

Photothermal-responsive polydopamine magnetic nanomotors with anti-inflammatory and anti-oxidative properties for thrombolysis

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Research Article

Keywords: Magnetic nanomotor, polydopamine, ROS, thrombus, drug delivery

Posted Date: June 3rd, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-9659016/v1>

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Additional Declarations: No competing interests reported.

Version of Record: A version of this preprint was published at Journal of Nanobiotechnology on October 8th, 2026. See the published version at <https://doi.org/10.1186/s12951-026-05142-2>.

Abstract

Recombinant tissue plasminogen activator (rt-PA) is the standard thrombolytic agent that clinical guidelines recommend, while its administration is often associated with systemic bleeding risks. Here, we present a novel photothermal-responsive magnetic nanomotor (rPMP) for safely rt-PA thrombolysis. rPMP comprises Fe_3O_4 cores and mesopore SiO_2 shells for rt-PA loading, facilitating rapid response to magnetic fields and delivery of rt-PA at the thrombus site. In addition, polydopamine (PDA) is coated around the outermost layer of rPMP to alleviate oxidative stress in vascular endothelial cells, suppress pro-inflammatory cytokine expression via the Wnt signaling pathway, and facilitate thrombolysis through the photothermal effect. Taken together, these features demonstrate that rPMP enables efficient thrombus dissolution in rat models, as evidenced by decreased thrombus area, reduced inflammatory cytokines, and less oxidative damage. Thus, we believe that the photothermal-responsive magnetic nanomotors represent a promising therapeutic platform for clinical thrombolysis.

Introduction

A thrombus is an aberrant aggregation of tissue that forms in the vascular lumen, which restricts blood flow and is responsible for numerous life-threatening diseases. Thrombosis usually results from an imbalance of the vascular coagulation and anticoagulation system[1–6]. Given its significant morbidity and mortality worldwide, the dissolution of thrombus to restore blood flow is a critical therapeutic priority. Recombinant tissue plasminogen activator (rt-PA) is a widely used clinical thrombolytic agent with specific advantages, which can rapidly convert plasminogen into plasmin and degrade fibrin in thrombus[7–14]. However, intravenous administration of rt-PA lacks specificity for thrombi, resulting in widespread plasmin activation and disruption of hemostatic balance, thereby substantially increasing the risk of severe hemorrhagic complications. In addition, low thrombolysis efficiency places higher demands on the timeliness of treatment. Therefore, developing innovative approaches that offer both high therapeutic efficacy and a strong safety profile has emerged as a critical focus in thrombolysis research.

Here, we propose a novel photothermal-responsive magnetic nanomotor for thrombolysis (Fig. 1). Nanomotors are nanoscale functional platforms designed at the nanoscale and capable of responding to external stimuli[15–22]. Their strategic design can improve the physicochemical properties of the drug, aiding in prolonged circulation and enhanced efficiency[23–30]. In contrast, polydopamine (PDA) is a highly efficient broadband photothermal conversion material that can maintain a stable structural morphology under near-infrared (NIR) irradiation with minimal energy loss for photothermal conversion[31–34]. At the same time, PDA is capable of reactive oxygen species (ROS) scavenging and anti-inflammation, which is important for preventing thrombus recurrence[35–39]. Therefore, it is believed that combining magnetically driven nanomotors with photothermal elements will open novel avenues for thrombolytic therapy.

In this paper, we fabricate PDA-coated magnetic mesoporous nanoparticles (MMN) with oxidative stress regulation and anti-inflammatory capacity as the desired nanomotors aimed at thrombolytic applications. These magnetic nanomotors are composed of Fe_3O_4 cores, mesoporous silica shells for rt-PA loading, and outermost layers of PDAs, termed rPMP. Incorporating magnetic cores enables the nanomotors to swiftly respond to magnetic fields, facilitating their rapid accumulation at targeted sites within blood vessels under remote control. The PDA coating on the mesopore nanoparticles is achieved through electrostatic adsorption. Benefiting from PDA, the nanomotors enhance the thrombolysis process, scavenge ROS, and alleviate inflammation. *In vitro* studies demonstrated that these magnetic nanomotors had significant biosafety, rapid accumulation, and efficient thrombolysis properties. Based on these features, rPMP was utilized to treat Sprague-Dawley (SD) rats with a femoral artery thrombus model, achieving superior therapeutic efficiency, as demonstrated by reduced thrombus area, attenuated inflammatory cytokine expression, and diminished oxidative damage. Collectively, these findings highlight PDA-coated, NIR-responsive magnetic nanomotors as promising candidates for the clinical treatment of thrombosis.

Results and Discussion

As the first step, Fe_3O_4 nanoparticles were prepared through a hydrothermal method. [40, 41]. As shown in **Fig. S1**, to improve the dispersibility of the mesoporous nanoparticles, monodisperse magnetite nanoparticles were first encapsulated within a thin silica shell using a sol–gel process, yielding $\text{Fe}_3\text{O}_4@\text{mSiO}_2$ (**Fig. S2**). Subsequently, the $\text{Fe}_3\text{O}_4@\text{mSiO}_2$ nanospheres were further modified with a cetyltrimethylammonium bromide (CTAB)-containing silica layer, resulting in the formation of $\text{Fe}_3\text{O}_4@\text{mSiO}_2@\text{CTAB}/\text{SiO}_2$ [42, 43]. CTAB templates were extracted with NH_4NO_3 to generate a mesoporous SiO_2 shell, yielding uniformly dispersed mesoporous $\text{Fe}_3\text{O}_4@\text{mSiO}_2@\text{nSiO}_2$ nanoparticles, hereafter referred to as MMN. For thrombolytic application, rt-PA—an FDA-approved plasminogen activator—was loaded into MMN through the mesoporous channels (rt-PA/MMN) [44]. Subsequently, the rt-PA-loaded nanoparticles were coated with PDA to form core–shell structured nanomotors (rt-PA/MMN@PDA, termed rPMP) [45]. This design ensured the cooperation of drug-dependent thrombolysis and PDA-dependent photothermal effect, ROS scavenging, and inflammation alleviation. Transmission electron microscopy (TEM) scans revealed that the Fe_3O_4 cores had a consistent particle size of around 100 nm, as shown in Fig. 2A. A silica layer with no pores was applied to the Fe_3O_4 cores to create core-shell structured $\text{Fe}_3\text{O}_4@\text{mSiO}_2$ nanospheres. This resulted in a uniform silica shell with a mean thickness of ~ 18 nm (**Fig. S2**). TEM images revealed MMN particles approximately 186 nm in size, featuring a clear fluffy mesoporous layer (Fig. 2B). A low-contrast layer within the mesoporous region was observed after the rt-PA coating, indicating the successful grafting (Fig. 2C). Following PDA coating, a uniform outer layer of rt-PA/MMN can be seen in Fig. 2D with a particle size of about 198.8 ± 1.7 nm (**Fig. S3**). The morphology of rPMP was shown in the high-angle annular dark-field (HAADF) picture (Fig. 2E). Elemental mapping was further employed to characterize the composition of rPMP. Figure 2E showed that Fe was concentrated in the core, while the distribution of SiO_2 related elements were on the

