

Mesenchymal Stem Cells Membrane Biomimetic NanoplatforM for Glioblastoma-Targeted Combinatorial Chemotherapy

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Introduction: Glioblastoma, the most aggressive form of brain tumor, continues to present significant therapeutic challenges, including the limited delivery of drugs posed by the blood-brain barrier (BBB) and the blood-brain tumor barrier (BBTB), severe systemic toxicity associated with conventional chemotherapy, and the complexity arising from tumor heterogeneity.

Methods: To overcome these challenges, this study developed a novel biomimetic drug delivery system. Specifically, we prepared poly(lactic-co-glycolic acid) (PLGA) nanoparticles co-loaded with the chemotherapeutic agent doxorubicin (DOX) and the natural polyphenol curcumin (CUR), and subsequently functionalized them with the membrane of human umbilical cord mesenchymal stem cells (hUC-MSCs), which possess inherent tumor-homing capability.

Results: In vitro studies demonstrated that the hUC-MSCs membrane coating significantly enhanced targeted recognition and cellular uptake by glioblastoma cells, and the biomimetic nanoplatforM exhibited superior synergistic cytotoxicity and induced greater cellular apoptosis compared to free drug combinations and uncoated nanoparticles. Antitumor mechanism analysis indicated that biomimetic nanoplatforM inhibited glioblastoma migration, invasion, and angiogenesis. In vivo anti-tumor efficacy studies showed that the biomimetic nanoparticles effectively suppressed the growth of tumor. Notably, CUR contributed to the system by amplifying the anticancer activity of DOX and alleviating its associated toxicity.

Discussion: This work demonstrates that hUC-MSC membrane-camouflaged PLGA nanoparticles enable successful co-delivery of DOX and CUR, offering a promising strategy to address the critical barriers of delivery and toxicity in GBM chemotherapy, supported by their excellent in vitro targeting, in vivo anti-tumor efficacy, and reduced toxicity profile.

Keywords: biomimetic nanoparticles, glioblastoma, combinatorial therapy, targeted delivery

Introduction

Glioblastoma (GBM) is a highly aggressive primary malignant tumor originating from glial cells in the central nervous system (CNS). Its high rates of recurrence and mortality pose severe clinical challenges. Despite multimodal combination therapies, including surgical resection, radiotherapy, and chemotherapy,¹ the median survival of patients remains below 15 months and less than 5% patients can survive for about 5 years,² indicating a poor prognosis. Furthermore, during tumor progression, the blood-brain barrier (BBB) undergoes significant structural and functional alterations, evolving into the blood-brain tumor barrier (BBTB). Although microvascular proliferation in the core region of the tumor leads to leakage of newly formed blood vessels, resulting in an overall higher permeability of the BBTB compared to the normal BBB, its heterogeneous and unpredictable permeability often leads to inconsistent and suboptimal drug delivery.^{3,4} This specific and highly selective barrier impedes the entry of small-molecule drugs, particularly anthracyclines such as doxorubicin (DOX), from entering the brain parenchyma.⁵ In addition, DOX causes dose-dependent systemic toxicity, with irreversible cardiotoxicity being especially prominent.⁶ These unresolved challenges underscore the urgent need to develop novel targeted delivery strategies.

Nanotechnology-based drug delivery systems (DDS), such as polymeric nanoparticles and liposomes, are readily developed to complement conventional pharmacology.⁷ Among these, poly(lactic-co-glycolic acid) (PLGA) nanoparticles have attracted significant attention due to their favorable biocompatibility, controllable drug release kinetics, and co-delivery capability. However, these materials are often recognized as “foreign” and are readily identified and rapidly cleared by the immune system, particularly via the mononuclear phagocyte system (MPS). Furthermore, their passive targeting mainly relies on the inefficient enhanced permeability and retention (EPR) effect within brain tumors, and the lack of active tumor-targeting capability leads to non-specific distribution.⁸ Therefore, active targeting is introduced to engineer DDS with ligands which can selectively bind to over-expressed receptors on the surface of the target organ, accompanied with minimal toxicity on the adjacent normal cells. Various active targeting ligands, including antibodies,⁹ aptamers,¹⁰ peptides,¹¹ lactoferrin,¹² folic acid¹³ and carbohydrates,¹⁴ have been explored for the targeted delivery of nanomedicine. Nevertheless, compelling evidence from a meta-analysis of nanoparticle distribution in tumor-bearing mice, encompassing 297 studies, revealed a median tumor delivery efficiency of only 0.67% of the injected dose.¹⁵ Thus, the insufficient tumor delivery efficiency of nanoparticles may largely account for the low clinical translation rate observed for NP-based drug formulations.

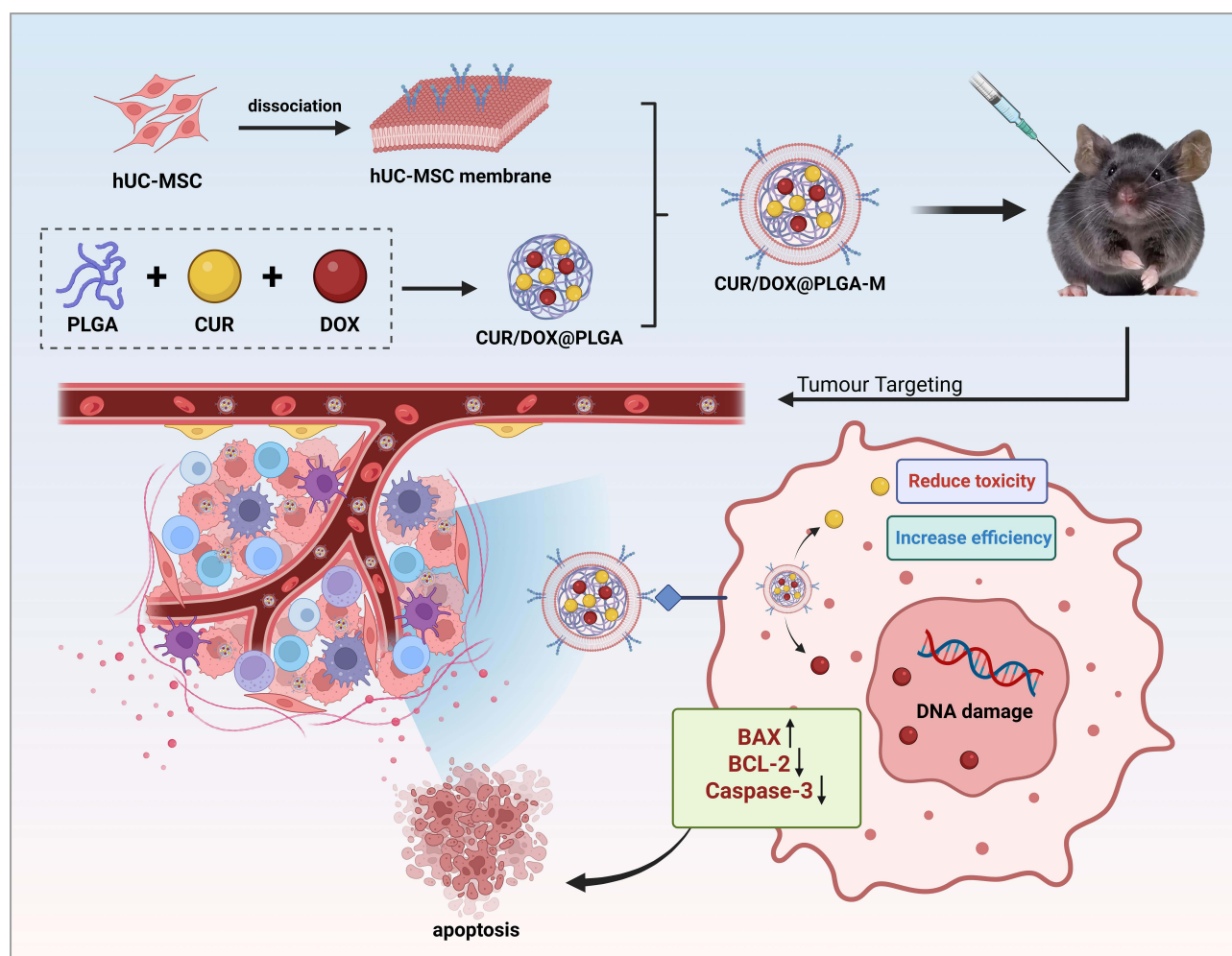
In practice, intravenously administered nanomedicines undergo a multi-step cascade, including systemic circulation, accumulation at the tumor site, penetration into the tumor tissue, cellular internalization, and ultimately, drug release.¹⁶ Mesenchymal stem/stromal cells (MSCs) are multipotent stromal cells mainly derived from bone marrow, umbilical cord, and adipose tissue, etc. Recently, MSC therapy against tumor is gaining great interest due to their immunomodulatory properties, tumor tropism, and multipotency, as well as their ease of acquisition, high proliferative ability, and low immunogenicity.^{17,18} Notably, it has been well documented that MSCs exhibit tumor-homing capacity which is mainly mediated by the cooperation of cytokines, chemokines, and other functional molecule. The adhesion and traversing through the vascular endothelial layer of circulating MSCs is similar to that carried out by leukocytes, which is dominated by various cytokines, such as TNF- α , IL-6, IL-1 β and interferon- γ ,¹⁹ etc. Afterwards, the affinity between stromal cell-derived factor-1 on the surface of tumor cells and CXCR4 chemokine receptor 4 on MSCs induces MSCs migration towards tumors.^{20,21} In virtue of tumor tropism, MSCs have been leveraged to function as therapeutic vehicle of anti-tumor drugs, including chemotherapeutic agents,^{22,23} suicide genes,²⁴ oncolytic viruses,²⁵ etc. Furthermore, biomimetic modification of nanoparticles using cell membranes or exosomes has emerged as a prominent research focus.²⁶ Collectively, taking advantage of biointerface reaction, MSC membrane-camouflaged NPs combine active targeting capacity from MSC with the unique physicochemical properties of NPs, such as controllable synthesis and high capacity of drug loading,²⁷ thus holding the prospect in tumor therapy.

