



Mitochondria-targeting amphiphilic polymers enable idebenone to promote neuronal regeneration following spinal cord injury

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Keywords:

Mitochondria-targeting, spinal cord injury, poorly water-soluble, amphiphilic polymer

Citation:

Zhong, J.; Zhou, P.; Ge, L.; Zhou, Z.; Zheng, S.; Liu, S.; Qin, R.; Zhu, L.; Jiao, G.; Chen, F.; Liu, X. Mitochondria-targeting amphiphilic polymers enable idebenone to promote neuronal regeneration following spinal cord injury. *Micro Nano Sci.* 2026, 1, 15. <https://dx.doi.org/10.20517/mns.2026.01>

Received: 7 Jan 2026

First Decision: 22 Apr 2026

Revised: 28 Jun 2026

Accepted: 24 Sep 2026

Published: 30 Sep 2026

Academic Editor:

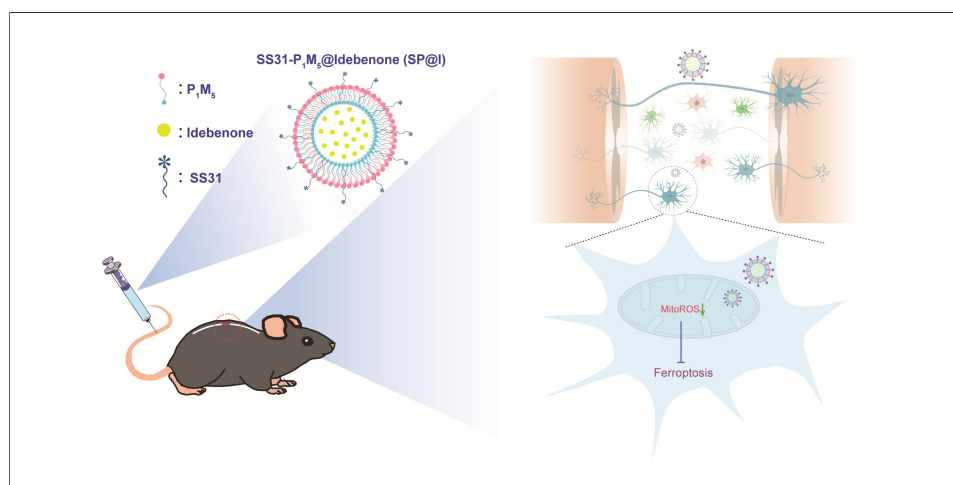
Yu Chen

Copy Editor:

Shu-Yuan Duan

Production Editor:

Shu-Yuan Duan



Abstract

Rescuing impaired function of neuronal mitochondria in the early stage of secondary injury after spinal cord injury (SCI) is a potential treatment for SCI. However, targeting delivery of therapeutics to neuronal mitochondria in SCI remains a significant challenge due to multiple barriers, such as the blood-spinal cord barrier, cell and mitochondrial membranes. In this work, we engineered mitochondria-targeting therapeutics SP@I by encapsulating amphiphilic polymers with Idebenone, followed by modification with the mitochondria-targeting peptide SS31. SP@I efficiently accumulated at SCI lesions after intravenous administration owing to the targeting capacity of the SS31 peptide. SP@I protected neuronal mitochondria in SCI mice by reducing excessive reactive oxygen species (ROS) from damaged mitochondria, thus significantly improving neuronal regeneration and functional recovery after SCI. This mitochondria-targeting therapeutic holds great promise

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for the treatment of neurological disorders related to mitochondrial dysfunction.

INTRODUCTION

Spinal cord injury (SCI) disrupts the intrinsic connections of the nervous system, resulting in impaired basic neurological functions, severe motor disorders, or even paralysis^[1-4]. The pathological progression of SCI is sophisticated, which stems from primary traumatic injury and subsequent cascading secondary damage^[5-7], characterized by excessive reactive oxygen species (ROS) accumulation^[8-10], neuronal ferroptosis^[11-14], and mitochondrial dysfunction^[15-18]. These aberrant biological events ultimately trigger extensive neuronal cell death^[19,20]. Given that the tissue and neuronal damage induced by primary SCI is irreversible^[21-23], there is an urgent need to develop effective strategies for neuronal protection and regeneration during the secondary injury phase.

Excessively elevated glutamate levels drive robust ROS and lipid peroxide accumulation throughout secondary SCI injury^[24-26], thereby inducing neuronal apoptosis and ferroptosis, and further aggravating neuronal loss^[11,27-29]. Accumulating evidence has demonstrated that ferroptosis predominantly arises during the secondary injury, serving as a pivotal contributor to neuronal death after SCI^[12,30-33]. Meanwhile, ROS-mediated mitochondrial dysfunction acts as another critical barrier to neuronal regeneration following SCI^[34-36]. Accordingly, scavenging excessive ROS during secondary injury is beneficial for neuronal protection and functional restoration. Although neuroprotective therapies targeting a single mechanism have been widely investigated, their clinical translation remains challenging. In contrast, multi-modal therapeutic strategies with synergistic protective effects hold greater potential to facilitate long-term neuronal survival and functional recovery post-SCI.

Idebenone is a potent antioxidant agent that scavenges excess ROS and suppresses lipid peroxide generation^[37-44]. On this basis, we hypothesized that Idebenone could alleviate mitochondrial dysfunction-associated SCI and thereby protect neurons after injury^[45,46]. In this study, we fabricated mitochondria-targeted functional micelles termed SS31- P_1M_5 @Idebenone (SP@I) by encapsulating the poorly water-soluble Idebenone with amphiphilic polymers P_1M_5 , followed by conjugation with mitochondrial-targeting peptide SS31. This micellar formulation is designed to improve idebenone bioavailability by prolonging systemic blood circulation, which enhances local drug accumulation and achieves elevated therapeutic concentrations. Furthermore, the modified SS31 peptide enables precise targeted delivery of the therapeutics to neuronal mitochondria, thereby restoring impaired mitochondrial function.

METHODS

Synthesis of P_1M_5

To synthesize the amphiphilic polymer P_1M_5 , we performed acylation between the anhydride groups of PMHC₁₈ [poly(maleic anhydride-alt-1-octadecene)] and mPEG-NH₂ (average Mw = 5 kDa). Briefly, PMHC₁₈ (70.2 mg, 0.2 mmol; Sigma-Aldrich, USA) was dissolved in dichloromethane (DCM), followed by the addition of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (75.4 mg, 0.4 mmol). The mixture was stirred for 30 min to activate carboxyl groups. Subsequently, mPEG-NH₂ (200 mg, 0.04 mmol) and triethylamine (TEA, 0.8 mmol; Macklin, China) were introduced, and the reaction proceeded for 24 h under stirring. The resulting product was dried under a nitrogen stream to yield a white solid, which was

redissolved in dimethyl sulfoxide (DMSO) with stirring until fully dissolved. The solution was then diluted with ultrapure water, transferred to a dialysis membrane (MWCO = 14 kDa), and dialyzed against distilled water for 24 h. The final product was lyophilized and preserved at -20 °C for subsequent use.

