($n=3$). ns: not significant; * $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$. DAPI: 4',6-diamidino-2-phenylindole

3.4 In vitro anti-tumor efficacy

Ferroptosis is an iron-dependent form of cell death, and the first key step in this process is the disruption of iron metabolism [52]. Both Fe^{3+} and Fe^{2+} can participate in the Fenton reaction and enhance ferroptosis. However, a more precise distinction is that Fe^{3+} serves mainly as the stable structural form of nanoparticles and the “precursor” of ferroptosis within cells, achieving targeted delivery and acid-responsive release. Fe^{2+} is the direct catalyst of lipid peroxidation and the “executor” of ferroptosis, generating free radicals through the Fenton reaction, a decisive step for ferroptosis [53]. It is crucial to determine whether nanoparticles can increase intracellular iron content. As depicted in Figs. 3h and 3i, the FerroOrange content diagrams show enhanced fluorescence in the HIONs, DOX, HIONs@DOX, and MFDNs groups, with the MFDNs group exhibiting the strongest signal. This indicates that cells treated with MFDNs have the highest levels of Fe^{2+} , providing the necessary condition for the subsequent Fenton reaction. The Fenton reaction, a pivotal step in ferroptosis, is catalyzed by ferrous ions and consumes H_2O_2 to produce a large amount of toxic ROS [54]. The DCFH-DA probe, which fluoresces green in the presence of ROS, confirms this process. Figure 3j and Fig. S5 (supplementary information) show that cells treated with MFDNs exhibited significantly stronger green fluorescence than the control group, indicating a higher ROS production. This finding supports the hypothesis that MFDNs effectively induce ferroptosis by increasing intracellular Fe^{2+} levels and subsequent ROS production. In cells undergoing ferroptosis, reduced GPX4 activity is often central to the mechanism [55, 56]. WB experiments (Figs. 4a and 4b) show GPX4 expression in 4T1 breast cancer cells after treatment with different nanoformulations. Compared to the control group, GPX4 activity in the material-only group remained unchanged. In the DOX group, GPX4 activity decreased, but the most significant reduction was observed in the MFDNs group, which showed the lowest GPX4 expression. This suggests a synergistic effect between HIONs and DOX, indicating that the nanodrug delivery platform effectively inhibits GPX4 activity, thereby inducing ferroptosis in 4T1 TNBC cells. High intracellular levels of GSH can counteract toxic ROS and inhibit ferroptosis in tumor cells by virtue of its reducibility [57, 58]. Therefore, we aimed to reduce intracellular GSH levels using our magnetically driven bionic nanorobots. The results of the GSH detection kit show that the MFDNs group consumed about 70% of GSH after entering the cells (Fig. 4c). This indicates that MFDNs can significantly deplete intracellular GSH, thereby enhancing the tumor’s antioxidative microenvironment and improving ferroptosis efficacy. In the process of cell ferroptosis, the accumulation of a large number of ROS disrupts the intracellular redox balance. It impairs antioxidant functions, leading

to a lipid peroxidation state of the cell membrane, which ultimately results in membrane rupture and cell death [59, 60]. We used LPO fluorescent probes and MDA kits to assess LPO levels. After treating 4T1 cells with the control, HIONs, DOX, HIONs@DOX, and MFDNs groups, we observed a gradual increase in green fluorescence and a decrease in red fluorescence (Figs. 4d and 4e). The MFDNs group exhibited the strongest green fluorescence and the weakest red fluorescence, indicating the highest LPO level. The MDA kit, which quantitatively measures the lipid peroxidation product MDA in the cell membrane, confirmed these findings (Fig. 4f), considering that ROS accumulation and mitochondrial damage may also lead to apoptosis [61, 62]. We used TUNEL staining to assess the ability of nanoformulations to induce apoptosis. The results showed a gradual increase in apoptosis levels in the DOX, HIONs@DOX, and MFDNs groups compared to the control group (Figs. 4g and 4h).