This study designed a biomimetic nano-platform integrating synergistic chemotherapy for GBM targeting. We employed a one-step double emulsion method to co-encapsulate curcumin (CUR), a natural chemosensitizer, and doxorubicin (DOX) into PLGA nanoparticles (NPs). It's reported CUR potentiates DOX efficacy by inhibiting P-glycoprotein (P-gp)-mediated drug efflux while mitigating DOX-induced cardiotoxicity through antioxidant pathway activation.^{28,29} Through ultrasonic coating, hUC-MSCs membranes were functionalized onto the nanocarriers, yielding CUR/DOX@PLGA-M with enhanced bio-interfacial properties. The platform demonstrated significantly enhanced active tumor targeting ability and tumor penetration ability in tumor multicellular spheroids. In addition, *in vitro* and *in vivo* studies showed that CUR/DOX@PLGA-M exhibits potent antitumor efficacy by not only inhibiting glioblastoma proliferation but also exerting multimodal mechanism, including promoting apoptosis, suppressing migration and invasion, as well as inhibiting angiogenesis. These findings collectively establish the engineering of hUC-MSC membranes as a potent and versatile strategy for the tumor-specific delivery of combinatorial chemotherapeutics (Scheme 1).

Materials and Methods

Materials

PLGA (15000–24000 Da) was purchased from Jinan Daigang Biomaterial Co., LTD, China. CUR was supplied by Shanghai Macklin Biochemical Technology Co., LTD, China. Doxorubicin hydrochloride was obtained from Shanghai Aladdin Biochemical Technology Co., LTD, China. Poly(vinyl alcohol) (PVA) (31,000–50000 Da) was from Sigma-Aldrich, USA. Antibody were from Cell Signaling Technology, USA.



Scheme 1 Mesenchymal Stem Cells Membrane Biomimetic Nanoplatfor for Glioblastoma-Targeted Combinatorial Chemotherapy. Upward arrow, upregulated protein expression; downward arrow, downregulated protein expression.

Cell Culture

U87 cells, C6 cells, and HCMEC/D3 cells were purchased from National Collection of Authenticated Cell Cultures, China. hUC-MSCs were prepared at the Stem Cell Clinical Research Center of the First Affiliated Hospital of Dalian Medical University. The cell quality was reviewed and certified by the China National Medical Products Administration. U87 and C6 cells were cultured in DMEM supplemented with 10% FBS and 1% penicillin-streptomycin (P/S). HCMEC/D3 cells were maintained in Endothelial Cell Medium containing 5% FBS, 1% P/S and 1% endothelial growth factor (EGF). hUC-MSCs were expanded in AMMS[®] MSC complete medium. All cells were incubated at 37°C in a humidified 5% CO₂ atmosphere.

Preparation of hUC-MSCs Membrane

The hypotonic lysate contained 30 mM Tris-HCl, 0.2 mM EGTA, 75 mM sucrose, and 225 mM mannitol in deionized water, with pH adjusted to 7.5. hUC-MSCs at passages 5–9 were harvested and lysed on ice for 30 min in pre-cooled hypotonic lysate containing 1×protease inhibitors, with a cell density of 1×10^7 cells/mL. The lysate was sonicated in an ice bath (100 W, 5 s on/off) for 5 min and centrifuged at 4°C, 2000 g for 10 min. The supernatant was further centrifuged at 4°C, 20,000 g for 30 min, then the pellet containing crude membrane fragments was collected. Membranes were resuspended in PBS containing 0.2 mM EDTA and stored at –80°C. Protein concentration was determined using a BCA assay kit.

Synthesis of DOX/CUR@PLGA

DOX/CUR@PLGA were prepared by the modified emulsion-solvent evaporation method. Briefly, PLGA and CUR were co-dissolved in dichloromethane. Then, 2 mL of complex solution was mixed with 200 μ L of DOX in saline solution. Ice bath sonication was performed (200 W, 5 s on, 5 s off) for 5 min to form the primary emulsion. Subsequently, this primary emulsion was slowly dripped into 10 mL of PVA solution, followed by another round of ice-bath sonication under the same pulse conditions for 5 min to obtain the secondary emulsion. The secondary emulsion was then added into 0.1% (w/v) PVA aqueous solution and stirred for 4 h at room temperature to evaporate the organic solvent. Samples were centrifuged (13000 g, 1 h) and the precipitate was washed three times with deionized water to obtain DOX/CUR@PLGA. Empty PLGA nanoparticles were also prepared in a similar way.

Synthesis of DOX/CUR@PLGA-M

The DOX/CUR@PLGA solution was mixed with the cell membrane solution at a ratio of 5:1 (w/w), then sonicated in an ice bath (100 W, 5 s on, 5 s off) for 5 min to form the hUC-MSCs cell membrane cloaked DOX/CUR@PLGA (DOX/CUR@PLGA-M). The solution was subjected to centrifugation at 4 °C (13000 g, 1 h) in order to remove the excess membrane and isolate the DOX/CUR@PLGA-M, which were then washed three times with PBS.

Characterization of the DOX/CUR@PLGA-M

The morphology of hUC-MSCs membrane, DOX/CUR@PLGA, and DOX/CUR@PLGA-M was examined by TEM. The hydrodynamic size and zeta potential of DOX/CUR@PLGA and DOX/CUR@PLGA-M were determined by NTA system (ZetaView, Particle Metrix, Germany). The DOX/CUR@PLGA, and DOX/CUR@PLGA-M were incubated in PBS at 4°C for 7 days, and stability was monitored through NTA. Drug encapsulation efficiency of CUR and DOX in the DOX/CUR@PLGA-M was quantified via UV-Vis spectrophotometry.

To validate membrane protein profiles, equal protein quantities from hUC-MSC whole-cell lysates, hUC-MSC membranes, and DOX/CUR@PLGA-M were separated on 4–12% precast polyacrylamide gels. Following electrophoresis, gels were stained with Coomassie Brilliant Blue, destained with 1×TBST buffer until clear band resolution, and imaged.

In vitro Release of CUR and DOX Under Different pH

The in vitro release profiles of CUR and DOX from DOX/CUR@PLGA-M were evaluated using a dynamic dialysis method under simulated physiological (pH 7.0) and tumor microenvironment (pH 5.6) conditions. DOX/CUR@PLGA-M were suspended in dialysis bags (MWCO 3.5 kDa) and immersed in PBS buffers (pH 7.0 or pH 5.6) with constant shaking at 150 rpm and 37°C. 1 mL samples were taken at 1, 3, 7, 12, 24, 48, 72, 96, 120 h, and an equal volume medium was supplemented. The concentrations of released CUR and DOX were quantified via UV-Vis spectrophotometry.

Tumor-Targeting of DOX/CUR@PLGA-M

U87 or HCMEC/D3 cells were seeded in glass-bottom confocal dishes. After complete adhesion, the culture medium was replaced with fresh medium containing either CUR/DOX@PLGA or CUR/DOX@PLGA-M. Following 4 h co-incubation at 37°C, cells were gently washed three times with PBS and fixed with 4% PFA for 30 min. Nuclear staining was performed using DAPI, followed by three PBS washes. Cellular uptake of CUR or DOX was visualized using a Yokogawa CQ1 high-content confocal imaging system (Japan) and quantitatively analyzed with Image J.

Cellular uptake was further quantified by flow cytometry. HCMEC/D3 and U87 cells were incubated with CUR, CUR/DOX@PLGA or CUR/DOX@PLGA-M formulations for 4 h. Following incubation, cells were washed, trypsinized, and resuspended in PBS. CUR fluorescence was measured using a Sony SH800S flow cytometry (Japan). Data analysis was performed using FlowJo software.