nanoparticle shells, which was aligning with the morphology of MMN. The detection of the latter three elements provided further evidence for the successful loading of rt-PA.

N₂ adsorption-desorption studies have been conducted to further validate the successful creation of an ordered mesostructure on the MMN. The results confirmed an ordered mesoporous structure with an average pore size of approximately 3.4 nm, which enabled the efficient loading of rt-PA (Fig. 2F). Zeta potential analysis revealed distinct surface charge variations during the stepwise fabrication of rPMP, confirming both the successful formation of the mesostructure and the loading of rt-PA (Fig. 2G). Bovine serum albumin (BSA), with a molecular weight similar to rt-PA, was utilized as a model medication to assess the loading efficiency of MMN. **Fig. S4** illustrates that the encapsulation effectiveness of BSA in MMN was 41%. In addition, the saturation magnetization value of the rPMP indicated favorable magnetic responsiveness and superparamagnetic characteristics for immediate aggregation (Fig. 2H). To further assess magnetic controllability, the collective motion of rPMP swarms was investigated in saline solution with the viscosity adjusted to 4 cP by glycerol addition. It can be clearly observed that rPMP nanomotors exhibited clear directional motility under magnetic guidance (**Fig. S5**).

As PDA possesses photothermal conversion capability, enabling the conversion of NIR light into heat, its photothermal efficiency was evaluated. A real-time infrared thermal camera recorded a significant temperature difference among PBS, MMN, and MMN@PDA (Fig. 2I and **Fig. S6A**), which was consistent with the temperature curve in **Fig. S6B**. In addition, following a 5-min illumination with 808 nm light, different concentrations of MMN@PDA (0, 80, 160, and 320 µg/mL) were heated up to 24.1°C, 37°C, 44.3°C, and 51.3°C, respectively, indicating that the photothermal effect of MMN@PDA was proportional to the sample concentration (Fig. 2J). 160 µg/mL MMN@PDA was also illuminated with an NIR laser with different intensities for 10 min (2–3 W/cm²), and the temperature and the laser intensity were positively correlated (Fig. 2K). Considering these results and the possibility of heat damage to vascular tissues, a laser intensity of 2.5 W/cm² was selected for subsequent arterial thrombolysis studies. In addition, MMN@PDA exhibited near-identical heating and cooling curves after five cycles of NIR light irradiation at 2.5 W/cm² (**Fig. S6C**). In each cycle, NIR irradiation caused the MMN@PDA to quickly heat to 42°C and return to its original temperature immediately after the removal of NIR exposure. It demonstrated their good stability of photothermal conversion, which was essential for *in vivo* use. All the above results suggested the successful synthesis of rPMP with excellent superparamagnetic property, abundant loading of drugs, and efficient photothermal capability.

Using human umbilical vein endothelial cells (HUVECs), the biocompatibility of rPMP was assessed by CCK-8 assays and live/dead staining, both of which demonstrated favorable biocompatibility (**Fig. S7B-C**). In addition, rPMP's hemocompatibility is shown by the red blood cell (RBC) hemolysis test (**Fig. S7A**). Given the favorable biocompatibility, the biological functions of the nanomotors were further evaluated in HUVECs. Considering H₂O₂ is important among biologically relevant ROS, it was applied for inducing oxidative damage. Different concentrations of rPMP were exposed to H₂O₂ (100 µM). rPMP reduced ROS in a concentration-dependent manner, with 4 mg/mL rPMP scavenging 10.8% of the total H₂O₂ level

(Fig. 3A). This effect was further validated at the cellular level. HUVECs were cultured in DMEM/F12 medium with H_2O_2 and various doses of rPMP. Results from flow cytometry demonstrated that when rPMP was administered at a dose of 4 mg/mL, the intracellular ROS level was considerably decreased (Fig. 3B-C). However, rt-PA/MMN without PDA showed little significant change in ROS scavenging (Fig. 3D). With a 70% cell viability, H_2O_2 markedly reduced the proliferation of HUVECs. Conversely, rPMP therapy may shield HUVECs from H_2O_2 -mediated oxidative damage in contrast to the H_2O_2 group. (Fig. 3E). It suggests that PDA-coated magnetic nanomotors may protect cells against damage induced by highly oxidative environments.

Given the pronounced antioxidative properties of rPMP, *in vitro* cytokine expression was analyzed to evaluate its anti-inflammatory performance using quantitative polymerase chain reaction (qPCR) and multiplex secretome analysis. As shown in Fig. 3F-G, consistent with qPCR results (**Fig. S8**), the rPMP group significantly reduced the expression of interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α), demonstrating its anti-inflammatory efficacy.