3.5 In vivo anti-tumor efficacy of MFDNs

The anti-tumor efficacy of drug-loaded nanoformulations was further evaluated in vivo through animal experiments (Figs. 5a and 5b). On Day 18 of treatment, mice were euthanized, and tumor tissues were excised, photographed, and weighed (Figs. 5f and 5g). Tumor volume growth curves (Figs. 5c and 5d) revealed that treatment effects began to manifest on Day 6. By the end of the treatment period, tumors in the DOX, HIONs@DOX, MFDNs, and MFDNs+RMF groups were significantly smaller than those in the control group, with the MFDNs+RMF group exhibiting the smallest tumors and the most potent tumor-suppressing effect. During the experiment, we meticulously monitored the mice’s body weight. As depicted in Fig. 5e, no significant weight loss was observed, and there were no notable differences between groups following treatment. To more intuitively observe the cytotoxic effects of DOX-loaded nanoparticles in vivo, we performed H&E staining and Ki67 IHC staining on tumor sections (Fig. 5h). H&E staining results showed that tumor cells in the control and HIONs groups were relatively intact with no apparent apoptosis. In contrast, the MFDNs+RMF group exhibited large necrotic areas and apoptotic cells with nuclear cleavage. The HIONs@DOX and MFDNs groups also showed some necrotic foci and apoptotic cells. The expression levels of the cell proliferation marker Ki67 in tumor tissues, which reflect tumor proliferation levels, were consistent with the H&E results. The control group had the highest Ki67 antigen expression, while Ki67 expression was significantly downregulated in the MFDNs and MFDNs+RMF groups. As depicted in Fig. 5h, IF staining for GPX4, a key enzyme in ferroptosis, mirrored the results of the WB assay. The control group exhibited the highest GPX4 expression, while GPX4 expression decreased progressively in the other groups,