Preparation of P@I by the self-assembly method

Idebenone (MedChemExpress, USA) was encapsulated with amphiphilic polymer P_1M_5 by the self-assembly method. In short, 10 mg of Idebenone and 10, 20, 40, 80, 120, 160, and 200 mg of P_1M_5 were dissolved in dimethyl sulfoxide (DMSO), respectively. Idebenone solution was added to the P_1M_5 solution at different mass ratios (P_1M_5 : Idebenone) and mixed thoroughly. Then, it was added dropwise to a round-bottom flask filled with double-distilled water, and the P@I solution was obtained by ultrasonic reaction for 30 min.

Synthesis of SP@I

SP@I was synthesized by conjugating SS31 (DGpeptides, China) to P@I via an amide reaction. In brief, carboxyl groups on the P@I solution (containing 160 mg P_1M_5 , equivalent to 0.188 mmol COOH) were activated by reacting with EDC (145.2 mg, 0.752 mmol) and Sulfo-NHS (159.7 mg, 0.830 mmol) for 0.5 h. SS31 (15.1 mg, 0.0236 mmol) was dissolved in 200 μ L of double-distilled water and then slowly added to the activated P@I solution. The reaction was allowed to proceed for 12 h under light-protected conditions. For fluorescent labeling, Cy5.5 (10 mg/mL; Aladdin, China) was added during the P@I preparation to obtain P@I-Cy5.5. SP@I-Cy5.5 was then synthesized using the same conjugation method as described above, starting from P@I-Cy5.5. The final products (SP@I and SP@I-Cy5.5) were purified by centrifugal filtration using an Amicon Ultra ultrafiltration tube (MWCO = 10 kDa) and washed three times with double-distilled water until no drug residue was detected in the filtrate.

Characterization of P@I and SP@I

The successful PEGylation and SS31 conjugation were confirmed by ^1H NMR spectroscopy (Bruker DRX 600, USA) and analyzed using MestReNova software (version 11.0.4). The hydrodynamic diameter (Dh) and zeta potential were measured using a Zetasizer Nano ZS instrument (Malvern, UK) at 25 °C. Each sample was equilibrated for 120 s before measurement, and data were collected from six repeated runs. The morphology and size of the nanoparticles were further characterized by transmission electron microscopy (TEM; Hitachi HT7800, Japan). The drug loading efficiency was determined by high-performance liquid chromatography (HPLC).

Induction of ferroptosis in HT22 cells by RSL3

HT22 cells, a mouse hippocampal neuron cell line, were provided by the Central Laboratory of the Third Affiliated Hospital of Sun Yat-sen University. Cells were plated in 96-well plates at a density of 1×10^4 cells per well and cultured for 24 h. Upon reaching confluence, the medium was exchanged with 100 μ L of fresh DMEM (Thermo Fisher Scientific, USA) containing graded concentrations of RSL3 (Selleckchem, USA), and cells were incubated for an additional 12 h. CCK-8 reagent (TargetMol, China) was prepared following the manufacturer's protocol. Subsequently, 100 μ L of the CCK-8 working solution was added to each well, and incubation proceeded for 2 h. Absorbance at 450 nm was recorded using a microplate reader to determine the IC_{50} value of RSL3.

Determination of the optimal SP@I concentration

HT22 cells were seeded into 96-well plates at 7×10^3 cells per well and incubated for 24 h. The cells were then treated with 100 μ L of different concentrations of SP@I, all containing a fixed concentration of RSL3 (2 μ M), for 12 h. After treatment, the medium was discarded, and the CCK-8 working solution was added. Following 2 h of incubation, the OD at 450 nm was measured using a microplate reader to calculate cell viability.

Mitochondrial co-localization of therapeutics

The mitochondrial targeting of the therapeutics was assessed using laser scanning confocal microscopy. HT22 cells (2.8×10^4 cells/well) were seeded and cultured for 24 h, followed by incubation with 1 μ M SP@I-Cy5.5, P@I-Cy5.5, or free Cy5.5 for 2, 6, or 10 h. Cells were subsequently stained with MitoLite™ Green (2 mL in DMEM) for 1 h to label mitochondria. Confocal imaging was performed with excitation/emission settings at 498/520 nm for mitochondria (green) and 640/710 nm for therapeutics (red).

Cell viability assay

HT22 cells were seeded in 96-well plates at 10×10^3 cells per well and incubated for 24 h. The cells were then treated with 100 μ L of 1 μ M SP@I or P@I, each containing 2 μ M RSL3, for 12 h. After treatment, cell viability was evaluated using the CCK-8 assay as described above.

Determination of mitochondrial superoxide (MitoSOX)

HT22 cells were seeded in 6-well plates at 1.6×10^5 cells per well and incubated for 24 h. The cells were then divided into four groups: (1) untreated Control, which received 2 mL of fresh medium alone; (2) RSL3-only group, which received 2 mL of medium containing 2 μ M RSL3; (3) SP@I group, which received 2 mL of medium containing 1 μ M SP@I and 2 μ M RSL3; and (4) P@I group, which received 2 mL of medium containing 1 μ M P@I and 2 μ M RSL3. All groups were incubated for 12 h. Following treatment, the cells were incubated with 1 μ M MitoSOX Red reagent for 30 min in the dark. After being washed three times with phosphate buffered saline (PBS), the cells were collected and analyzed by flow cytometry to quantify mitochondrial superoxide levels.