Encouraged by the excellent photothermal conversion efficiency of rPMP, we further explored the *in vitro* thrombolysis activity. Artificial thrombi were constructed using fresh blood and thrombin. All the groups were exposed to NIR light for 5 min at 30 and 60 min after placement of the blood clots into the solution, respectively. NIR irradiation alone exerted a minimal impact on the thrombus owing to the change in temperature. However, after exposure to NIR, the blood clots significantly shrank when treated by rPMP. The thrombolytic efficiencies of rt-PA and rt-PA/MMN were also evaluated, which showed only moderate clot dissolution (**Fig. S9**). The thrombus mass reduction after various treatments was used to quantify thrombolytic efficiency. The thrombolytic rates of rt-PA + NIR, rt-PA/MMN + NIR, and rPMP + NIR were 47.7%, 44.9%, and 64.1% in 60 min (Fig. 3H). The rt-PA + NIR, rt-PA/MMN + NIR, and rPMP + NIR groups showed significantly higher absorption values of fibrin and hemoglobin (Fig. 3I), whereas NIR-only treatment produced no significant change. Furthermore, the photothermal effect could have contributed to the PDA modified group's (rPMP + NIR) greater absorption than the other groups. Hematoxylin and eosin (H&E) staining of the residual blood clots further confirmed that the rPMP + NIR laser group exhibited the strongest thrombolytic activity, as evidenced by the degradation of blood clots into numerous small fragments (Fig. 3J).

rPMP significantly lowers the expression of pro-inflammatory cytokines, as was previously shown. The molecular processes behind the rPMP-based therapy were then clarified by RNA sequencing (Fig. 4A). Figure 4B-C illustrated that the H_2O_2 group and the H_2O_2 + rPMP group had 1676 substantially differentially expressed genes (DEGs). To further explore the biological processes and signaling pathways involved in H_2O_2 -induced alterations and their modulation by rPMP, subsequent pathway enrichment analyses were carried out. The Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis exhibited that several pathways have been altered, including Wnt pathway and Hippo signaling pathway (Fig. 4D). Meanwhile, Gene Ontology (GO) analysis further confirmed the dominant role of Wnt pathway in cellular gene changes after rPMP treatment (Fig. 4E). Studies have demonstrated that both the canonical and non-canonical Wnt pathways play essential regulatory roles in cardiovascular diseases.

These effects are thought to be mediated through pathological mechanisms that are closely associated with inflammation[46–48]. To further characterize transcriptional responses, a heat map was generated to visualize expression changes of representative Wnt-related genes (Fig. 4F). Our analysis identified FOSL1, CSNK1A1, PPARD, APC2, CCND3, TLE3, and TLE4 as being tightly correlated to the canonical Wnt pathway and RYK and PRICKLE2 as crucial genes involved in the non-canonical Wnt pathway. The above DEGs and some other crucial genes related to the Wnt pathway were further validated by qPCR (Fig. 4G). Notably, canonical Wnt pathway genes (Wnt7B, FZD, LRP6, PP2A, and β -catenin) were significantly upregulated, a change generally associated with anti-inflammatory activity through the promotion of anti-inflammatory cytokines and inhibition of pro-inflammatory responses[49, 50]. In contrast, downregulated genes such as CSNK1A1 and TLE3 were linked to the non-canonical Wnt pathway, where their decreased expression is likewise associated with anti-inflammatory activity[47]. Western blot (WB) analysis further validated these findings by confirming the expression of several critical proteins (Fig. 4H). Collectively, transcriptomic, mRNA, and protein analyses demonstrated that rPMP suppresses non-canonical Wnt pathways while activating canonical Wnt signaling to have anti-inflammatory effects.

Based on the favorable biocompatibility and function of rPMP *in vitro*, a Sprague–Dawley (SD) rat femoral artery thrombus model was established to further elucidate their efficacy *in vivo*. The model was established by applying ferric chloride (FeCl_3)-soaked filter paper to the femoral artery for 5 min, inducing localized endothelial injury. Previous studies have emphasized efficient carrier design to prevent premature drug leakage and, critically, to enable rapid and precise delivery to thrombus sites. In this study, a Fe_3O_4 -core and SiO_2 -based mesoporous nanoparticle was designed for drug loading and delivery. Given the urgent nature of arterial thrombosis, the magnetic core was used as the targeting component because of its rapid responsiveness. To quantitatively assess magnetically guided thrombus targeting, non-magnetic rt-PA-packed mesoporous nanomotors (rt-PA/MN@PDA) and rPMP were labeled with Cy5.5 dye to obtain rt-PA/MN@PDA-Cy5.5 and rPMP-Cy5.5. As shown in Fig. 5B&C, the femoral artery was surgically exposed during imaging to enable clear visualization after 1 h of magnetic guidance in order. Fluorescence signals were acquired using an *in vivo* imaging system, and the results indicated that no significant signal was detected in the Cy5.5 and rt-PA/MN@PDA-Cy5.5 group. On the contrary, a visible signal was detected in the rPMP-Cy5.5 group, which was 4.7 times that of the Cy5.5 group, indicating that the Fe_3O_4 core conferred effective thrombus-targeting capability to the nanomotors.

Afterwards, thrombotic rats were randomly assigned to five treatment groups, namely, the PBS, the NIR, the rt-PA + NIR, the rt-PA/MMN + NIR, and the rPMP + NIR, respectively (Fig. 5A). Doppler flow imaging was employed to monitor and quantify hemodynamic changes in real time. The therapeutic effects were shown in Fig. 5D&F, and the changes in blood flow were analyzed before and after the induction of the thrombus model. Following a 5-min exposure of the artery to FeCl_3 , all groups' blood flow was seen to be significantly reduced due to thrombus development. Then, different administrations, including PBS, rt-PA-loaded mesoporous nanoparticles (rt-PA/MMN) without PDA wrapping and rPMP, were injected via the tail vein. The NIR group showed no appreciable effects compared with the control group receiving PBS

treatment. In contrast, intravenous administration of rt-PA exhibits a certain thrombolytic efficacy and partially restores blood flow. However, because of their targeting capacity, rt-PA/MMN and rPMP exhibited better thrombolysis effect. The rPMP + NIR group exhibited the most pronounced thrombolytic effect, attributable to synergistic photothermal therapy. Following treatment, Fig. 5E&G displayed the H&E staining of the thrombus in the vascular after different treatments. With only 13.2% of the thrombus area remaining, the rPMP-treated group exhibited the most pronounced thrombolytic effect.