In vitro BBB Transcytosis Study

2×10^5 HCMEC/D3 cells were seeded onto the apical chamber of 6-well transwell inserts. The in vitro BBB model was established once the transendothelial electrical resistance (TEER) exceeded $200 \Omega \cdot \text{cm}^2$, confirming the formation of an intact cell monolayer. To assess the trans-BBB transport efficiency of the nanoparticles, U87 cells were cultured in the

basolateral chamber. After 24 h of incubation, the relative cumulative permeability of CUR/DOX@PLGA-M across the BBB was quantified by measuring the fluorescence intensity.

Penetration Evaluation in Tumor Multicellular Spheroids

The U87 cells (1×10^3 cells/well) were seeded in low-adhesion 96-well plates and cultured for 7 days to form the GBM spheroids. The GBM spheroids were aspirated into 96-well plates and incubated with CUR+DOX, CUR/DOX@PLGA, and CUR/DOX@PLGA-M for 24 h. The spheroids were gently aspirated and washed three times with PBS. The fluorescence at different depths in GBM spheroids was scanned with CQ1 using Z-stack.

In vitro Cytotoxicity Study and Apoptosis Assay

The viability of U87 cells treated with CUR/DOX@PLGA-M was determined using a CCK-8 assay kit. U87 spheroids treated with CUR/DOX@PLGA-M for 24 h were stained with Calcein-AM/PI. Apoptosis of U87 cells following CUR/DOX@PLGA-M treatment was assessed using an Annexin V-FITC/PI staining kit and quantified by flow cytometry. The expression levels of apoptotic proteins, Bcl-2, Bax and Caspase3 in U87 cells treated with DOX/CUR@PLGA-M were analyzed by Western blotting.

Migration and Invasion Assays

Wound healing assays were performed to evaluate alterations in cell migration capacity after exposure to DOX/CUR@PLGA or CUR/DOX@PLGA-M. C6 cells were co-cultured with nanoparticle formulations for 48 h. Wound widths were documented using microscope and quantified with Image J software.

The anti-invasive potential of CUR/DOX@PLGA-M was further examined. U87 cells pretreated with nanoparticles for 24 h were harvested and suspended in serum-free medium. Subsequently, 2×10^4 cells were seeded into Matrigel-coated Transwell upper chambers. Lower chambers contained medium with 10% FBS. After 24 h incubation at 37°C, invaded cells were fixed with 4% PFA, stained with crystal violet, and gently washed. Non-invading cells on the upper membrane surface were removed with cotton swabs. Invaded cells were imaged and counted under inverted microscope (CKX53, Olympus, Japan).

Tube Formation Assay

After 24 h incubation with drug-containing media, 1.5×10^4 HCMEC/D3 cells were seeded onto Matrigel-coated 96-well plates. After incubation at 37°C for 4 h, the tube formation in different groups was captured by microscope.

Establishment of Subcutaneous GBM Model in C57BL/6 Mice

C57BL/6 mice (SPF, Female, 4–6 weeks) were purchased from Liaoning Changsheng Biotechnology Co., Ltd. (Benxi, Liaoning, China). All procedures were performed under aseptic conditions with approval from Dalian Medical University Animal Ethics Committee. C57BL/6 mice were anesthetized with 2.5% tribromoethanol. A suspension containing 1×10^6 GL261 murine glioblastoma cells in 100 μ L PBS/Matrigel mixture (1:1 v/v) was subcutaneously inoculated into the right flank. Tumor growth was monitored everyday by digital caliper measurements, with volume calculated as $(\text{length} \times \text{width}^2)/2$.

In vivo Anti-Glioblastoma Effects

Following establishment of subcutaneous glioblastoma models in C57BL/6 mice, animals were randomized into PBS control, CUR, DOX, CUR/DOX@PLGA and CUR/DOX@PLGA-M. From day 10 post-inoculation, treatments were administered via tail vein injection every 48 h for 7 consecutive doses. Tumor volumes and body weights were monitored throughout the study period.

On day 24, tumor tissues were harvested for paraffin sectioning. Histopathological evaluation was performed using hematoxylin and eosin (H&E) staining to assess glioblastoma morphology. TUNEL staining was performed to detect DNA fragmentation in tumor tissue, and apoptosis was analyzed using the Yokogawa CQ1 high-content imaging system.

Biocompatibility Assessment

Major organs (heart, liver, spleen, lungs, kidneys) were harvested from euthanized mice, fixed in 4% PFA for 48 h, and embedded in paraffin. Sections were stained with H&E following standard protocols. H&E staining was observed by inverted microscope (CKX53, Olympus, Japan). Blood samples were collected from mice for analysis of hematological parameters (WBC, RBC, HGB, MCV, PLT) and serum biochemical markers, including liver function indices (ALT, ALB, ALP, AST) and renal function indices (urea, creatinine).

Statistical Analyses

All statistical tests were performed in GraphPad Prism 9.5.0 software. Data are presented as mean $\pm$ SD ($n\geq 3$, ns $p>0.05$, * $p<0.05$, ** $p<0.01$, *** $p<0.001$). The statistical significance was determined using Student's *t*-test and one-way ANOVA followed by Tukey's post test.

Results and Discussion

Preparation and Characterization of CUR/DOX@PLGA-M

PLGA, a biodegradable polymer, is widely utilized in pharmaceutical industry.³⁰ PLGA nanoparticles serve as ideal drug delivery carriers for treating various diseases due to their high drug-loading capacity and tunable properties. To prepare PLGA nanoparticles with optimal drug encapsulation efficiency, we systematically investigated key parameters including PLGA monomer concentration, drug ratios, PVA concentration, and ultrasonication power. The results demonstrated (Table 1) that the formulation with a PLGA:CUR:DOX mass ratio of 150:1:1, 3% (w/v) PVA, and 200 W sonication power achieved the highest encapsulation efficiency, ie. 78.5% for CUR and 88.5% for DOX. NTA revealed that DOX/CUR@PLGA exhibited a hydrodynamic diameter of 142.1 ± 0.7 nm and zeta potential of -28.1 ± 0.7 mV (Figure 1a and c).

The innate limitations of the conventional drug-loaded nanoparticles, such as fast elimination by the immune system, low accumulation in tumor, and severe toxicity to the organism, expedite the development of their surface functionalization to enhance the therapeutic effect. Especially, numerous researchers have exploited cell membrane-camouflaged nanoparticles for targeted drug delivery.³¹ In this way, engineered nanoparticles naturally inherit the surface adhesive molecules, receptors, and functional proteins from cell membrane, making them versatile as the natural cells. Compared to bare DOX/CUR@PLGA, the average size of DOX/CUR@PLGA-M increased from 142.1 ± 0.7 nm to 181.6 ± 2.0 nm (Figure 1b). After cell membrane coating, the surface potential of DOX/CUR@PLGA-M is more negative, ie. -39.44 ± 0.34 mV (Figure 1c), which would inhibit non-specific adsorption of proteins in bloodstream and facilitate uptake by receptor cells.³² The microscopic morphology of the nanoparticles was observed by TEM. As shown in Figure 1d, the purified cell membranes formed empty vesicles exhibiting a typical bilayer structure. Figure 1e shows that DOX/CUR@PLGA display a uniform spherical nanostructure. DOX/CUR@PLGA-M exhibited typical core-shell morphology (Figure 1f). The PLGA core is seamlessly surrounded by a continuous and uniform lipid layer, confirming the effective coating of DOX/CUR@PLGA with hUC-MSC membrane. Furthermore, SDS-PAGE results showed that DOX/CUR@PLGA-M and hUC-MSCs cell membranes possess similar protein profiles, which proved that the extracted cell membrane on nanoparticles retained most of the functional proteins and might had similar functions of the source cells

Table 1 Size, Zeta Potential and the Drug Encapsulation Efficiency (EE) of CUR/DOX-PLGA

Formulation and Synthesis Parameters		Size(nm)	Zeta potential (mV)	EE of CUR (%)	EE of DOX (%)
PLGA:CUR:DOX (W: W: W)	40:1:1	144.6 $\pm$ 1.6	-22.1 $\pm$ 0.6	30.1 $\pm$ 0.4	41.8 $\pm$ 0.5
	100:1:1	142.8 $\pm$ 1.3	-26.2 $\pm$ 0.8	61.4 $\pm$ 0.4	48.6 $\pm$ 1.3
	150:1:1	142.1 $\pm$ 0.7	-28.1 $\pm$ 0.7	78.5 $\pm$ 0.7	88.5 $\pm$ 1.2
PVA concentration	1%	193.4 $\pm$ 4.8	-25.1 $\pm$ 0.8	63.2 $\pm$ 1.0	43.0 $\pm$ 0.4
	3%	142.1 $\pm$ 0.7	-28.1 $\pm$ 0.7	78.5 $\pm$ 0.7	88.5 $\pm$ 1.2
	5%	131.7 $\pm$ 1.5	-27.5 $\pm$ 0.8	43.0 $\pm$ 0.7	40.1 $\pm$ 0.4
Ultrasonic power	100W	143.6 $\pm$ 1.6	-26.2 $\pm$ 0.6	74.2 $\pm$ 0.7	64.4 $\pm$ 0.5
	200W	142.1 $\pm$ 0.7	-28.1 $\pm$ 0.7	78.5 $\pm$ 0.7	88.5 $\pm$ 1.2
	300W	170.4 $\pm$ 1.1	-30.4 $\pm$ 1.0	89.3 $\pm$ 1.7	73.0 $\pm$ 0.5