SCI modeling and treatments

All animal experiments were approved by the Laboratory Animal Welfare and Ethics Committee of Jinan University (approval no. GZJLAW-20231124-03). Female C57BL/6J mice (9–10 weeks, 20–22 g) were purchased from Beijing HFK Bioscience Co., Ltd. A total of 33 mice were used in this study. Specifically: For the pharmacokinetic study, 9 mice were randomly assigned to three groups ($n = 3$ per group): free Cy5.5, P@I-Cy5.5, and SP@I-Cy5.5. For *in vivo* imaging and biodistribution, 12 mice were randomly assigned to four groups ($n = 3$ per group): PBS, free Cy5.5, P@I-Cy5.5, and SP@I-Cy5.5. Mice were imaged at 1, 3, 6, 12, and 24 h post-injection and then euthanized at 24 h for *ex vivo* imaging of the spinal cord and brain. For the therapeutic study, 12 mice were randomly assigned to four groups ($n = 3$ per group): Sham, PBS, P@I, and SP@I. Mice were anesthetized with 4% sodium pentobarbital (50 mg/kg, i.p.)^[47] for all surgical procedures. A laminectomy was performed at T10 to expose the spinal cord, followed by contusive injury at the same segment using a Louisville Injury System impactor (0.6 mm drop height, 0.6 s dwell time). Post-operatively, gentamicin (10 mg/kg; Guangzhou Tianxin Pharmaceutical, China) was given subcutaneously for 3 days. Mice were housed under standard conditions (22–24 °C, 12 h light/dark cycle), and bladders were manually expressed twice daily until spontaneous voiding resumed. Sham-operated mice and PBS controls received 100 μ L of PBS via the tail vein. Treatment groups (SP@I, P@I) received equivalent idebenone doses (5 mg/kg) via tail vein once daily for 7 consecutive days.

Basso mouse scale scoring

The Basso mouse scale (BMS) consists of 0 to 9 points, where 0 indicates no movement of any kind observed and 9 indicates normal. Using a single-blind method, the average score of the two hindlimbs recorded by the two observers was considered as the BMS of the sample. BMS scores of each treatment group were assessed on the 1st, 3rd, 5th, and 7th day, and once a week until 8 weeks after model establishment, while videos were recorded on day 1, 7, 14, 28, and 56 post-operation.

Pharmacokinetic study

For the pharmacokinetic study ($n = 9$), mice were administered free Cy5.5, P@I-Cy5.5, or SP@I-Cy5.5 via tail vein injection post-operatively. For P@I-Cy5.5 and SP@I-Cy5.5, the idebenone-equivalent dose was 5 mg/kg. The free Cy5.5 group received an equivalent Cy5.5 dose matching the Cy5.5 content in the SP@I-Cy5.5 formulation. Blood samples were collected via the tail vein or retro-orbital plexus into heparinized tubes at pre-dose, 5 min, and 1, 3, 6, 12, 24, and 48 h post-injection. After centrifugation, plasma fluorescence intensity was measured at 640/710 nm (Ex/Em) using a multifunctional microplate reader.

For the *in vivo* imaging and biodistribution study ($n = 12$), mice were administered PBS, free Cy5.5, P@I-Cy5.5, or SP@I-Cy5.5. The P@I-Cy5.5 and SP@I-Cy5.5 groups received an idebenone-equivalent dose of 5 mg/kg, while the free Cy5.5 group received a Cy5.5 dose equivalent to that of the SP@I-Cy5.5 group. Mice were anesthetized and imaged at 1, 3, 6, 12, and 24 h post-injection using a small-animal *in vivo* imaging system (excitation: 640 nm). At 24 h, these mice were euthanized, and the spinal cord and brain were harvested for *ex vivo* imaging.

CatWalk gait analysis

The gait of each group of mice was analyzed using the CatWalk XT at day 56. Deficits in hindlimb motor function were assessed by the animal's ability to walk on a 50 cm-long runway. Footprints were recorded and transferred to a computer via a connected camera. Footprints were analyzed using XT version 9.0.

Nissl staining

On day 56, the spinal cord segment centered on the injury site was harvested and fixed in 4% paraformaldehyde for 24 h. After dehydration and paraffin embedding, the tissue was sectioned into 4 μ m thick slices. The sections were deparaffinized, rehydrated, and stained with an aniline blue solution for 10 min. Finally, the sections were dehydrated, cleared, and mounted. Images were captured using an upright light microscope.

Immunofluorescence staining

Spinal cord paraffin sections adjacent to those used for Nissl staining were prepared. After deparaffinization and antigen retrieval, the tissue sections were encircled with a hydrophobic barrier pen and blocked with 2% bovine serum albumin for 30 min. The sections were then incubated overnight at 4 °C with a mixture of primary antibodies: rabbit anti-NeuN (GB11096, Servicebio, China) and goat anti-GFAP (GB13138-1, Servicebio, China). After washing, the sections were incubated for 50 min at room temperature in the dark with a mixture of appropriate fluorescent secondary antibodies. Finally, the sections were mounted with an anti-fade mounting medium. Images were captured using a fluorescence microscope. The fluorescence intensity of NeuN-positive and glial fibrillary acidic protein (GFAP)-positive areas was quantified using ImageJ software.

Toxicity assessment

In vitro cytotoxicity: The cytotoxicity of SP@I and P@I was evaluated on HT22 cells. Cells were incubated with each formulation at concentrations of 0.1, 0.5, 1, 5, 10, and 15 μ M for 24 h. Subsequently, cell viability was assessed using the CCK-8 assay according to the manufacturer's protocol. After incubating with the CCK-8 solution for 2 h, the optical density (OD) at 450 nm was measured with a microplate reader, and the cell viability rate was calculated.

Body weight monitoring: The body weights of the mice were recorded before anesthesia (baseline) and then monitored weekly until 8 weeks after surgery.

Histopathological analysis: On day 56, mice were deeply anesthetized with 4% sodium pentobarbital (50 mg/kg, i.p.) and perfused via the left ventricle with 50 mL of PBS followed by 50 mL of 4% paraformaldehyde. Major organs (heart, liver, spleen, lungs, kidneys, and brain) were harvested, fixed in 4% paraformaldehyde for 24 h, dehydrated, paraffin-embedded, and sectioned at 4 μ m. Sections were stained with hematoxylin and eosin (H&E), mounted, and examined under an upright light microscope (Nikon, Japan) for morphological evaluation.

Statistical analysis

Data are expressed as mean $\pm$ standard deviation (SD) ($n = 3$ unless otherwise stated). Two-way repeated-measures ANOVA followed by Bonferroni's post-hoc test was used to evaluate group differences over time in BMS scores, body weights, and plasma fluorescence intensity in the pharmacokinetic study. One-way analysis of variance (ANOVA) with Tukey's multiple comparison test was applied for other comparisons. Pharmacokinetic parameters, including T_{max}, terminal half-life ($t_{1/2}$), and mean residence time (MRT), were calculated by non-compartmental analysis using Phoenix WinNonlin. The terminal half-life was calculated as $\ln(2)/\lambda_z$, where λ_z is the terminal elimination rate constant determined by linear regression of the terminal phase of the log-transformed plasma concentration–time curve. Fluorescence intensity from *in vitro* confocal imaging and *ex vivo* tissue imaging was quantified using ImageJ and expressed as mean fluorescence intensity (a.u.). A significance level of $P < 0.05$ was adopted.