Moreover, to verify the anti-inflammatory effects of PDA-wrapped nanomotors, the vascular tissue sections' levels of β -catenin, IL-6, and TNF- α expression were analyzed. As shown in Fig. 6A, rats treated with PBS, NIR, rt-PA + NIR, and rt-PA/MMN + NIR exhibited elevated expression levels of IL-6 and TNF- α in the endothelium layer, indicating severe inflammatory responses. Furthermore, vascular sections from these groups showed markedly decreased β -catenin expression, suggesting suppression of the canonical Wnt-mediated anti-inflammatory pathway. In contrast, rats treated with rPMP + NIR showed a reduction in IL-6 and TNF- α expression and a clear recovery of β -catenin expression, indicating restoration of the canonical Wnt signaling pathway. These results further confirm that PDA coating not only endows nanomotors with photothermal thrombolytic capacity, accelerating thrombus dissolution, but also facilitates vascular endothelial recovery through anti-inflammatory effect. These findings demonstrate the synergistic effect of magnetic targeting and PDA-dependent anti-inflammatory activity, providing valuable insights for the advancement of *in vivo* drug delivery systems.

The combination of targeted delivery and photothermal therapy not only achieved excellent thrombolytic efficacy but also minimized systemic side effects. As shown in Fig. 6E-F, compared with the rt-PA group, the targeted drug delivery group exhibited restored fibrinogen levels and shortened thrombin time (TT). These results suggested that magnetic guidance effectively enhanced targeting, thereby reducing bleeding risk. *In vitro* fluorescence imaging of major organs after being injected with Cy5.5-stained rPMP was further investigated to determine their biosafety. As shown in Fig. 6B, fluorescence signal could be found in the liver, lung, and kidney immediately at 1 h after injection, gradually fading afterwards, and notably dropping after 24 h. Quantitative analysis further indicated that rPMP deposition was highest in the liver and lungs at 6 h, with the kidneys coming next, though at lower but still meaningful amounts (Fig. 6D). This implies that rPMP can gather and be metabolized by multiple organs. Notably, rPMP failed to cause organ damage or raise inflammatory levels *in vivo*, as shown by standard blood analysis, biochemical blood indices, and H&E staining of primary organs, confirming rPMP's excellent biocompatibility (**Fig. S10-12**).

In addition, to further confirm the biosafety of different treatments, especially NIR laser irradiation, various stainings were applied to observe vascular structure after administration (Fig. 6C). Compared to the control group without any treatments, rt-PA, nanomotor, or NIR administration did not show significant evidence of damage to the vessel structure. Collectively, these results demonstrate the excellent biocompatibility of rPMP nanomotors, highlighting their potential for thrombolytic applications.

Conclusion

In this study, we proposed a PDA-coated mesoporous nanomotor with a magnetic core for thrombolysis. The nanomotors consist of Fe_3O_4 cores, mesoporous silica shells for rt-PA loading, and an outer PDA coating. The magnetic core enabled the nanomotor to react rapidly and move fast under remote control, which is critical for a high-velocity environment. The PDA layer endowed the nanomotor with a photothermal effect under NIR irradiation, thereby accelerating thrombolysis. In addition, PDA was demonstrated to alleviate oxidative stress in vascular endothelial cells and suppress pro-inflammatory cytokine expression via the Wnt signaling pathway, thereby promoting vascular wall recovery. The thrombolytic efficacy of the nanomotor was further validated in a rat femoral artery thrombosis model *in vivo*. Overall, the PDA-coated magnetic nanomotor represents a promising platform for arterial thrombosis and other vascular diseases.

Methods

Materials

CTAB, FeCl_3 , sodium acetate, tetraethyl orthosilicate (TEOS), 4-(bromomethyl)phenylboronic acid, ammonium hydroxide ($\text{NH}_3 \cdot \text{H}_2\text{O}$), sodium hydroxide (NaOH), (3-aminopropyl)triethoxysilane, and poly(4-styrenesulfonic acid-co-maleic acid) sodium salt (PSSMA) were from Aladdin (China). Dopamine hydrochloride was obtained from Sigma-Aldrich (USA). Ethylene glycol, L-ascorbic acid, acetone, and ethanol were purchased from Xiong Scientific (China). BCA protein assay kits, DCFH-DA assay kits, and Propidium iodide (PI) were obtained from Beyotime Biotechnology (China). Calcein-AM was purchased from Thermo Fisher Scientific (USA). Thrombin was from Yuanye Bio-Technology (China). All primers were synthesized by Sangon Biotech (China). Antibodies against IL-6, TNF- α , and β -catenin for immunohistochemistry were obtained from Servicebio (China). rt-PA was obtained from Cell Sciences (USA). Primary antibody against CSNK1A1 was obtained from HuaAn Biotechnology (China), while antibodies against β -catenin, LRP6, and GAPDH were purchased from ABclonal (China). RNA extraction kit was from Vazyme Biotech (China).

Synthesis of FeO and FeO@mSiO_2

Fe_3O_4 and $\text{Fe}_3\text{O}_4@\text{mSiO}_2$ were synthesized according to a previous method[51]. Briefly, the mixture of Fe^{3+} mixed salt solution and precipitating agents were fully sonicated and reacted at 190°C for 9 h. The resulting product was further subjected to a reaction in the presence of ethanol, ammonia, and TEOS for 1 h.

Synthesis of MMN and rt-PA/MMN

A mixture of water (80 mL), ammonia (1.00 mL, 28 wt%), CTAB (0.30 g, 0.823 mmol), and $\text{Fe}_3\text{O}_4@\text{mSiO}_2$ nanoparticles was transferred to a flask. After 0.5 h, TEOS (0.4 g) was added, and the reaction was maintained for an additional 5.5 h. To eliminate the CTAB template, the purified nanospheres were

redispersed in acetone and subjected to reflux at 80°C for three consecutive cycles. The resulting MMN were then redispersed in a solution containing rt-PA. After further incubation for 4 h at 4°C, rt-PA/MMN were obtained.

Preparation of rPMP

After sonication for 5 min, rt-PA/MMN, dopamine hydrochloride, and Tris-HCl buffer were stirred for 1 day at 4°C. The products were washed with water to get rPMP.

Characterization of rPMP

TEM (FEI Tecnai and Talos, USA) was employed to examine the nanostructure and particle size of rPMP. Surface zeta potential was assessed (Malvern, ZEN3600, UK). Magnetic behavior was evaluated by a vibrating sample magnetometer (LakeShore 7404, USA), while the BET surface area and pore size distribution were obtained from N₂ adsorption–desorption measurements (Micromeritics, ASAP 2460, USA).