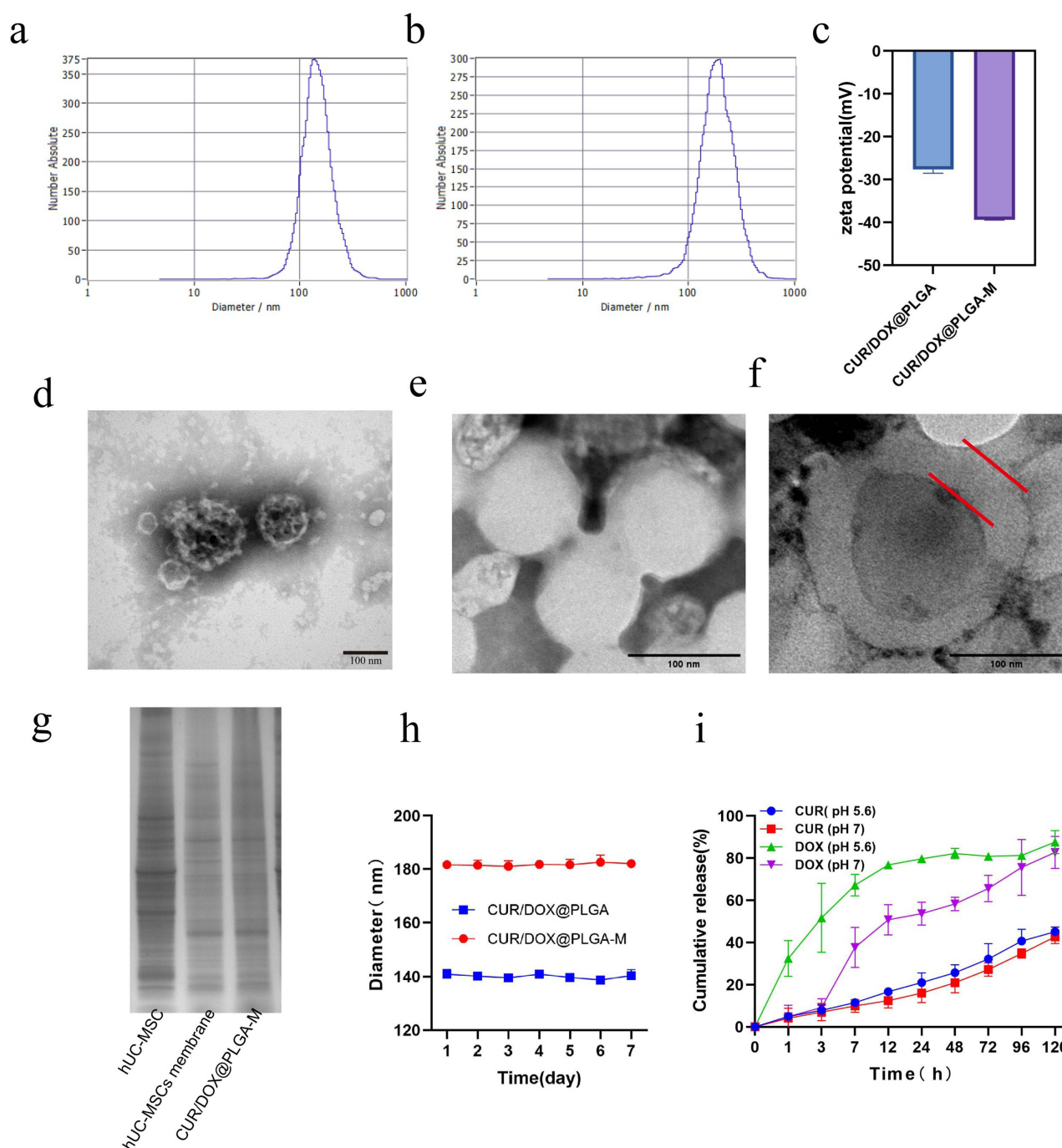


Figure 1 Characterization of CUR/DOX@PLGA-M. The particle size distribution of DOX/CUR@PLGA(a) and CUR/DOX@PLGA-M (b) and (c) Zeta potential of DOX/CUR@PLGA and CUR/DOX@PLGA-M. (d) TEM images of hUC-MSCs membrane. (e) TEM images of DOX/CUR@PLGA. (f) TEM images of CUR/DOX@PLGA-M. The distance between the two red lines indicates the thickness of the cell membrane layer on the nanoparticle surface. (g) The image of sodium dodecyl sulfate-polyacrylamide gel electrophoresis within hUC-MSC, hUC-MSCs membrane and CUR/DOX@PLGA-M. (h) Average size of DOX/CUR@PLGA and CUR/DOX@PLGA-M over 7 days in DI water. (i) Accumulated drug release of CUR and DOX from DOX/CUR@PLGA as a function of time in PBS at pH 7.0 and pH 5.6. All data are presented as mean $\pm$ s.d (n=3).

(Figure 1g). We evaluated the stability of nanoparticles by monitoring their size change under 4 °C preservation. It's revealed that both DOX/CUR@PLGA and DOX/CUR@PLGA-M maintain stable size distribution for 7 consecutive days (Figure 1h). Overall, these results indicated successful translocation of natural cell membranes onto the nanoparticles with long-term stability. We adopted pH 5.6 and pH 7.0 PBS to simulate the tumor and physiological microenvironment, respectively, in order to study the in vitro drug release kinetics of DOX/CUR@PLGA. The results are shown in Figure 1i. DOX/CUR@PLGA displayed similar

release kinetics to CUR in neutral and weak acidic PBS, which reached cumulative release of $42.7 \pm 3.2\%$ and $45.1 \pm 2.3\%$ after 120 h respectively. However, acidic environment significantly accelerates DOX release, probably owing to the decreased electrostatic interaction between PLGA and DOX.

Enhanced Cellular Uptake in vitro, BBB and Tumor Spheroids Penetration

First, cellular uptake of different formulations in HCEC/D3 or U87 cells were investigated. The CUR+DOX group exhibited weak intracellular fluorescence in both HCEC/D3 and U87 cells (Figure 2a). In HCEC/D3 cells, CUR