RESULTS AND DISCUSSION

Preparation and characterization of SP@I micelles

P₁M₅ was synthesized via an acylation reaction between anhydride groups on poly (maleic anhydride-alt-1-octadecene)(PMHC₁₈) and amino groups on 5 k mPEG-NH₂^[48]. The characteristic peaks of PMHC₁₈ and PEG were detected at chemical shifts of 1.1–1.4 ppm and 3.5–3.9 ppm, respectively [Supplementary Figure 1]. The PEG conjugation efficiency on PMHC₁₈ was calculated to be 12.43% based on ¹H nuclear magnetic resonance (¹H NMR). To improve the bioavailability of poorly water-soluble idebenone, the drug was subsequently encapsulated with P₁M₅ at a mass ratio of 1:16 (Idebenone: P₁M₅) to fabricate polymeric P₁M₅@Idebenone (P@I) micelles [Supplementary Figures 2 and 3]. Both P@I and SP@I solutions showed no significant changes in size during incubation for 7 days at room temperature [Supplementary Figure 4], confirming remarkable stability for poorly water-soluble idebenone after well-designed formulation, which is conducive to further *in vivo* experiments.

The synthetic route for SP@I micelles is illustrated in Figure 1A. To confer mitochondrial targeting to P@I micelles, they were modified with the mitochondrial-targeting SS31 peptide by conjugating it to carboxyl groups on P@I via EDC/NHS-activated amidation, yielding SP@I micelles [Figure 1A]. Dynamic light scattering (DLS) measurements showed that the average hydrodynamic diameter increased from approximately 9 nm for P@I to 16 nm for SP@I [Figure 1B], which was attributed to successful surface conjugation of SS31 peptides. The zeta potential of SP@I micelles was nearly electrically neutral (−0.2 mV), much higher than that of P@I (−8.3 mV) [Figure 1C], further verifying the successful modification with the positively charged SS31 peptide. Transmission electron microscopy (TEM) images showed that both P@I and SP@I micelles possessed uniform, spherical morphologies [Figure 1D]. Fourier-transform infrared spectroscopy (FT-IR) spectra of SP@I displayed new characteristic stretching signals at 1,245 cm^{−1}, 1,559 cm^{−1}, and 1,654 cm^{−1}, corresponding to amide bonds formed during SS31 peptide conjugation with P₁M₅@Idebenone^[49,50] [Figure 1E]. Moreover, characteristic ¹H NMR peaks of SS31 were observed at approximately 5.4–5.8 ppm and 6.1–6.6 ppm, confirming successful conjugation of SS31 onto P@I micelles. The conjugation efficiency of the SS31 peptide to P@I was quantified to be 7.56% by ¹H NMR [Figure 1F].

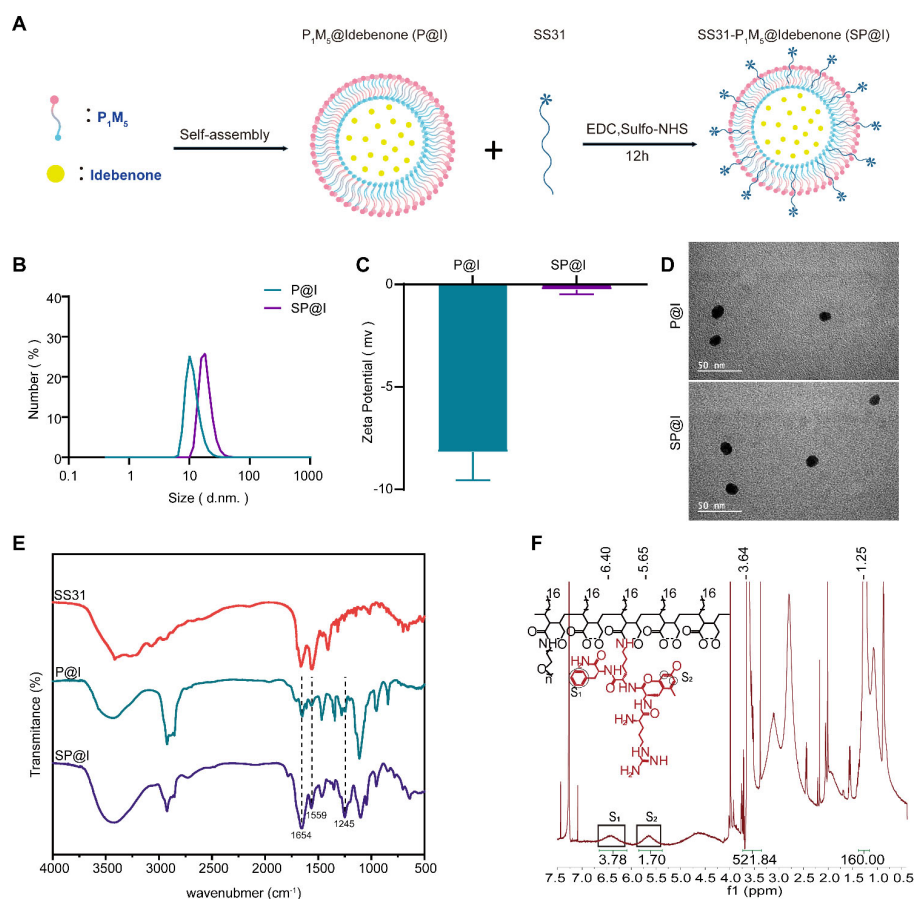


Figure 1. Synthesis and characterization of SP@I, P@I. (A) Schematic diagram of synthesis of SP@I; (B) Particle size distribution of SP@I, P@I; (C) Zeta potential of SP@I, P@I; (D) Representative TEM image of SP@I, P@I. Scale bar is 50 nm; (E) FT-IR Spectrum of SS31, P@I, and SP@I. (F) 1H -NMR Spectrum of SP@I. EDC: NHS: TEM: transmission electron microscopy; FT-IR: Fourier-transform infrared spectroscopy; 1H -NMR: 1H nuclear magnetic resonance.

***In vitro* neuroprotection of SP@I on the ferroptosis cell model**

Ferroptosis accelerates neuronal death and functional loss in SCI^[12], and this pathological process is dominated by mitochondrial ROS overproduction^[35]. Accordingly, normalizing ROS in neuronal mitochondria would inhibit ferroptosis and rescue neurons. We first validated the mitochondrial targeting capability of SS31-modified micelles. HT22 cells were co-incubated with MitoLiteTM mitochondrial tracker dyes and Cy5.5-labeled P@I or Cy5.5-labeled SP@I. Confocal fluorescence images were then collected at 2, 6, and 10 h post-incubation, respectively [Figure 2A]. Strong overlap between green fluorescence from MitoLiteTM and red fluorescence from Cy5.5-labeled SP@I was observed at 6 h after co-incubation, verifying the efficient mitochondrial accumulation of SP@I micelles. In comparison, the P@I group exhibited only faint intracellular red fluorescence with a significantly lower fluorescence intensity, indicating negligible mitochondrial uptake of non-targeted P@I micelles. Collectively, these results confirm the precise mitochondrial targeting capacity conferred by the surface-grafted SS31 peptide.