Photo-thermal conversion test

MMN@PDA with different concentrations (0–320 µg/mL) were treated by 808 nm NIR light (2.5 W/cm, 5 min). MMN@PDA with the same concentration (160 µg/mL) were irradiated by a 2–2.5 W/cm NIR laser for 5 min. The temperature change was recorded by a real-time infrared thermal camera (Fotric 225s, German). H₂O, MMN, and MMN@PDA solutions with the same concentration (160 µg/mL) were put in tubes. All samples were exposed to NIR irradiation at 2.5 W/cm², then images were captured. The photostability of the material was investigated by irradiating MMN@PDA (160 µg/mL) with a laser (2.5 W/cm²) for five cycles.

In vitro antioxidant test

rPMP at concentrations of 0.5, 2, and 4 mg/mL was incubated with a 100 µM H₂O₂ solution at 37°C under mild shaking for 1 h, after which the residual H₂O₂ level was determined using an H₂O₂ Content Assay Kit following the supplier's protocol.

Cells and animals

HUVECs (Cat. No. 2Q0476) were routinely maintained in DMEM containing 10% FBS. SD rats aged 6–7 weeks were acquired from SPF (Beijing) Biotechnology (China). All animal experiments complied with the Laboratory Guidelines and received approval from the hospital Ethics Committee (2025AE02009).

In vitro cellular-level ROS scavenging assay

An *in vitro* cellular-level ROS scavenging assay was performed using 2',7'-dichlorofluorescein diacetate (DCFH-DA) to assess intracellular ROS generation by flow cytometry and fluorescence imaging, as previously reported[51]. Briefly, the supernatant from nanoparticle-pretreated H₂O₂ solutions was incubated with HUVECs. After 24 h of incubation, the cells were processed for fluorescence imaging and flow cytometric analysis.

rPMP protects cells from oxidative stress

HUVECs were cultured in the 96-well plate for 24 h with a cell density of ~ 70%. Different concentrations of nanoparticles were mixed with the medium containing H₂O₂ (100 µM) at 37 °C for 1 h. Magnetic accumulation was used to remove the reacted nanoparticles. Then, cells were incubated with the H₂O₂- or nanoparticle- pretreated medium and cultured for 24 h. The cells' viability was examined through the CCK-8 assay kit.

Measurements of cytokines

For cytokine measurements, HUVECs were first cultured and then incubated with H₂O₂- and rPMP- pretreated medium, with PBS and H₂O₂ (100 µM) used as control treatments. After another 24 h of incubation, the culture supernatants were collected. The levels of IL-6 and TNF-α were measured by multiplex secretome analysis (XMplex02240714 XMplex Human 12-Plex Custom panel) according to manufacturer's instructions with the assistance of SXM Biotechnology Co., Ltd. (WuHan, China). Besides, the total RNA was extracted and reverse transcription. Primer sequences are presented in Table S1.

In vitro thrombolysis assessment

Artificial thrombi were prepared by mixing fresh whole blood with thrombin at 37°C, followed by storage at 4°C. The prepared thrombi were then transferred into reaction vessels containing 1 mL of different sample solutions (0.3 mg/mL) and maintained at 37°C. At selected time intervals, thrombi were collected for mass measurement and imaging, while fibrin and hemoglobin levels in the corresponding supernatants were determined by absorbance readings.

RNA Transcriptome Sequencing

HUVECs cocultured with H₂O₂ (400 µM) were taken as the control group. HUVECs cocultured with rPMP- pretreated H₂O₂ (400 µM) were set as the treated group. The cells were harvested via pepsin digestion and immersed in a Trizol reagent. Library preparation for sequencing was performed in accordance with

the manufacturer's guidelines (Illumina NovaSeq 6000 platform). The read counts mapped to each gene were quantified using HTSeq, version 0.13.5, and FPKM values were calculated for each gene based on its length and the corresponding read counts.

Femoral artery thrombosis model establishment and group treatment

Rats were anesthetized by isoflurane inhalation, followed by surgical exposure of the right femoral artery. Thrombosis was induced by placing filter paper impregnated with 10% FeCl₃ onto the vessel for 5 min. Modeled rats were divided into five groups and administered with PBS, PBS + NIR laser, rt-PA + NIR laser, rt-PA/MMN + NIR laser, and rPMP + NIR laser treatment, respectively. All treatment groups received the equivalent dose of rt-PA (7 mg/kg). Femoral artery blood flow velocity was monitored and recorded using color Doppler flow imaging (VINNO 6VET) before modeling, during thrombus induction, after 1 h of magnetic guidance (60 min), and following 10 min of NIR laser irradiation (70 min).

In vivo magnetic-targeting assessment

Rats with thrombus were administered Cy5.5, rt-PA/MN@PDA-Cy5.5, and rPMP-Cy5.5 at a same concentration. For a clearer observation, femoral arteries were isolated from the rats following 1 h of magnetic guidance. Fluorescence signals were captured using an *in vivo* animal imaging system (Boluteng, Aniview100, China).

In vivo anti-inflammation property evaluation

24h after the PBS, NIR, or nanoparticles administration, immunohistochemistry (β -catenin, IL-6, and TNF- α) was performed to evaluate the thrombus area and inflammation index.

In vivo safety evaluation

After administration with Cy5.5-labeled rPMP, major organs were isolated at different time points. The fluorescence signals were captured through Aniview100. In addition, blood vessels treated with rPMP + NIR or PBS were stained to evaluate the safety of the photothermal effect. Blood was collected simultaneously for various tests.

Declarations

Competing interests

The authors declare no competing financial interest.

Data and materials availability

All data are available in the main text or the supplementary materials.

Funding Declaration

This research was supported by the National Natural Science Foundation of China (Grants 82300494 and 82272098), Project of Jiangsu Provincial Frontier Technology R&D Program (Health Sector) (Grant BF2025624), and the Medical Scientific Research Project of Jiangsu Provincial Health Commission (Grant MQ2025014).

Author Contribution

M. Zhou, Y. Zhao, and G. Yang conceived the idea and designed the experiment. S. Zhou conducted experiments and data analysis, and wrote the manuscript. W. Ding, Y. Cheng, and Y. Ding helped revise the manuscript writing.