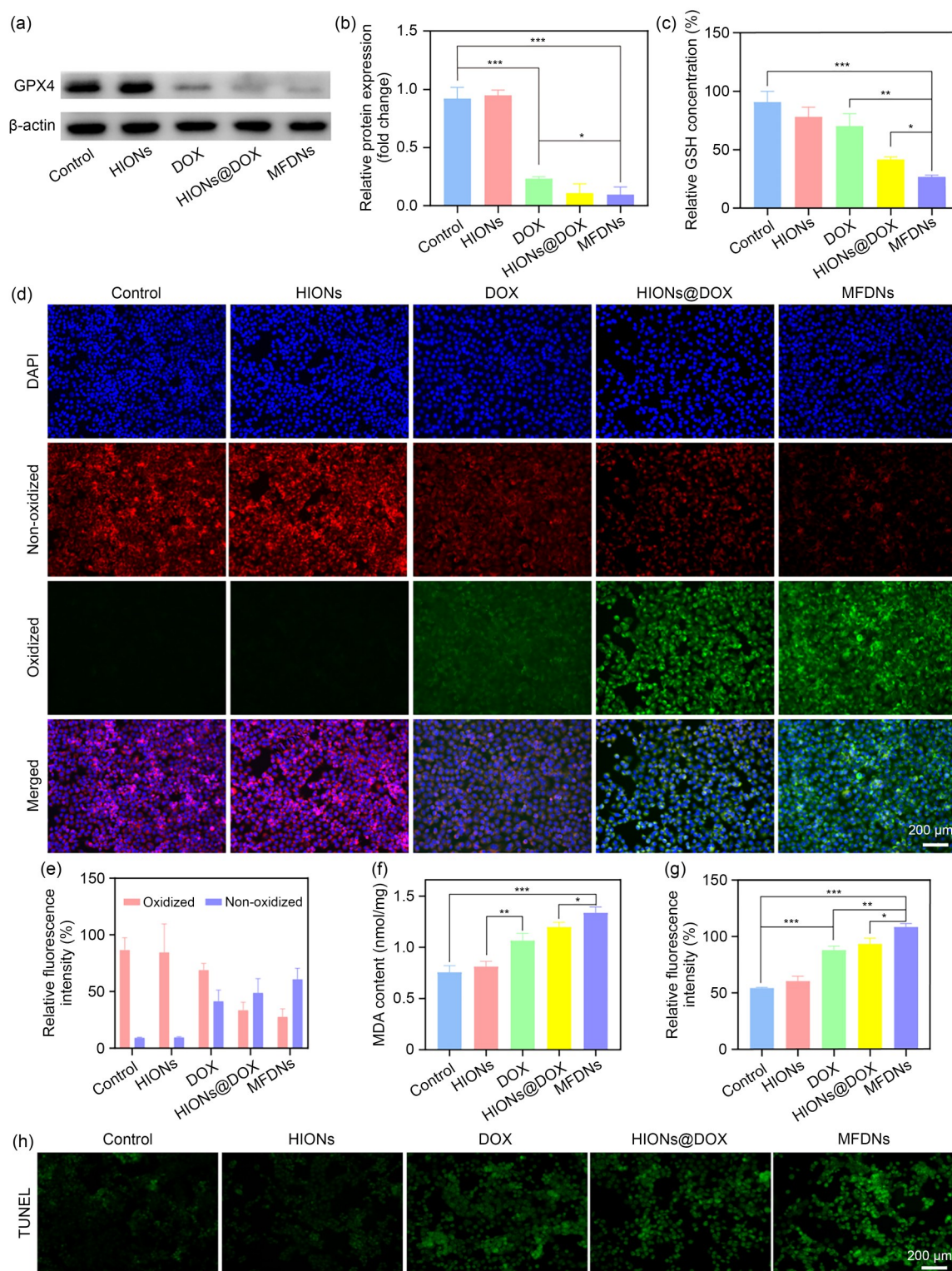


Fig. 4 Magnetic field-driven nanorobots (MFDNs) induced ferroptosis in 4T1 cells via glutathione peroxidase 4 (GPX4) downregulation, glutathione depletion, and lipid peroxidation, along with associated DNA damage. (a) Western blot analysis of GPX4 protein in 4T1 cells after incubation with different groups of treatments. (b) Quantitative analysis of relative protein expression of (a). (c) Intracellular glutathione (GSH) levels after different groups of treatments. (d) Intracellular lipid peroxide (LPO) levels after different groups of treatments. (e) Quantitative analysis of fluorescence intensity of oxidized and reduced cell states after different groups of treatments. (f) Intracellular malondialdehyde (MDA) content after different groups of treatments. (g) Quantitative analysis of fluorescence intensity by terminal deoxynucleotidyl transferase-mediated dUTP nick-end labeling (TUNEL) staining. (h) TUNEL images of 4T1 cells after different groups of treatments. Data in (b, c, e–g) are expressed as mean±standard deviation ($n=3$). * $p<0.05$, ** $p<0.01$, and *** $p<0.001$. DAPI: 4',6-diamidino-2-phenylindole