An *in vitro* ferroptosis model was established by incubating HT22 cells with ferroptosis inducer RSL3 for 12 h. The half-maximal inhibitory concentration (IC₅₀) of RSL3 was determined to be 1.95 μM [Figure 2B]. Cytotoxicity assays demonstrated that P@I and SP@I micelles exhibited no obvious toxic effects on HT22 cells within the concentration range of 0–15 μM [Figure 2C], confirming satisfactory biocompatibility. To further evaluate the therapeutic effect of SP@I, the cell viability was assessed after HT22 cells were co-treated with 2 μM RSL3 and different concentrations of SP@I for 12 h. SP@I exerted a dose-dependent

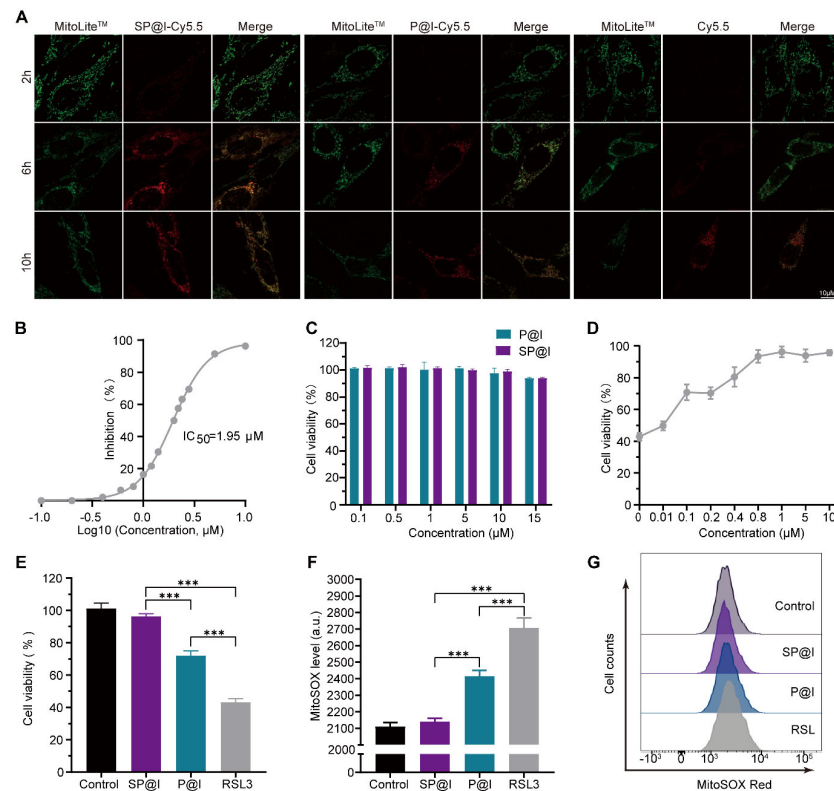


Figure 2. Inhibits RSL3-induced ferroptosis in HT22 cells. (A) Distribution of P@I and SP@I after 2, 6, and 10 h co-incubation with HT22 cells. The scale bar is 10 μm; (B) Half-inhibitory concentration of RSL3-induced HT22 cell death; (C) Cytotoxic effects of P@I and SP@I on HT22 cells after 24 h of co-incubation; (D) The optimal concentration of SP@I for inhibiting RSL3-induced ferroptosis in HT22 cells; (E) Protective effect of 1 μM P@I and SP@I against RSL3-induced ferroptosis in HT22 cells. SP@I versus P@I, $P < 0.001$; SP@I versus RSL3, $P < 0.001$; P@I versus RSL3, $P < 0.001$; (F-G) Analysis and quantification of Flow cytometry of mitochondrial superoxide. SP@I versus P@I, $P < 0.001$; SP@I vs. RSL3, $P < 0.001$; P@I versus RSL3, $P < 0.001$. Data are expressed as the mean $\pm$ SD ($n = 3$). SD: Standard deviation.

anti-ferroptosis effect at concentrations below 1 μM [Figure 2D], and the cell viability reached 96.23% at 1 μM SP@I, signifying the prominent neuroprotective function. In contrast, cell viability was only 70.94% after treatment with the same concentrations of RSL3 and P@I [Figure 2E]. This suggests that the mitochondrial-targeting peptide SS31 could improve ferroptosis resistance, probably by facilitating uptake of idebenone formulations by mitochondria.

Mitochondrial superoxide homeostasis plays a vital role in normal cellular physiological functions, and excessive mitochondrial superoxide can mediate ferroptosis^[35,51]. We further studied whether SP@I could reduce mitochondrial superoxide in an *in vitro* ferroptosis model, which features excess superoxide. Mitochondrial superoxide was detected and quantified after HT22 cells were incubated with RSL3+SP@I, RSL3 + P@I, and RSL3 for 12 h, respectively. MitoSOX in HT22 cells was quantified by flow cytometry [Figure 2F and G]. HT22 cells treated with RSL3 showed the highest mitochondrial superoxide levels. The P@I treatment reduced mitochondrial superoxide levels by approximately 49%. Notably, the SP@I group exhibited mitochondrial superoxide content comparable to that of normal untreated cells. These results verify that the synergistic effect of SS31-mediated mitochondrial targeting and idebenone-based antioxidant activity enables SP@I to efficiently eliminate mitochondrial superoxide and inhibit neuronal ferroptosis.