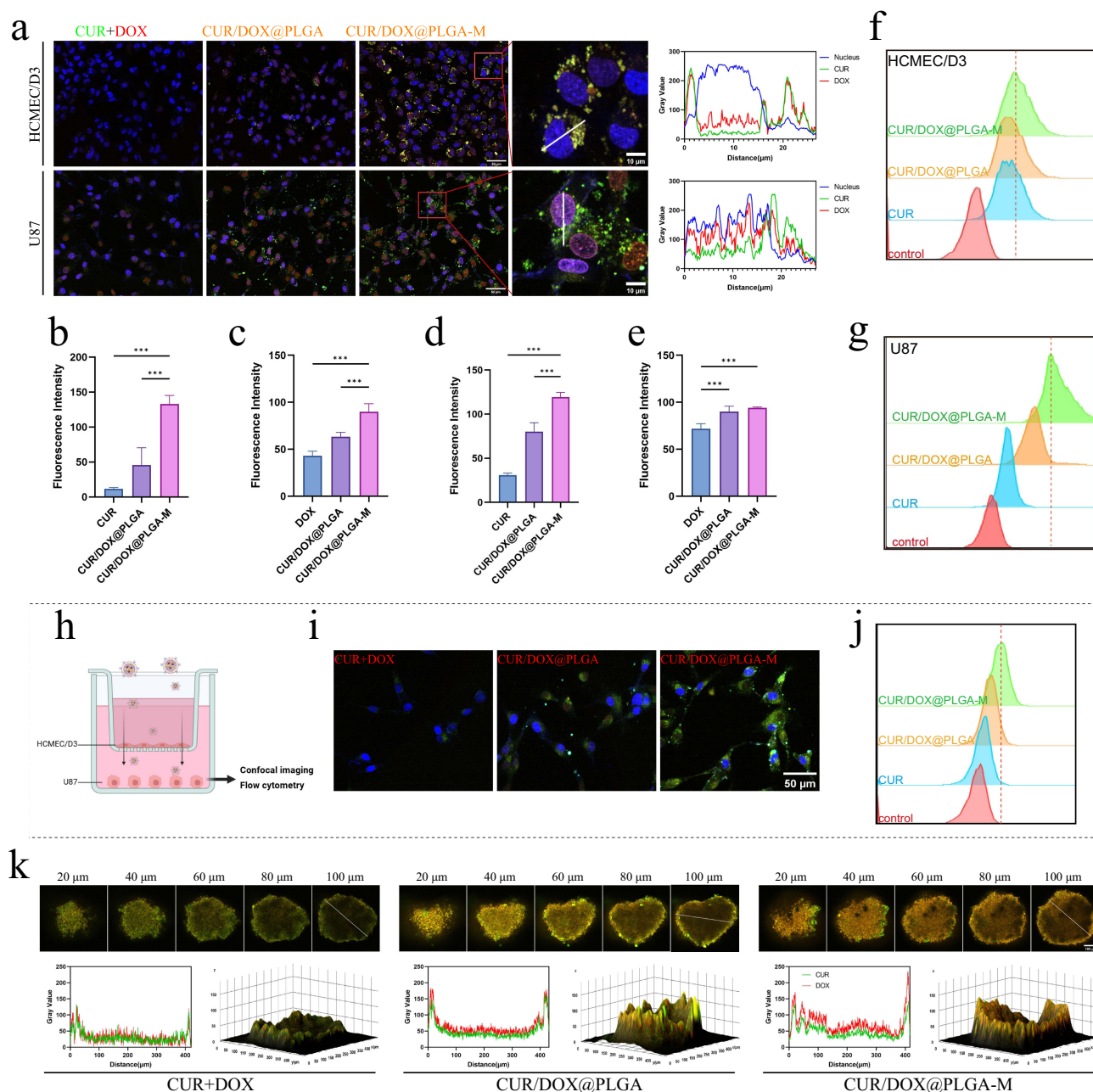


Figure 2 Cellular uptake of CUR/DOX@PLGA-M in vitro. (a) Cellular uptake in HCEC/D3 and U87 cells (scale bar: 50 μm). The white line indicates the region for line scan analysis; the fluorescence intensity profiles of DOX (red) and CUR (green) along this line were used to assess their co-localization. (b and c) Quantitative analysis of CUR and DOX uptake in HCEC/D3 cells. (d and e) Quantitative analysis of CUR and DOX uptake in U87 cells. (f) Flow cytometry analysis of CUR uptake in HCEC/D3 cells. (g) Flow cytometry analysis of CUR uptake in U87 cells. (h) Schematic diagram of in vitro BBB model establishment and transport of CUR/DOX@PLGA-M across the BBB. (i) Confocal imaging of U87 cells in the lower compartment of the in vitro BBB model (scale bar: 50 μm). (j) Flow cytometry of U87 cells in the lower compartment of the BBB model. (k) Penetration profiles of nanoformulations in 3D GBM spheroids (scale bar: 100 μm). All the data are presented as mean $\pm$ s.d (n=3), *** p < 0.001.

fluorescence was 2.6-fold and 3.9-fold higher for CUR/DOX@PLGA and CUR/DOX@PLGA-M, respectively, compared to free CUR, while DOX fluorescence was approximately 3.0-fold higher for both nanoformulations than free DOX (Figure 2b and c). Co-localization imaging confirmed cytoplasmic accumulation of both drugs (Figure 2a), indicating enhanced endothelial affinity conferred by the hUC-MSC membrane modification. In U87 cells, CUR fluorescence was 1.5-fold and 4.3-fold higher for CUR/DOX@PLGA and CUR/DOX@PLGA-M, respectively, relative to free CUR. DOX fluorescence increased by 2.1-fold and 2.9-fold, respectively (Figure 2d and e). Notably, CUR accumulated in the cytoplasm, while DOX entered the nucleus (Figure 2a), highlighting the role of the carrier in preserving the bioactive site of the drugs and promoting synergistic anti-tumor mechanisms. Flow cytometry further validated these trends. As shown in Figure 2f, CUR/DOX@PLGA-M demonstrated the highest uptake in HCMEC/D3 cells. Notably, a 7.5-fold increase in CUR fluorescence for CUR/DOX@PLGA and an additional 5.5-fold enhancement for CUR/DOX@PLGA-M over free CUR were observed in U87 cells (Figure 2g). This suggests that the hUC-MSC membrane endows the nanoparticles with a high affinity for tumor cells, which is consistent with a previous report.³³ Collectively, these findings demonstrate that the tumor-targeting capability of hUC-MSCs was successfully conferred onto the nanoparticles. To systematically investigate the brain-targeting efficiency and tumor penetration capabilities of different delivery systems, an in vitro BBB model was established using HCMEC/D3 and U87 cells (Figure 2h). U87 cells in the basolateral chamber of the transwell system were subjected to fluorescence quantification to assess the BBB penetration capability (Figure 2i). Confocal imaging and flow cytometric analysis demonstrated that the penetration efficiency of CUR/DOX@PLGA-M was significantly higher than that of the control groups, exhibiting an approximately 3.6-fold increase compared to free CUR and a 2.1-fold increase relative to CUR/DOX@PLGA (Figure 2j).

To validate the tumor penetration capacity of nanoformulations in vitro, we established GBM spheroids that better recapitulate the in vivo tumor microenvironment. High-content imaging was employed to capture fluorescence signals at varying z-depths within the spheroids, followed by ROI quantification to evaluate nanoparticle penetration (Figure 2k). Imaging analysis of 400 μm -diameter spheroids revealed significantly enhanced fluorescence intensity for both CUR/DOX@PLGA and CUR/DOX@PLGA-M compared to free drugs at all depths. Notably, strong CUR and DOX signals persisted even at 100 μm depth for nanoformulation-treated groups. Furthermore, ROI quantification and reconstruction of 100 μm -depth sections corroborated superior fluorescence intensity in nanoparticle-treated spheroids. Collectively, these results demonstrate the enhanced deep-tumor penetration capacity of the membrane-engineered nano-system.

CUR/DOX@PLGA-M Promotes Apoptosis

Curcumin (CUR), a natural polyphenol derived from *Curcuma longa*, exhibits multifaceted pharmacological activities including anti-inflammatory, antioxidant, and potent anticancer properties. Its capacity to synergistically enhance chemotherapeutic agents was leveraged in this study through strategic co-delivery with DOX for GBM treatment. CCK-8 proliferation assays revealed that free CUR minimally impacted U87 cell viability (Figure 3a). Notably, CUR potentiated DOX's anti-proliferative effect, reducing the IC₅₀ of free DOX (1.070 $\mu\text{g/mL}$) to 0.291 $\mu\text{g/mL}$. Nano-encapsulation further optimized efficacy, CUR/DOX@PLGA achieved an IC₅₀ of 0.299 $\mu\text{g/mL}$, while CUR/DOX@PLGA-M demonstrated superior potency (IC₅₀=0.238 $\mu\text{g/mL}$). These results unequivocally demonstrate CUR's role in sensitizing GBM cells to DOX-mediated cytotoxicity, with bioengineered membrane modification providing significant additional enhancement of therapeutic activity. Along with the increase of incubation time, the synergistic effect of CUR combined with DOX weakened after 48 h, which may be due to the low stability and easy decomposition of CUR. It is noteworthy that DOX/CUR@PLGA and DOX/CUR@PLGA-M caused a similarly dose-dependent cytotoxic effect within 72 h, which also demonstrated that the encapsulation of nanoparticles enhanced the stability of CUR.

Based on the encouraging results of high accumulation of DOX/CUR@PLGA-M in GBM spheres, the therapeutic effects of DOX/CUR@PLGA-M were further investigated in GBM model. As illustrated in Figure 3b, no significant morphology change was observed in GBM spheres treated with CUR and DOX compared to control group. However, the tumor spheres exhibit obvious structure change on 8th day in DOX-CUR@PLGA group, implying the beneficial therapeutic effects owing to the protective delivery of nanocarrier. Moreover, it was observed that the edge of the GBM spheres were well-defined at the beginning, while their diameters shrank along with loose edges with the extension