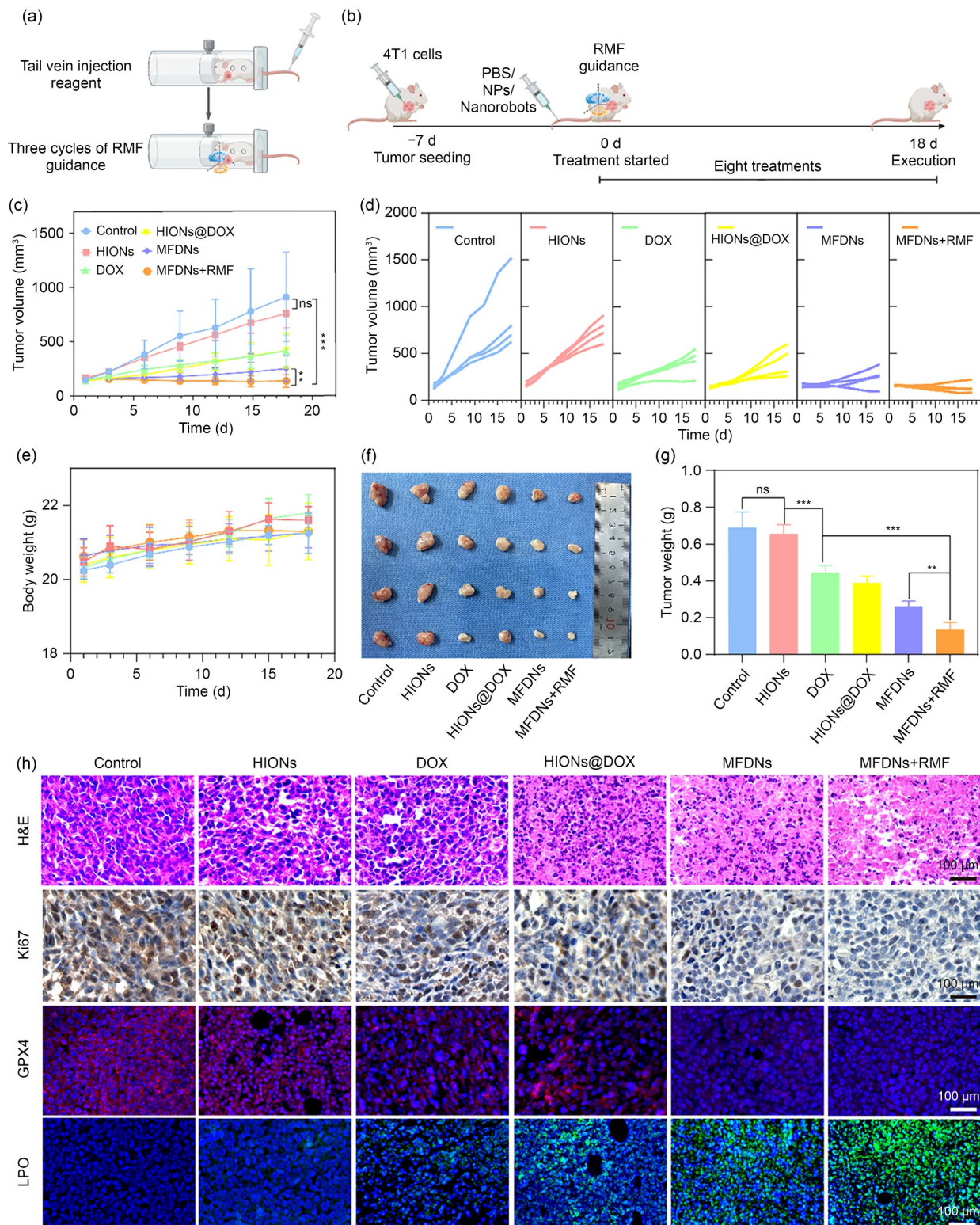


Fig. 5 In vivo anti-tumor effects of magnetic field-driven nanorobots (MFDNs). (a) Illustration of rotating magnetic field (RMF) targeting after tail vein injection. (b) Schematic drawing of the treatment process in cancer model mice. (c) Tumor growth curves. (d) Individual tumor growth curves of each group after different treatments ($n=4$). (e) Weight changes of 4T1 cancer-induced mice during treatment in different groups. (f) The photograph of tumors excised after treatment in different groups ($n=4$). (g) Average tumor weight. (h) Hematoxylin and eosin (H&E) and immunohistochemical staining (Ki67) of tumor sections from mice carrying 4T1 cancer at the end of the experiment ($n=4$); the GPX4 immunofluorescence staining and lipid peroxide (LPO) fluorescence staining after treatment in various groups. Data in (c, e, g) are expressed as mean $\pm$ standard deviation ($n=4$). ns: not significant; ** $p<0.01$ and *** $p<0.001$

with minimal expression observed in the MFDNs+RMF group. Additionally, LPO of the intracellular membrane was assessed, revealing minimal green fluorescence in the control group. In contrast, the MFDNs+RMF group exhibited significantly enhanced green fluorescence, indicating higher levels of membrane lipid peroxidation. These results demonstrate that MFDNs+RMF, which induced both apoptosis and ferroptosis, exhibited superior antitumor efficacy.