Tissue targeting and *in vivo* pharmacokinetics of SP@I micelles

Having validated the favorable mitochondrial targeting and anti-ferroptosis capacities of SP@I *in vitro*, we then investigated the *in vivo* pharmacokinetics and tissue accumulation of SP@I micelles. SCI mice were modeled by injury at the thoracic level 10 (T10). SCI mice were intravenously administered with SP@I-Cy5.5

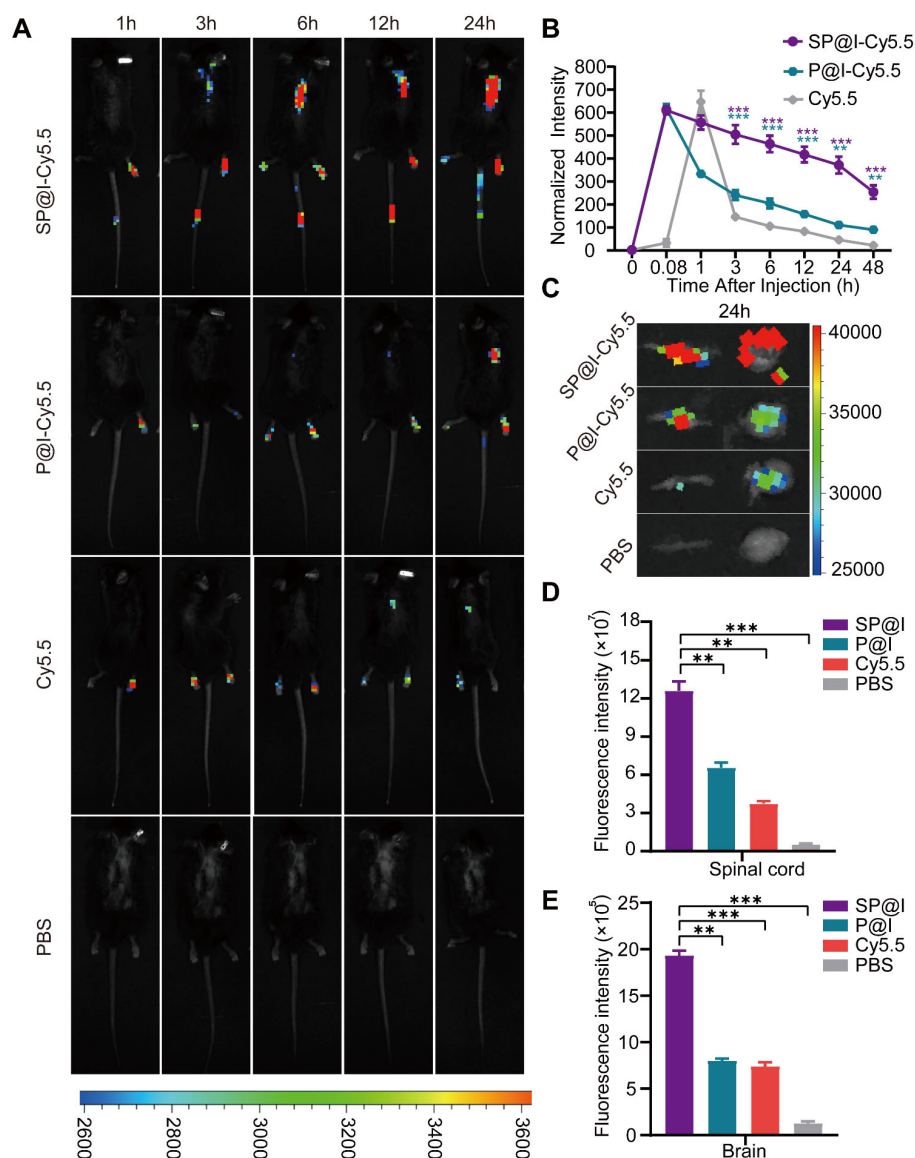


Figure 3. Pharmacokinetics and spinal cord enrichment of nanoparticles in mice. (A) *In vivo* imaging of mice at 1, 3, 6, 12, and 24 h after tail vein injection of SP@I-Cy5.5, P@I-Cy5.5, Cy5.5, and PBS; (B) Plasma fluorescence intensity at 0 h, 5 min, 1 h, 3 h, 6 h, 12 h, 24 h, and 48 h after i.v. injection of SP@I-Cy5.5, P@I-Cy5.5, Cy5.5. Statistical significance: SP@I-Cy5.5 vs. P@I-Cy5.5, $P < 0.001$ (3–48 h); P@I-Cy5.5 vs. Cy5.5, $P < 0.001$ (3 h), $P < 0.001$ (6 h), $P = 0.0006$ (12 h), $P = 0.0034$ (24 h), $P = 0.0022$ (48 h). (C) *Ex vivo* imaging of the spinal cord and brain of mice at 24 h after tail vein injection of SP@I-Cy5.5, P@I-Cy5.5, Cy5.5, and PBS. (D) Quantitative analysis of the spinal cord fluorescence at 24 h. SP@I vs. P@I, $P = 0.0013$; SP@I vs. Cy5.5, $P = 0.0019$; SP@I vs. PBS, $P = 0.0010$. (E) Quantitative analysis of the brain *ex vivo* imaging. SP@I vs. P@I, $P = 0.0048$; SP@I vs. Cy5.5, $P = 0.0010$; SP@I vs. PBS, $P = 0.0004$. Data are expressed as the mean $\pm$ SD ($n = 3$). PBS: Phosphate buffered saline; SD: standard deviation.

, P@I-Cy5.5, and free Cy5.5. Strong fluorescence was observed at the injured spinal cord and brain at 1, 3, 6, 12, and 24 h post-injection with SP@I-Cy5.5, indicating effective accumulation of SP@I-Cy5.5 [Figure 3A]. In contrast, markedly lower fluorescence signals were detected at the injured spinal cord and brain in the control or P@I-Cy5.5 treatment groups.

Subsequent blood pharmacokinetic analysis based on temporal blood fluorescence intensity changes revealed distinct circulation profiles among groups [Figure 3B]. The blood half-lives of SP@I-Cy5.5, P@I-Cy5.5, and free Cy5.5 were approximately 49.24 ± 5.32 , 24.52 ± 2.58 , and 18.72 ± 0.55 h, respectively, demonstrating that SS31 modification significantly prolonged the systemic circulation time of micellar nanoparticles. The

prolonged circulation time of SP@I prompted us to explore its potential enrichment in the injured spinal cord and brain. Mice were sacrificed at 24 h post-injection, and the spinal cord and brain were harvested for *ex vivo* fluorescence quantification. Consistent with *in vivo* observations, *ex vivo* imaging and quantitative fluorescence analysis confirmed remarkably enhanced accumulation of SP@I in the injured spinal cord and brain [Figure 3C-E]. In the spinal cord, the mean fluorescence intensities were 12.61×10^7 (a.u.) for SP@I-Cy5.5, 6.55×10^7 (a.u.) for P@I-Cy5.5, 3.73×10^7 (a.u.) for free Cy5.5, and 0.53×10^7 (a.u.) for PBS [Figure 3D]. In the brain, the corresponding values were 19.34×10^7 (a.u.) for SP@I-Cy5.5, 8.01×10^7 (a.u.) for P@I-Cy5.5, 7.40×10^7 (a.u.) for free Cy5.5, and 1.28×10^7 (a.u.) for PBS [Figure 3E]. These findings confirmed that modification of P@I-Cy5.5 with the SS31 peptide could prolong pharmacokinetics with advantageous neuronal tissue targeting and accumulation, providing a favorable prerequisite for subsequent SCI therapeutic intervention.