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Figures

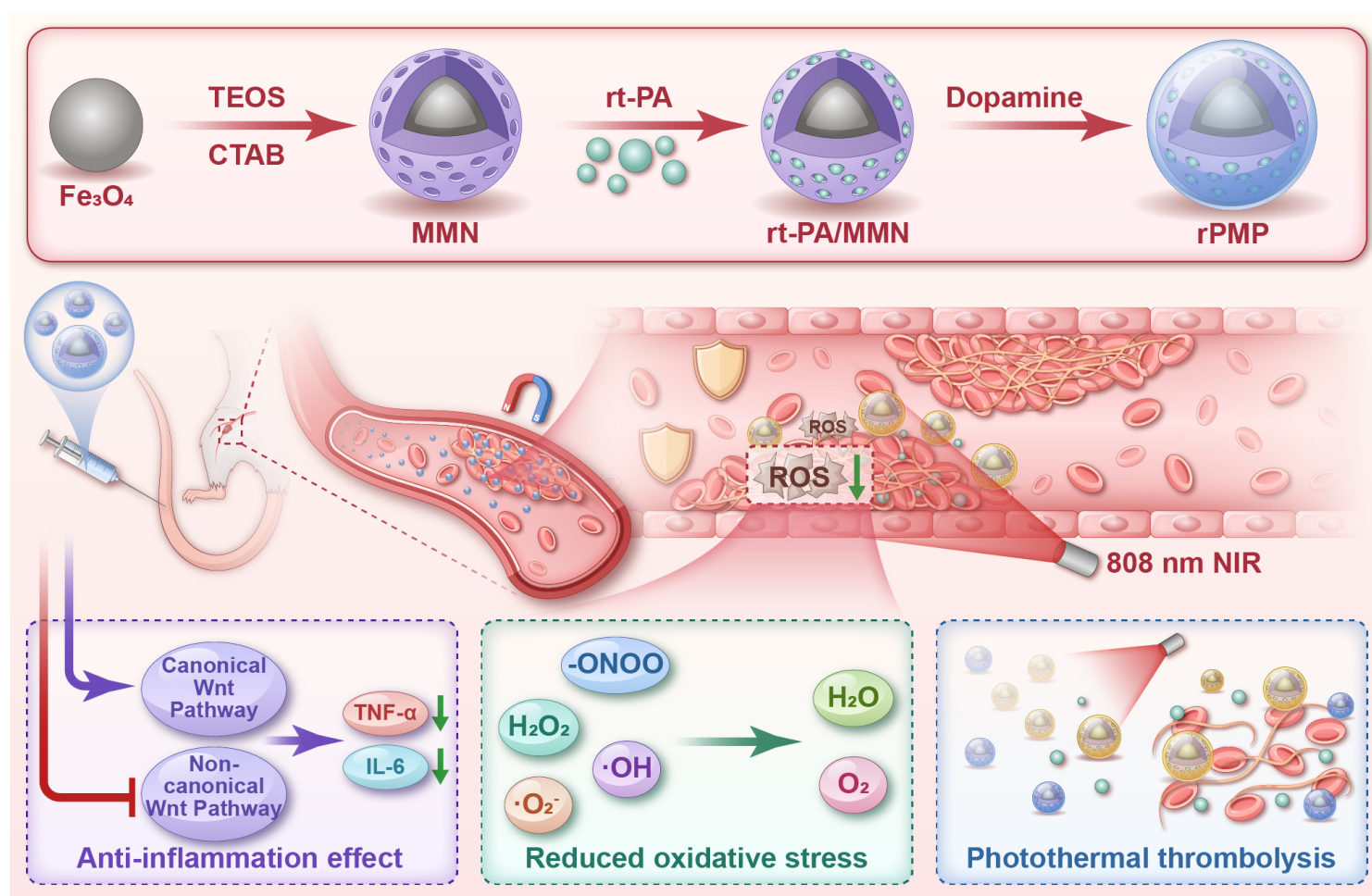


Figure 1

Schematic illustration of rPMP synthesis (comprising a Fe_3O_4 core, mesoporous silica shell for rt-PA loading, and polydopamine coating) and its synergistic thrombolytic mechanism involving anti-inflammatory effect mediated by Wnt pathway, anti-oxidative effect via ROS scavenging, and photothermal thrombolysis.