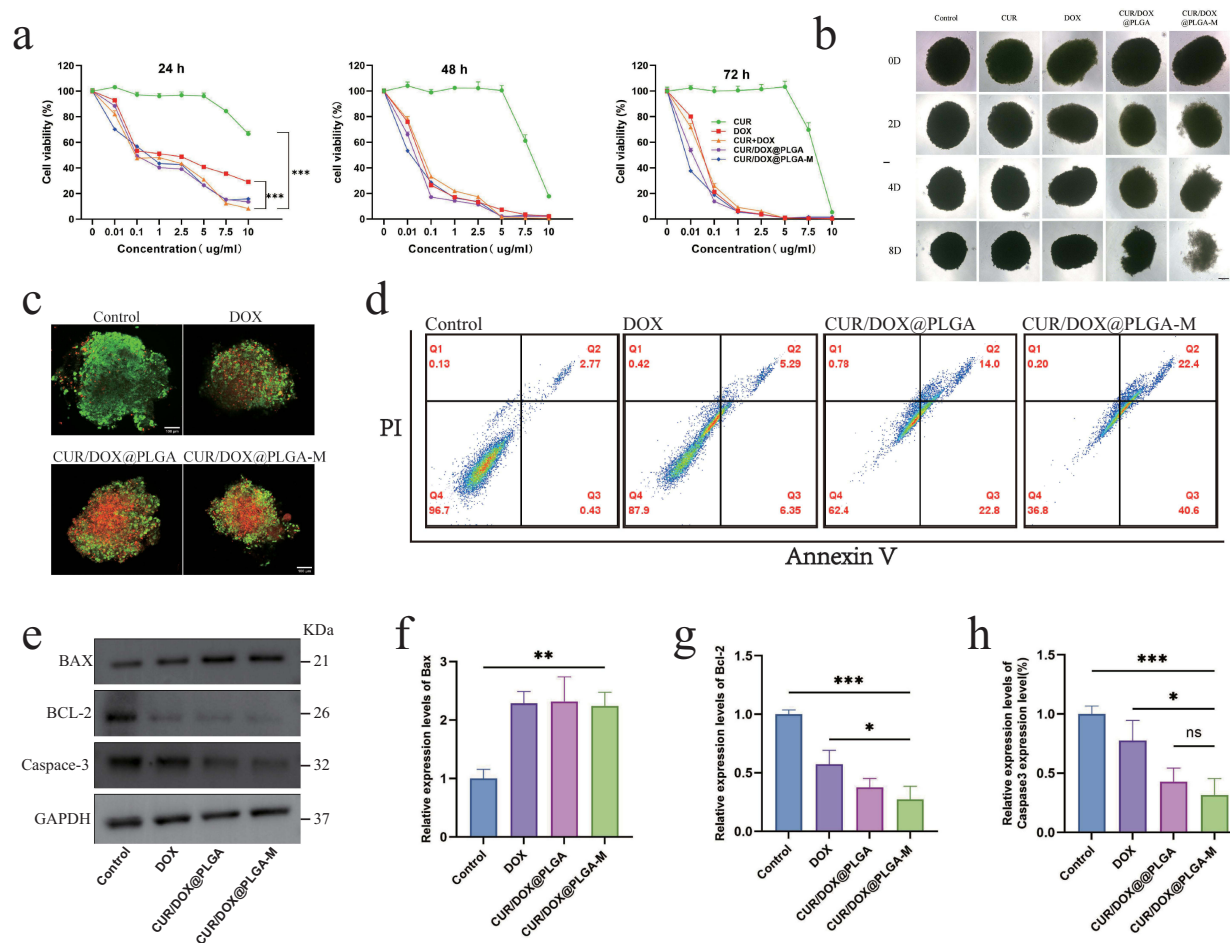


Figure 3 CUR/DOX@PLGA-M promotes apoptosis in glioblastoma cells. (a) Viability of U87 cells after 24, 48, and 72 h treatments. (b) Growth kinetics of 3D GBM spheroids over 8 days under different treatments (scale bar: 200 μm). (c) Viability staining of 3D GBM spheroids post-treatment (Green: live cells; red: dead cells, scale bar: 100 μm). (d) Western blot analysis of apoptosis-related proteins in U87 cells. (e) Apoptosis rates in U87 cells quantified by flow cytometry. (f-h) Quantification of apoptotic protein expression. All the data are presented as mean $\pm$ s.d (n=3), ns $p > 0.05$, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

of the cocubation time in CUR/DOX@PLGA-M group. This phenomenon might be caused by the efficient penetration and drug delivery by CUR/DOX@PLGA-M in GBM model. To visually assess anti-glioblastoma efficacy in vitro, Calcein-AM/PI dual staining was performed on GBM spheroids after 3-day (Figure 3c). Compared to the control, spheroids exposed to free DOX, CUR/DOX@PLGA, and CUR/DOX@PLGA-M exhibited differential cell death patterns. Notably, CUR/DOX@PLGA-M-treated spheroids displayed the smallest diameter with extensive PI-positive regions, indicating superior cytotoxicity against GBM spheroids.

Flow cytometry analysis further demonstrated that CUR/DOX@PLGA-M induced the highest apoptosis rate ($22.7 \pm 0.4\%$), representing an 8.4-fold, 4.2-fold, and 1.8-fold increase over the control ($2.7 \pm 0.7\%$), free DOX ($5.4 \pm 0.7\%$), and CUR/DOX@PLGA ($12.7 \pm 1.3\%$) groups, respectively (Figure 3d). We further examined the effect of DOX/CUR@PLGA-M on U87 cell expression of apoptosis-related proteins by Western blot (Figure 3e). The changes of Bcl-2, which plays an important role in cellular anti-apoptosis by forming dimers with Bax as well as dimerising itself, were first explored. The results showed that after treatment with DOX/CUR@PLGA-M, the expression of Bcl-2 was obviously suppressed while the expression of Bax was significantly increased (Figure 3f and g). Therefore, they promote apoptosis of U87 cells eventually. Caspase-3 is the most important terminal splicing enzyme in the process of cell apoptosis. Drug-loaded nanoparticles induced more significant inhibition of caspase-3 compared to free DOX, suggesting that nanoparticles could effectively trigger the activation or accelerate the degradation of caspase-3 (Figure 3h). All these results demonstrated the effective anti-tumor effect of DOX/CUR@PLGA-M.

Inhibition of Glioblastoma Migration, Invasion, and Neovascularization

To evaluate the effects of CUR/DOX@PLGA-M on GBM migration and invasion, we first performed a scratch healing assay. C6 rat glioblastoma cells were cultured with different drugs in serum-free DMEM medium to minimize interference from cell proliferation. As illustrated in Figure 4a and b, after 48 hours, the migration rate in the control group was $28.1 \pm 1.9\%$, significantly higher than other groups. CUR/DOX@PLGA-M demonstrated the most potent migration inhibition (migration rate $1.4 \pm 1.4\%$), exhibiting an approximately 10% lower migration rate compared to the free DOX group ($11.4 \pm 2.7\%$). These results indicate that CUR synergistically enhances DOX's inhibitory effect on migration, with the biomimetic CUR/DOX@PLGA-M nanoparticles showing the greatest inhibition rate.

The inhibitory effects of different formulations on GBM invasion were subsequently assessed using a transwell invasion assay (Figure 4c and d). Migrated cell counts yielded consistent trends with the scratch assay. Compared to the control group (266 ± 23 cells), the DOX group (110 ± 14 cells) showed significantly fewer invasive cells, while the CUR/DOX@PLGA group (53 ± 5 cells) exhibited an even greater reduction, further highlighting CUR's advantage in suppressing tumor invasion. Notably, the CUR/DOX@PLGA-M treatment group (25 ± 3 cells) displayed minimal tumor cell penetration through Matrigel, confirming the robust potential of this biomimetic nanoparticle to inhibit GBM invasion.

Furthermore, the inhibition of VEGF-induced HCMEC/D3 cell survival by CUR/DOX@PLGA-M suggested potential anti-angiogenic properties. This effect was further validated by an HCMEC/D3 tube formation assay (Figure 4e–g).