3.6 In vivo distribution and biosafety of MFDNs

To track the in vivo distribution of MFDNs, we replaced DOX with 20 µg/mL of the imaging dye DIR during preparation, yielding MFDNs@DIR and MFDNs@DIR+RMF. DIR emits near-infrared fluorescence, which can penetrate tissues and skin and be detected by an in vivo imaging system. As shown in Fig. 6a, the fluorescence intensity at the tumor sites in the armpits of mice (indicated by red circles) increased over time, showing that the nanoparticles accumulated at the tumor sites. Notably, the MFDNs@DIR group showed a stronger signal at the tumor site, indicating enhanced nanoparticle aggregation via magnetic-field targeting. Post-imaging, fluorescence photography of isolated heart, liver, spleen, lung, kidney, and tumor tissues (Fig. 6a) confirmed these findings. To dynamically monitor tumor enrichment following RMF treatment, we extended the observation period for the MFDNs+RMF group from 48 to 72 h, with results presented in Fig. 6e. Fluorescence intensity at the tumor site peaked at 48 h and significantly decreased by 72 h, indicating that maximal accumulation occurs within 48 h under our experimental conditions. To further quantitatively assess the effect of RMF on tumor enrichment and penetration, we performed Prussian blue staining on tumor tissue sections followed by image analysis (Fig. 6d). The MFDNs+RMF group exhibited significantly stronger Prussian blue staining than the MFDNs group without RMF, consistent with the in vivo imaging results. These findings directly demonstrate that RMF enhances both tumor penetration and accumulation of MFDNs. These results corroborate our cellular experiments, which demonstrated the passive targeting of DOX-carrying nanorobots by cell membranes, while in vivo experiments further validated the strong active targeting capability of the nanorobots via magnetic field-guided delivery to the tumor. The in vivo safety of nanomaterials is a crucial factor in determining their clinical applicability. Histological analysis of major organs, including the heart, liver, spleen, lung, and kidney, using H&E staining (Fig. 6f), revealed no significant pathological changes or cellular damage in mice treated with HIONs@DOX or MFDNs+RMF. This suggests that MFDNs+RMF did not adversely affect the major organs. Additionally, key liver function markers (alanine aminotransferase (ALT) and

aspartate aminotransferase (AST)) and renal function markers (creatinine (CRE) and blood urea nitrogen (BUN)) were measured (Figs. 6b and 6c). All these markers were within the normal physiological range, indicating that the MFDNs exhibit good biosafety in vivo.

4 Discussion

Our proposed ferroptosis-based cancer therapy is expected to overcome the limitations of traditional chemotherapy, which often leads to severe systemic side effects and chemotherapy resistance. In this study, we have shown that magnetic iron-based nanorobots combined with DOX can effectively induce ferroptosis in 4T1 TNBC cells. We developed MFDNs+RMF, a biomimetic nanoplatform composed of hollow mesoporous iron oxide nanoparticles loaded with DOX and wrapped with 4T1 cell membranes, which can be assembled into chain-like robots under an RMF and continuously target the tumor region. By adjusting the phase and current frequency of the RMF coil axes (*x/y/z* axes), the direction and speed of the MFDNs can be changed. This system uses a synergistic targeting strategy: RMF navigation enables directional delivery under an external magnetic field, while the membrane coating promotes homologous recognition and tumor-selective accumulation. Therefore, MFDNs improve drug delivery, enhance anti-tumor efficacy, and reduce systemic toxicity. Recent studies have also shown that DOX can trigger ferroptosis in tumor cells [63, 64], and that iron-based nanoparticles exhibit similar capabilities [65, 66]. Our research directly and synergistically combines these two strategies and establishes a comprehensive drug delivery platform to evaluate their combined efficacy and potential for inducing ferroptosis in cancer treatment. Importantly, although HIONs alone elevated intracellular Fe^{2+} levels, they failed to trigger ferroptosis due to the compartmentalization of Fe^{2+} within endolysosomal vesicles, which prevented its access to cytosolic H_2O_2 and membrane polyunsaturated fatty acids [67, 68]. In contrast, MFDNs enabled cytosolic delivery of bioavailable Fe^{2+} via biomimetic membrane fusion and DOX co-delivery, synergistically amplifying oxidative stress and suppressing GPX4 activity, thereby effectively inducing ferroptosis. In vitro studies showed that MFDNs effectively downregulated GPX4 and GSH levels. GPX4 is a key enzyme in ferroptosis, converting toxic lipid peroxides into non-toxic lipids and alcohols, effectively acting as an “antidote” [69, 70]. GSH is an important intracellular antioxidant that neutralizes excessive ROS [71]. The MFDN nanoplatform significantly disrupted intracellular iron metabolism, as evidenced by elevated levels of divalent iron ions (Fe^{2+}), increased ROS generation, and a significant accumulation of lipid peroxidation products (including MDA and LPO). At the same time, the concentrations of GSH and