SP@I micelles promoted hindlimb locomotor recovery after SCI

In the following, we evaluated the therapeutic outcome of SCI mice with each treatment. Standard contusive SCI mice were established and randomly grouped. SCI mice were intravenously administered SP@I, P@I, and PBS for 7 consecutive days, while sham-operated mice without spinal cord injury were set as the positive control. The Basso mouse scale (BMS) test was used to evaluate the motor function of mice in each group during the 56-day observation period^[52]. BMS scores in SP@I and P@I showed varying degrees of recovery [Figure 4A]. On post-operative day 7, the average BMS score of the SP@I group reached 2.67, which was significantly higher than that of the P@I and PBS groups, indicating early functional recovery. By day 56, the SP@I group reached a BMS score of 6, representing nearly complete motor functional restoration. In contrast, the PBS-treated SCI group only obtained a final BMS score of 0.66, and the P@I group exhibited limited functional improvement with a score of merely 3. Moreover, assessment of the mice's gait and locomotion patterns provided reliable insights into their motor function recovery after SCI^[53]. The mice in the SCI group walked with dragging hindlimbs even on day 56. Their heels could not even effectively touch the ground, showing barely visible footprints. No obvious hindlimb footprints were found in the P@I treatment group on day 56, and only weak average contact area and support strength of the hindlimb were detected. Notably, the SP@I group exhibited remarkably enhanced hindlimb contact area and mechanical support, as well as coordinated forelimb and hindlimb movements with regular gait patterns [Figure 4B-D].

Subsequently, mice were sacrificed for histological evaluation of spinal cord tissue. The spinal cord tissues from the SP@I treatment group showed more intact and regular tissue morphology [Figure 4E]. Consistently, Nissl staining results further confirmed integrated spinal cords with negligible cystic cavities in the SP@I treatment group [Figure 4F]. In comparison, the P@I and PBS groups displayed incomplete tissue structures and prominent lesion cavities. Collectively, these results indicated that SCI mice treated with SP@I could regain integrated spinal cord structures and effectively accelerate their motor function recovery.

SP@I micelles enhance neuroplasticity and nerve regeneration recovery after SCI

To further verify neuronal regeneration following different treatments, spinal cord tissues were immunofluorescently stained with anti-NeuN and anti-GFAP antibodies, labeling neurons and astrocytes, respectively. The SP@I group exhibited robust NeuN fluorescence intensity comparable to the sham group and markedly higher than the P@I and PBS groups, indicating substantial neuronal regeneration and effective spinal cord repair. Meanwhile, the fluorescence of GFAP in P@I and PBS treatment groups was significantly higher than that of SP@I treatment and the sham group [Figure 5A-C], suggesting excessive astrocyte activation and glial scar formation that impedes endogenous neuronal regeneration after injury. In addition, weight was monitored during the treatment period. Mice in the SP@I group weighed more than mice in the P@I and PBS groups, also confirming better functional recovery [Figure 5D]. No abnormal pathology was observed in the heart, liver, spleen, lung, kidney, and brain of H&E-stained tissues in all

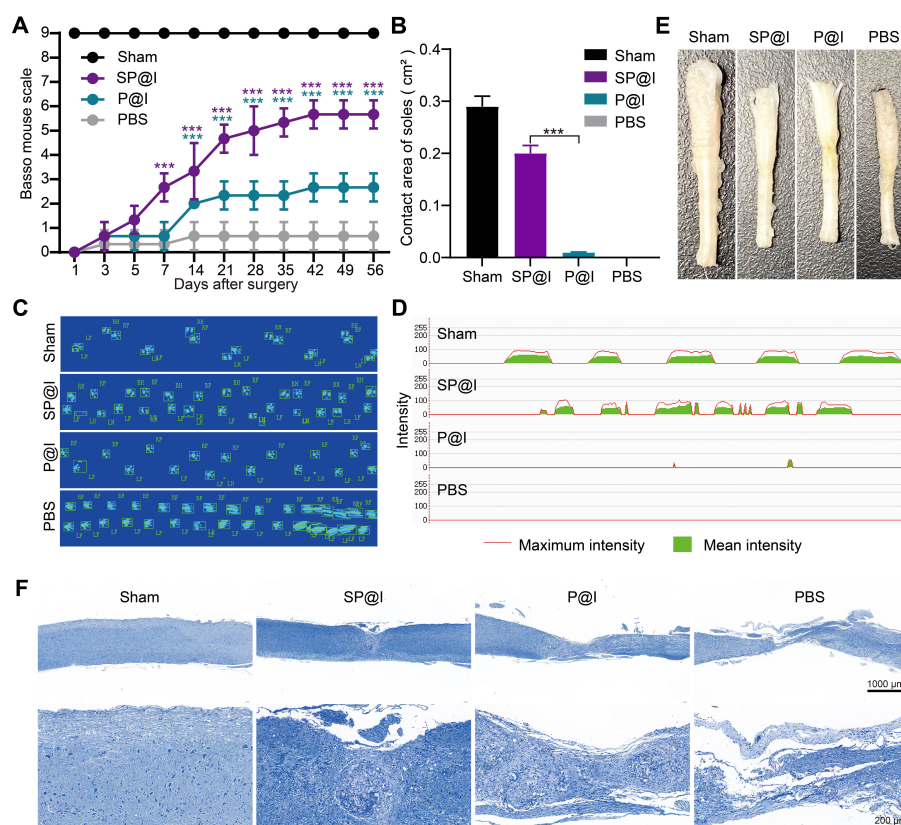


Figure 4. Functional and structural recovery after SCI. (A) BMS scores of each treatment group on the 1st, 3rd, 5th, and 7th day, and once a week until 8 weeks after model establishment. SP@I vs. P@I, $P < 0.0001$ (Day 7–56), P@I vs. PBS, $P < 0.0001$ (Day 14–56); (B) The area of the paw contacting the ground; (C) Footprints of mice in each treatment group on day 56; (D) The intensity of paw contact with the ground in each group on day 56; (E) Spinal cord morphology on day 56 for each treatment group; (F) Nissl staining of the spinal cord in each treatment group at 8 weeks. The upper scale bar is 1,000 μm , and the lower scale bar is 200 μm . Data are expressed as the mean $\pm$ SD ($n = 3$). PBS: Phosphate-buffered saline; LF: Left forelimb; LH: Left hindlimb; RF: Right forelimb; RH: Right hindlimb. SCI: spinal cord injury; BMS: basso mouse scale; SD: standard deviation.

treatment groups [Figure 5E]. These results suggested favorable biocompatibility and better recovery after SP@I treatment.