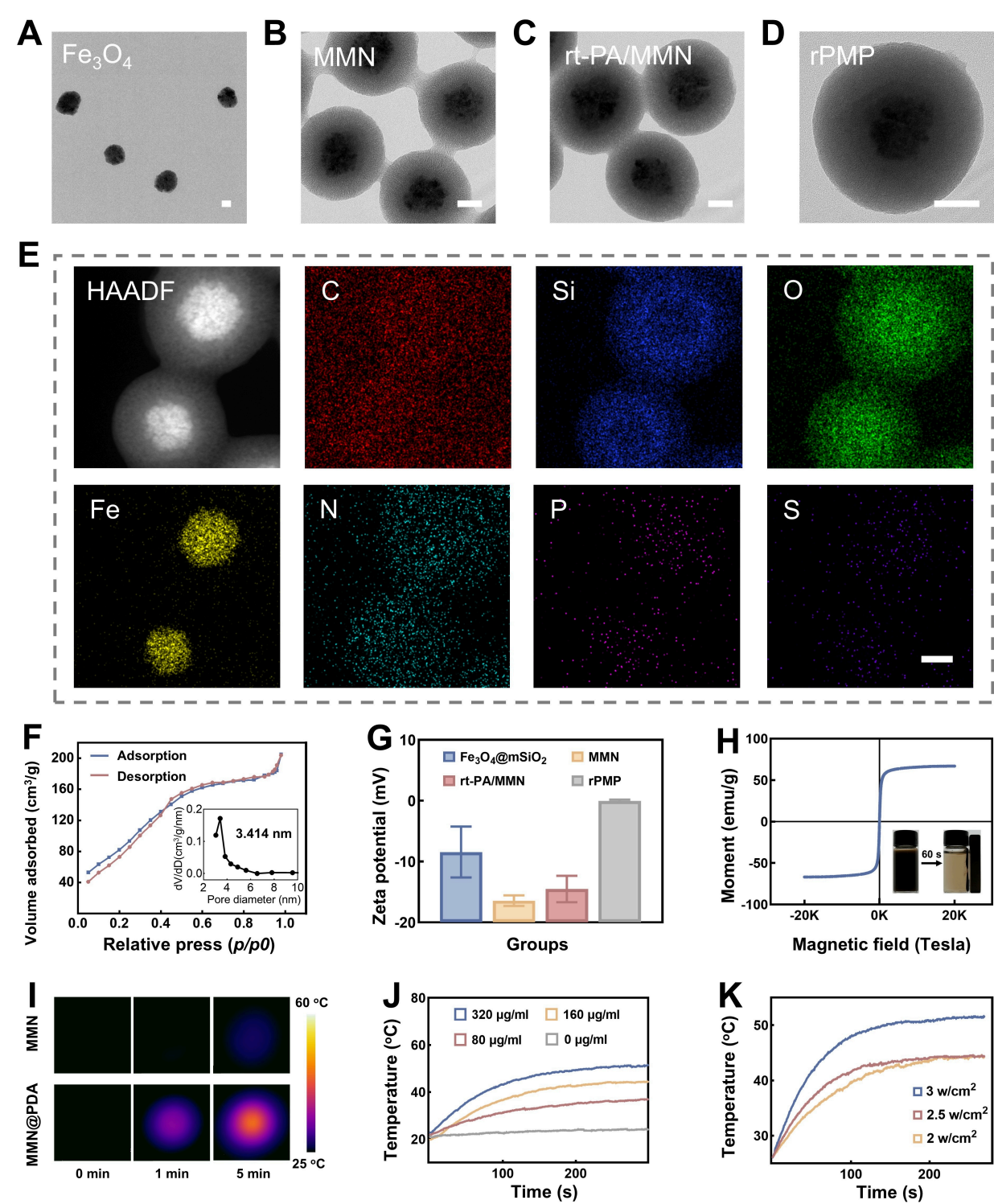


Figure 2

rPMP synthesis. (A-D) TEM results of Fe_3O_4 (A), MMN (B), rt-PA/MMN (C), and rPMP (D) (scale bar: 50 nm). (E) HAADF and TEM mapping of rPMP (scale bar: 50 nm). (F) N_2 adsorption–desorption profiles of MMN nanoparticles and their BJH-derived pore size distribution. (G) Zeta potential of the nanoparticles during synthesis. (H) The magnetization curve of rPMP. (I) Infrared thermal images of MMN and MMN@PDA (2.5 W/cm^2). (J) Temperature increasing curves of MMN@PDA with different concentrations (0-320 $\mu\text{g/mL}$ of MMN@PDA). (K) Temperature increasing curves of MMN@PDA under different NIR intensities ($2\text{-}3 \text{ W/cm}^2$).