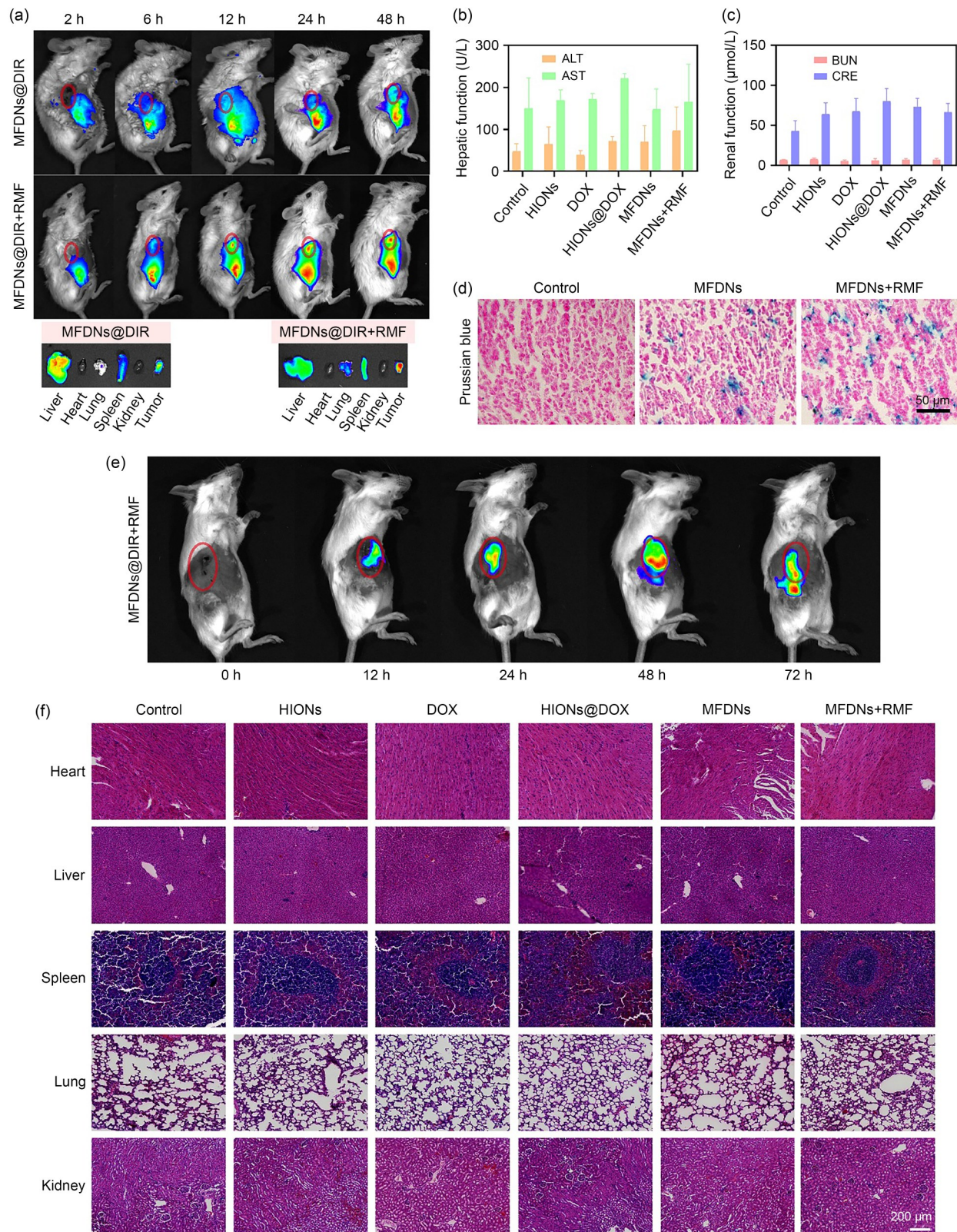


Fig. 6 In vivo tumor targeting and biosafety of MFDNs+RMF. (a) In vivo imaging results of mice (red circles indicate tumors, $n=3$). (b) Liver function tests of treated mice in each group: alanine aminotransferase (ALT) and aspartate aminotransferase (AST). (c) Kidney function tests of treated mice in each group: blood urea nitrogen (BUN) and creatinine (CRE). (d) Representative Prussian blue staining of tumor tissue sections. (e) Time-dependent in vivo fluorescence imaging of mice in the MFDNs+RMF group over 72 h (red circles denote tumor sites). (f) Hematoxylin and eosin (H&E) staining images of the major organs of the mouse ($n=3$). Data in (b, c) are expressed as mean $\pm$ standard deviation ($n=3$)