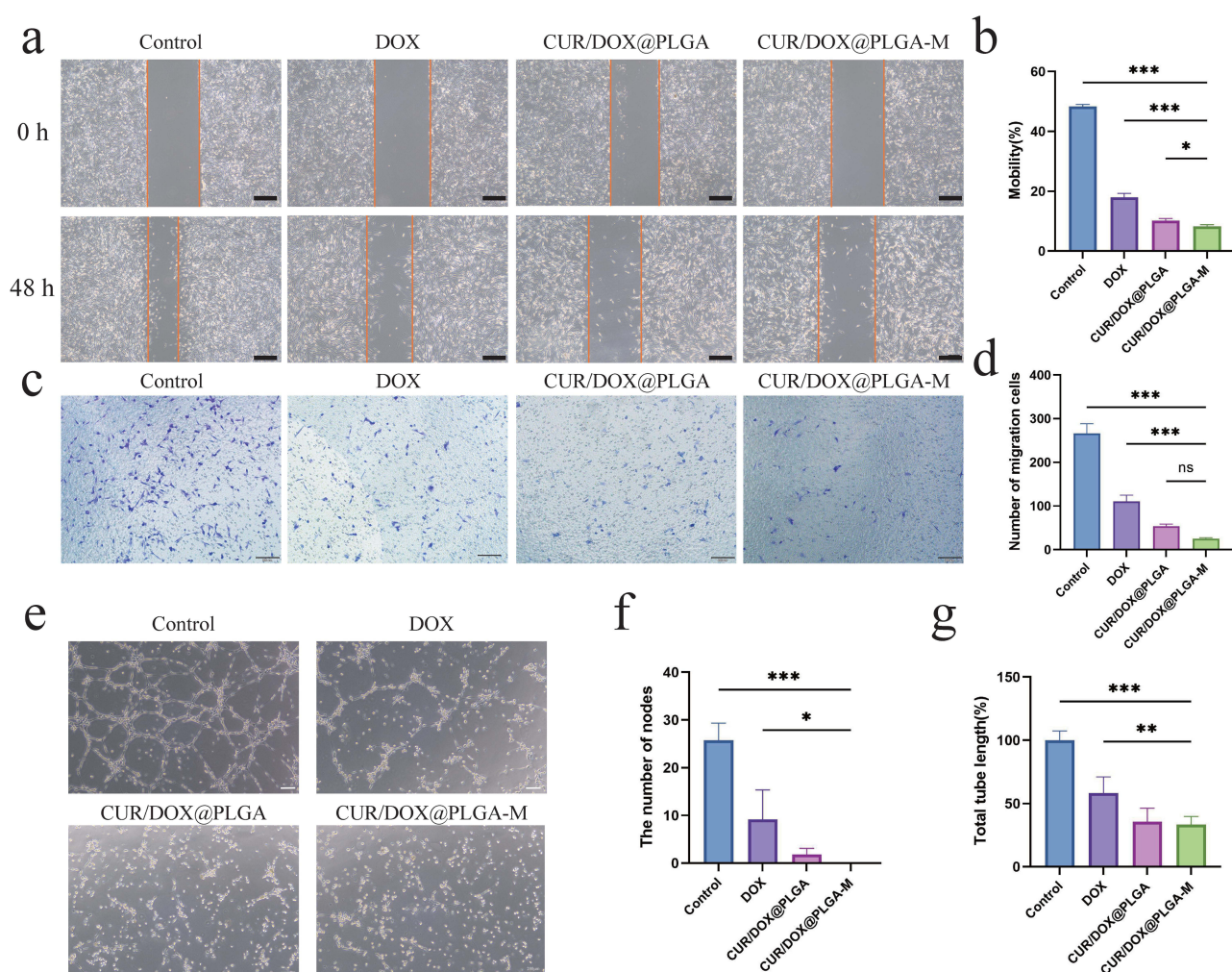


Figure 4 In vitro inhibition of glioblastoma migration, invasion, and neovascularization. (a) Cell migration profiles following 48 h drug treatments (scale bar: 400 μ m). (b) Mobility of C6 cells post 48 h drug exposure. (c) Representative images of U87 cell invasion after drug treatments (scale bar: 100 μ m). (d) Quantification of invaded U87 cells. (e) Tube formation capacity of HCMEC/D3 cells under drug treatments (scale bar: 200 μ m). (f and g) Statistical analysis of vascular network junctions and tube lengths in HCMEC/D3 cells. All the data are presented as mean $\pm$ s.d (n=3). Data are presented as mean $\pm$ SD. Student t test. ns $p > 0.05$, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Following a 4 h incubation on Matrigel containing 50 ng/mL VEGF, all drug-treated groups significantly inhibited VEGF-induced angiogenesis. Quantitative analysis of total tubular structure length revealed that, compared to the VEGF-treated control group, tubular structure formation in the CUR/DOX@PLGA-M-treated group was markedly reduced to $33.3 \pm 6.6\%$, with virtually no node formation observed.

In summary, CUR/DOX@PLGA-M demonstrates multifaceted inhibitory effects on the malignant GBM phenotype. It not only potently inhibits tumor cell migration and invasion but also effectively disrupts angiogenesis. This strategy overcomes the limitations of single-therapy approaches, underscoring the significant advantage of the biomimetic delivery system for achieving synergistic, multi-targeted antitumor therapy.

In vivo Anti-Glioblastoma Effects

To evaluate the in vivo anti-glioblastoma efficacy of CUR/DOX@PLGA-M, we established subcutaneous GBM model in C57BL/6 mice and administered 7 intravenous doses over 14 days (Figure 5a). As illustrated in Figure 5b, a statistically significant divergence in tumor volume emerged between the CUR/DOX@PLGA-M and PBS control groups as early as Day 2, persisting throughout the therapeutic course. This early-onset efficacy likely stems from enhanced tumor-targeted accumulation facilitated by the nanoengineered system. Rapid tumor progression was observed in PBS-treated mice,

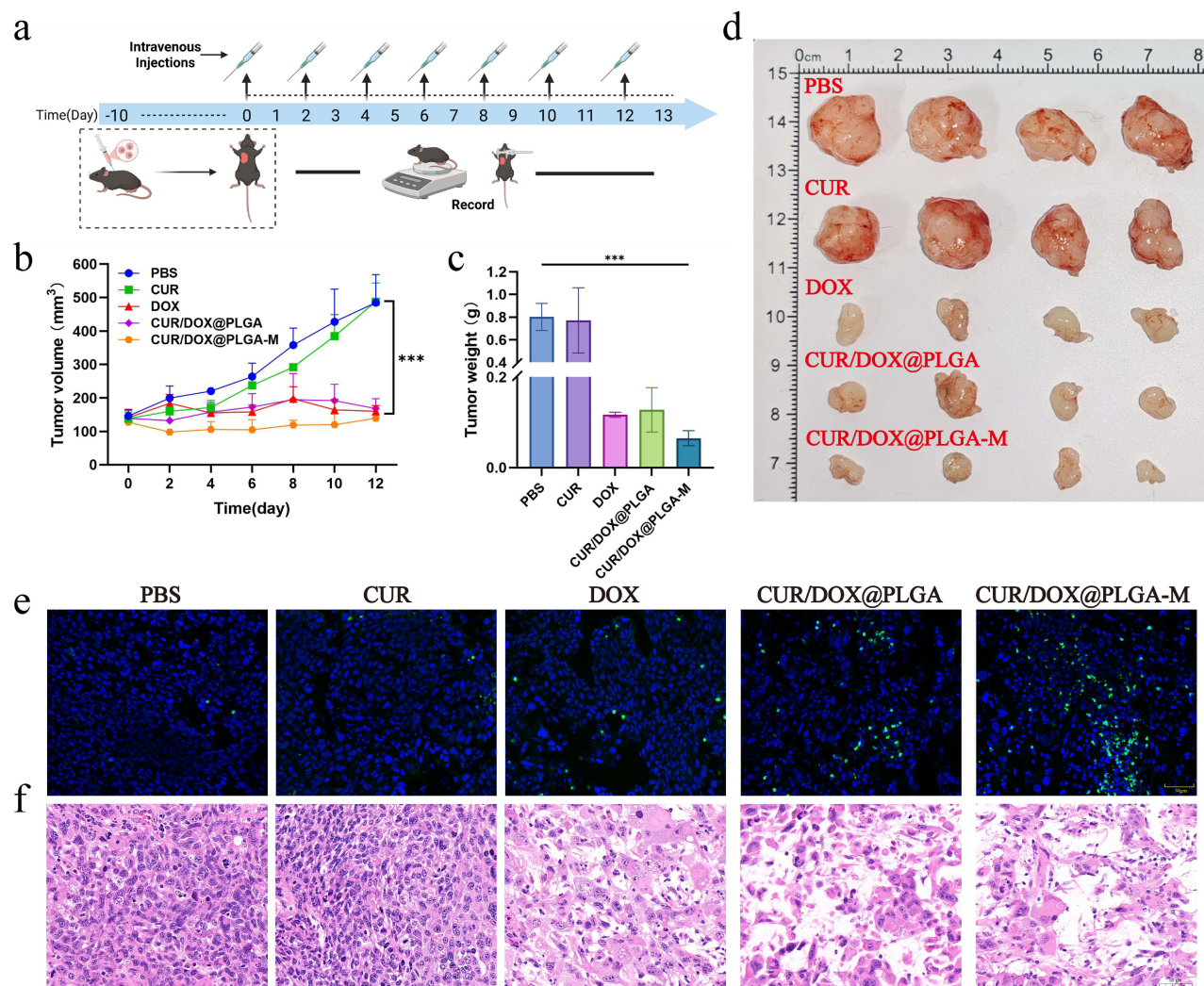


Figure 5 In vivo anti-glioblastoma effects of CUR/DOX@PLGA-M. (a) Schematic diagram of subcutaneous glioblastoma model establishment and therapeutic regimen. (b) Tumor volume kinetics in mice across treatment groups during the dosing period (n=4). (c) Tumor weights from mice after 7 treatment administrations (n=4). (d) Representative photographs comparing excised tumor sizes post-treatment (n=4). (e and f) TUNEL apoptosis assay and H&E analysis of tumor tissues (n=3) (scale bar: 50 μ m). Data are presented as mean $\pm$ SD. Student *t* test. *** *p* < 0.001.

whereas DOX, CUR/DOX@PLGA, and CUR/DOX@PLGA-M treatments substantially suppressed tumor growth. The minimal efficacy of CUR monotherapy confirmed DOX as the primary cytotoxic agent. Terminal tumor resection on Day 14 revealed a 12-fold greater tumor mass in PBS controls versus CUR/DOX@PLGA-M group (Figure 5c), with representative xenograft images corroborating this dramatic size change (Figure 5d).

TUNEL and H&E staining were used to further clarify the effects of each group of drugs on tumor. As shown in the Figure 5e, TUNEL analysis revealed extensive apoptotic fragmentation in tumors treated with CUR/DOX@PLGA-M, with the highest proportion of TUNEL-positive cells. H&E staining revealed extensive coagulative necrosis occupying the tumor area in CUR/DOX@PLGA-M group, accompanied by pyknotic nuclei and diminished cellularity (Figure 5f). In contrast, tumors exhibited hypercellularity with frequent mitotic figures in the control group. These histopathological alterations confirm potent tumor suppression by the nanoengineered system.