Limitations

The modest sample size and use of only female mice may limit generalizability. Moreover, the detailed molecular pathway of SP@I-mediated ferroptosis inhibition was not fully elucidated. In addition, long-term efficacy and safety beyond 56 days remain to be determined. Furthermore, the mechanism of blood-spinal cord barrier penetration requires further characterization. Nonetheless, our findings provide proof of concept for mitochondria-targeted idebenone delivery in SCI therapy.

CONCLUSIONS

In this study, a mitochondria-targeted nanoplatform (SP@I) was successfully constructed for the precise delivery of idebenone to ameliorate SCI progression. Experimental results demonstrated that SP@I micelles efficiently accumulate at injured spinal cord lesions, scavenge mitochondrial superoxides, suppress neuronal ferroptosis, and facilitate neuronal regeneration and functional restoration. This mitochondria-targeted idebenone delivery strategy provides a promising therapeutic approach for SCI treatment and holds broad application potential for other neurological disorders associated with mitochondrial dysfunction.

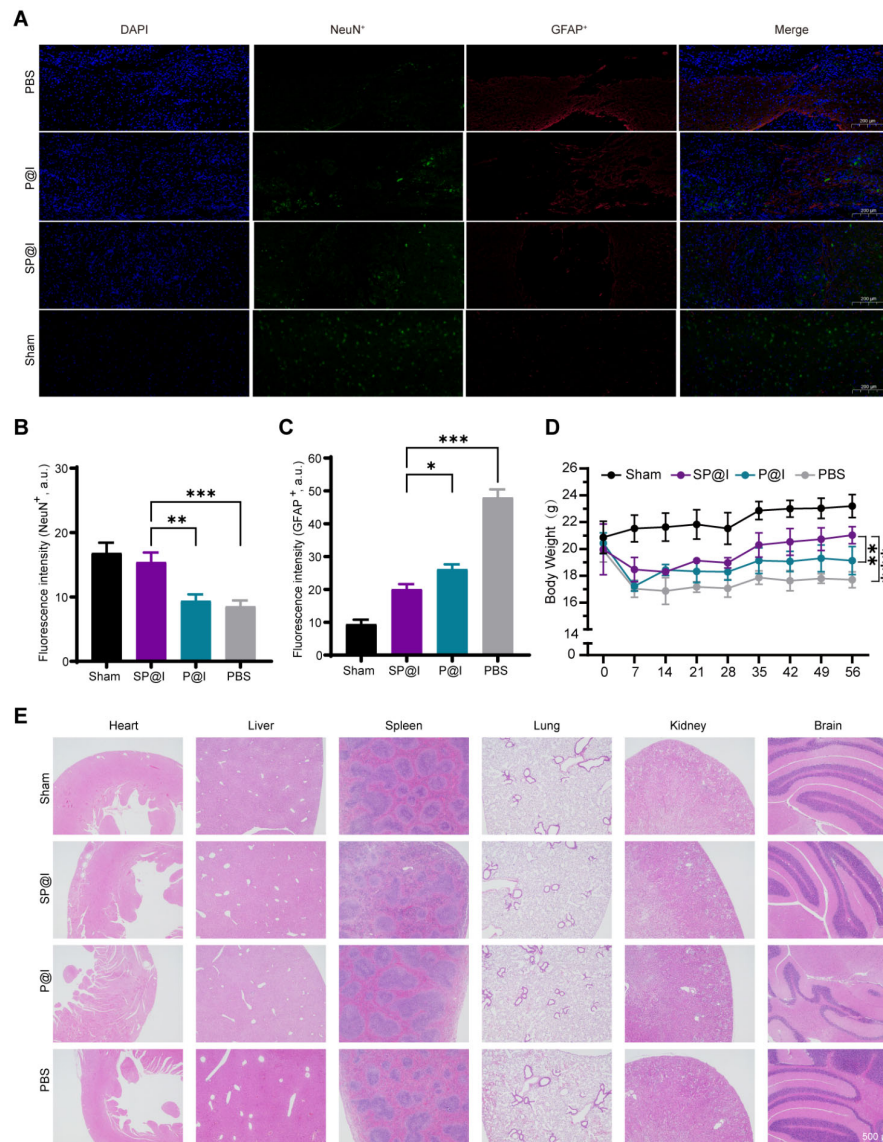


Figure 5. Evaluation of neuroprotective effects and systemic safety after SP@I treatment. (A) Representative immunofluorescence images showing NeuN⁺ (neurons) and GFAP⁺ (astrocytes) in the spinal cord sections of each group at day 56 post-injury. Scale bar: 200 μ m; (B) Quantitative analysis of NeuN fluorescence intensity. Statistical significance: SP@I vs. P@I, $P=0.0019$; SP@I vs. PBS $P=0.0008$; (C) Quantitative analysis of GFAP fluorescence intensity. SP@I vs. P@I, $P=0.0124$; SP@I vs. PBS, $P<0.0001$; (D) Body weight changes of mice in each group were monitored for 8 weeks post-modeling. Significant differences were observed at day 56: SP@I vs. P@I, $P=0.0044$; SP@I vs. PBS, $P<0.0001$; (E) Representative H&E-stained sections of major organs (heart, liver, spleen, lung, kidney, and brain) from each treatment group at day 56. Scale bar: 500 μ m. Data are expressed as the mean $\pm$ SD ($n=3$). PBS: Phosphate buffered saline; GFAP: glial fibrillary acidic protein; SD: standard deviation.

DECLARATIONS

Authors' contributions

Investigation: Zhong, J.; Zhou, P.; Liu, S.; Qin, R.

Methodology: Zhong, J.; Zhou, P.; Liu, S.; Liu, X.

Data curation: Zhong, J.

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Visualization: Ge, L.

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Availability of data and materials

The original contributions presented in this study are included in the article/[Supplementary Materials](#). Further inquiries can be directed to the corresponding authors.

AI and AI-assisted tools statement

Not applicable.

Financial support and sponsorship

This work was supported by the Guangdong Basic and Applied Basic Research Foundation (No. 2022A1515140171, No.2024A1515010377), Dongguan Science and Technology of Social Development Program (No. 20221800905542), Science and Technology Projects in Guangzhou (2023A03J0618), and Medical Joint Fund of Jinan University (No. YXJC2022011).

Conflicts of interest

All authors declare that there are no conflicts of interest.

Ethical approval and consent to participate

All animal experiments were approved by the Laboratory Animal Welfare and Ethics Committee of Jinan University, China (Approval No. GZJLAW-20231124-03).

Consent for publication

Not applicable.

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Supplementary Materials

[Supplementary Materials](#)

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