GPX4, which are key antioxidant defense mechanisms against ferroptosis, were significantly reduced intracellularly. This disruption of the redox balance led to excessive lipid peroxidation, destabilizing the cell membrane and triggering ferroptosis. In vivo studies showed that RMF-guided MFDN delivery significantly improved therapeutic efficacy, highlighting the potential of this dual-targeting strategy to enhance cancer treatment outcomes. In vivo, the movement behavior of MFDNs+RMF was similar to that of helical micro-robots, including frequency-dependent movement behavior and precise controllable navigation. Compared with the in vitro study, the MFDNs+RMF group showed stronger tumor-killing ability and promoted ferroptosis in 4T1 cells. MFDNs under an RMF promoted the sustained release of drugs and increased intracellular levels of divalent iron ions, leading to increased ROS generation, exacerbated lipid peroxidation, and ultimately inducing apoptosis and ferroptosis in TNBCs. These characteristics collectively and significantly improved the efficacy of MFDNs+RMF in the treatment of TNBC. Our research introduced an RMF-guided iron poisoning-based treatment using MFDNs, which is expected to become an additional treatment option for patients with TNBC that is resistant to traditional systemic therapy. One notable feature of MFDNs is the tumor cell membrane coating, which enhances biocompatibility and tumor targeting [72]. This dual effect enables chemotherapy drugs to enter tumor cells more effectively, thereby improving targeted therapeutic efficacy, making RMF-guided MFDN combination therapy a possibility for future clinical translation. However, there are still some aspects that need to be considered. For instance, some researchers have suggested that RMFs can also be used in in vitro experiments for a different application inducing magnetic hyperthermia [73, 74], rather than for active targeting as described in our study. Other researchers believe that during the Fe_3O_4 chain-formation process, a propeller-like rotation occurs, which can physically disrupt the biological membrane under an RMF [75]. Additionally, a changing electric field generates an RMF, and the resulting magnetic field enables MFDNs to penetrate the tumor cell membrane, thereby enhancing the targeted therapeutic effect [76, 77]. Our future research will focus on these variables, as well as a comprehensive assessment of long-term biological safety and potential immunogenicity, to fully exploit the therapeutic potential of this innovative approach.

5 Conclusions

In this study, we developed a chain-like biomimetic nanorobot, MFDN, for enhancing TNBC treatment. It integrates passive membrane targeting with RMF guidance, overcoming the drawback of nanoparticle aggregation in static magnetic fields. We systematically elucidated the magnetic driving principle

and motion behavior of the chain-like biomimetic nanorobot through both theoretical analysis and experimental validation. A simple, effective, and stable nanorobot system was successfully constructed, enabling remote magnetic field-controlled navigation and targeted delivery for TNBC therapy. In vitro and in vivo experiments showed that MFDNs effectively induced ferroptosis in 4T1 TNBC cells by inhibiting GPX4 activity, disrupting iron homeostasis, and increasing ROS and lipid peroxide levels. The cancer cell membrane coating enhanced the uptake of nanoparticles by tumor cells while reducing interactions with non-target cells. In vivo studies indicated that dual targeting synergistically inhibited tumors with minimal systemic toxicity and good biocompatibility. MFDNs represent a promising nanorobot therapeutic strategy for TNBC, providing a new approach to overcome chemotherapy resistance and improve treatment outcomes. Future research should focus on optimizing magnetic field guidance and exploring the mechanism of its penetration through tumor cell membranes to enhance clinical applicability.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1631/bdm.2500656>.

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Author contributions WS conceived and designed the study, performed the experiments, collected the data, analyzed the data, and wrote the manuscript. ZXL and JX performed the experiments and collected the data. ZHW and GXZ performed formal analysis. JFW provided software. QZ and KTZ performed formal analysis. AY conceived and designed the study, interpreted results, wrote the manuscript, and provided supervision. SHW and YS conceived and designed the study, interpreted results, provided supervision, and acquired funding. All authors read and approved the final version of the manuscript.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All protocols were approved by the Wenzhou Medical University Laboratory Animal Ethics Committee (approval no. Ymsq2021-0410) and adhered to the Animal Research: Reporting of In Vivo Experiments (ARRIVE) guidelines.

Data availability The data supporting the findings of this study are available from the corresponding authors upon reasonable request.

Use of generative AI tools No generative AI tools were used during the preparation of this manuscript.

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