Biocompatibility Assessment

Systemic toxicity was monitored via longitudinal body weight tracking (Figure 6a). Notably, DOX-treated mice exhibited progressive weight loss starting at day 4, reaching $17.9 \pm 3.7\%$ reduction by day 12. This toxicity was significantly

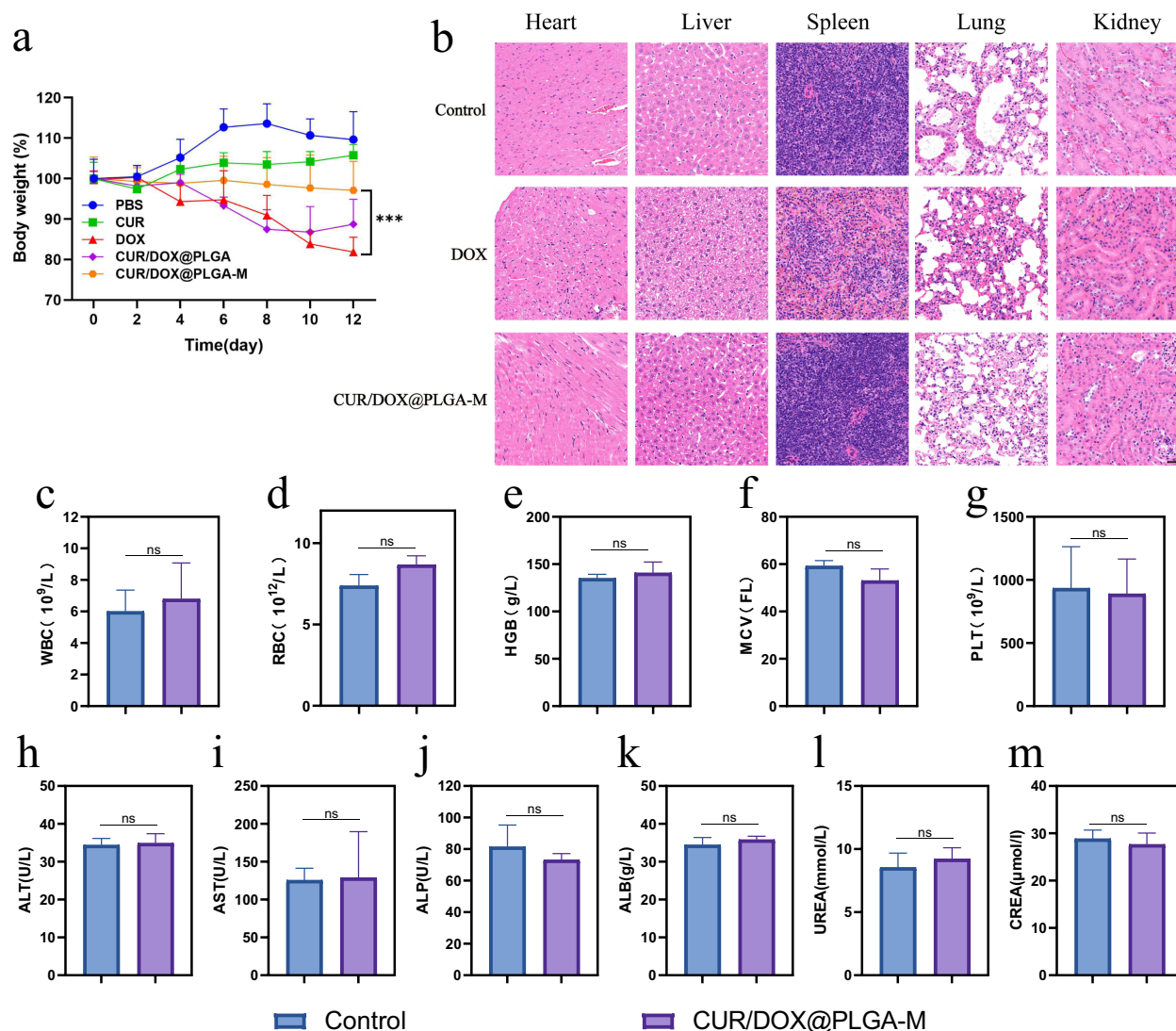


Figure 6 Biosafety assessment of CUR/DOX@PLGA-M. (a) Body weight changes in mice (n=4). (b) H&E staining results of the heart, liver, spleen, lungs, and kidneys of healthy mice and mice treated with DOX and CUR/DOX@PLGA-M (n=3) (scale bar: 100 μm). (c–g) The results of hematological analysis. (h–m) The results of serum biochemical analysis (n=3). Data are presented as mean ± SD. Student t test. ns p > 0.05, *** p < 0.001.

attenuated in the CUR/DOX@PLGA group ($11.5 \pm 6.1\%$ weight loss). Critically, the CUR/DOX@PLGA-M group exhibited no significant weight loss, demonstrating toxicity mitigation.

H&E staining results showed that (Figure 6b), the mice treated with DOX exhibited significant systemic toxicity compared to the healthy mice, characterized specifically by cardiac vacuolization, extensive cytoplasmic degeneration in hepatocytes, and a marked reduction in splenic lymphocytes. Importantly, treatment with CUR/DOX@PLGA-M resulted in significant amelioration of these pathological injuries in the heart, liver, and spleen. This finding demonstrates the advantage of CUR/DOX@PLGA-M in reducing the systemic toxicity of DOX and enhancing its biosafety profile. The underlying mechanisms likely involve the PLGA carrier enabling sustained and controlled drug release, thereby avoiding acute injury caused by high peak concentrations of DOX; the potent antioxidant and anti-inflammatory properties of CUR effectively neutralizing DOX-induced ROS bursts and inflammatory responses, protecting critical organ cells from oxidative stress damage; and crucially, the hUC-MSCs membrane coating facilitated the nanoparticles actively homing to injury or inflammation sites. This not only significantly enhances drug enrichment in the target regions but also substantially reduces the accumulation of DOX in healthy organs, minimizing its off-target toxicity. Therefore, by integrating multiple strategies including targeted delivery to reduce exposure, sustained release to lessen acute impact, and synergistic antioxidant protection, CUR/DOX@PLGA-M effectively mitigated DOX-induced damage to major organs and significantly expanded the therapeutic window of this treatment regimen. The biological safety of CUR/DOX@PLGA-M was further validated through H&E staining of major organs, as well as hematological and serum biochemical analyses. The hematological analysis (Figure 6c–g) revealed no statistically significant differences in the levels of white blood cells (WBC), red blood cells (RBC), hemoglobin (HGB), mean corpuscular volume (MCV), and platelets (PLT) between the CUR/DOX@PLGA-M group and the healthy control group, indicating that the formulation did not induce significant hematological toxicity or myelosuppression. Serum biochemical analysis further corroborated its biocompatibility (Figure 6h–m). Key liver function parameters, including alanine aminotransferase (ALT), albumin (ALB), alkaline phosphatase (ALP), and aspartate aminotransferase (AST), remained within normal physiological ranges. Likewise, renal functional parameters, such as urea, creatinine, also showed no statistically significant deviations from control values, suggesting the absence of drug-induced hepatotoxicity or nephrotoxicity.

Conclusion

In summary, this study successfully developed a CUR/DOX@PLGA-M nanoplatform for targeted glioblastoma therapy, leveraging the intrinsic tumor homing capacity of hUC-MSC membranes to achieve precise tumor targeting. Cellular uptake studies, BBB and GBM spheroid penetration assays demonstrated significantly enhanced drug accumulation and penetration efficacy following CUR/DOX@PLGA-M treatment. Additionally, the synergistic interaction between CUR and DOX, combined with the targeting capability of the hUC-MSC membrane, conferred superior cytotoxicity against tumor cells to CUR/DOX@PLGA-M compared to free DOX and conventional PLGA nanoparticles. Critically, this integrated platform significantly alleviates DOX-associated systemic toxicity. Although this study is based on preclinical animal models, the results have preliminarily validated the feasibility and safety of CUR/DOX@PLGA-M in the targeted treatment of glioblastoma, providing important insights for subsequent clinical translation. Leveraging the synergistic mechanism of CUR and DOX within this nanoplatform, the combination strategy holds promise for significantly reducing the clinical dosage of doxorubicin without compromising antitumor efficacy, thereby alleviating its cardiotoxicity and other adverse effects. Future clinical studies should further optimize the dosage and administration routes, explore the safety window for different dose combinations, and develop personalized treatment regimens based on individual patient characteristics to achieve an optimal balance between therapeutic efficacy and toxicity. Collectively, these findings establish CUR/DOX@PLGA-M as a promising targeted chemotherapeutic strategy for glioblastoma, warranting further investigation into its potential integration with established clinical regimens to enhance therapeutic efficacy.

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Disclosure

The authors declare that they have no competing interests in this work.

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