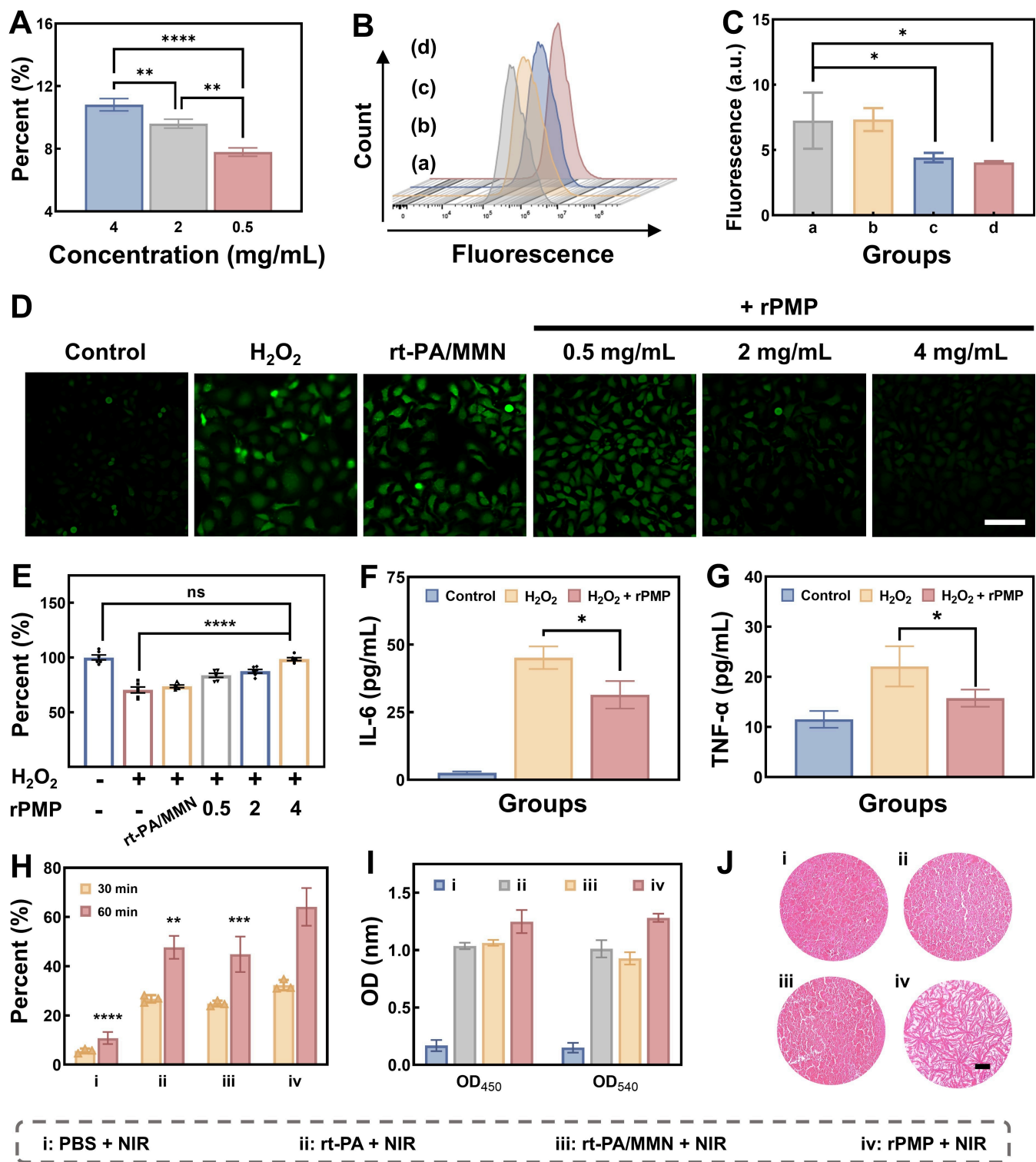


Figure 3

***In vitro* anti-oxidative, anti-inflammatory, and thrombolysis capabilities of rPMP.** (A) H₂O₂-scavenging ability of nanoparticles in solution (n = 3). (B-C) Flow cytometry results illustrating the ROS-scavenging capability of different samples (a: H₂O₂, b: H₂O₂ with 2 mg/mL rt-PA/MMN, c: H₂O₂ with 0.5 mg/mL rPMP, d: H₂O₂ with 4 mg/mL rPMP) (n = 3). (D) Confocal microscopy images illustrating the intracellular ROS-scavenging effects of different samples in HUVECs (scale bar: 100 μm). (E) rPMP protects HUVECs

from H₂O₂-induced oxidative stress (n = 4). (F, G) Inflammatory factors, including IL-6 and TNF- α expression changes in HUVECs after different treatments (n = 3). (H) Residual thrombus weight in the thrombolysis model (compare with group iv in 60 min) (n = 3). (I) Levels of fibrin (OD₄₅₀) and hemoglobin (OD₅₄₀) in the artificial blood clot supernatant (n = 3). (J) H&E staining of residual thrombus (scale bar: 100 μ m). Data is presented as mean $\pm$ SD. **P < 0.01, ***P < 0.001, ****P < 0.0001.

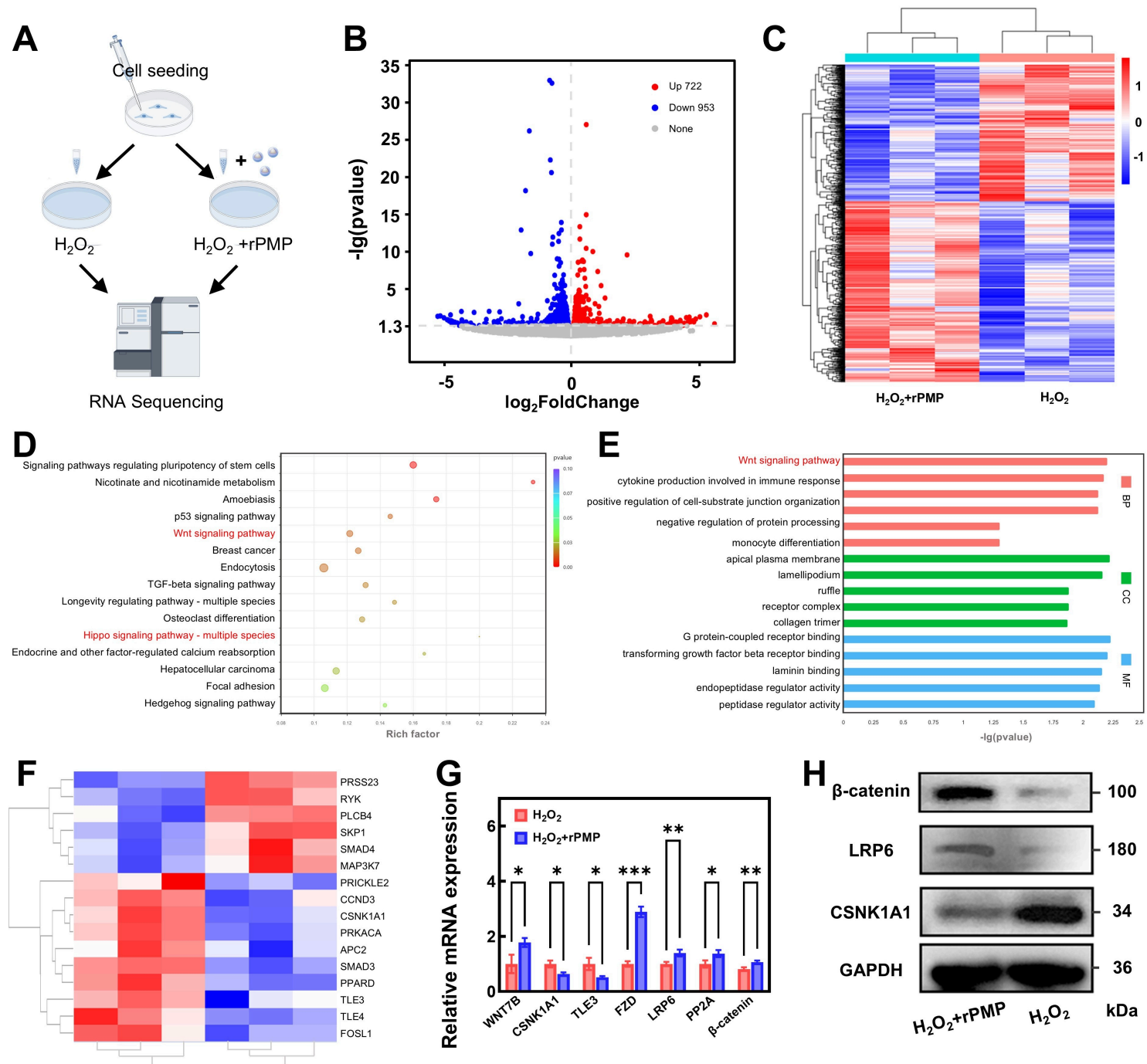


Figure 4

Transcriptomic insights into rPMP-regulated H₂O₂-induced inflammatory responses. (A) Schematic diagram illustrating the RNA-seq procedure. (B) Volcano plots depicting the distribution of significantly

upregulated and downregulated DEGs. (C) Heatmap of DEGs. (D-E) KEGG (D) and GO (E) enrichment analysis of the DEGs in the H₂O₂-stimulated HUVECs in the presence or absence of rPMP protection. (F) Heat map of the representative genes related to Wnt signaling. (G) Expression analysis of the selected genes by qPCR. (H) Western blot analysis of β -catenin, LRP6, and CSNK1A1 in HUVECs after treatment. Data is presented as mean $\pm$ SD. **P < 0.01, ***P < 0.001, ****P < 0.0001.

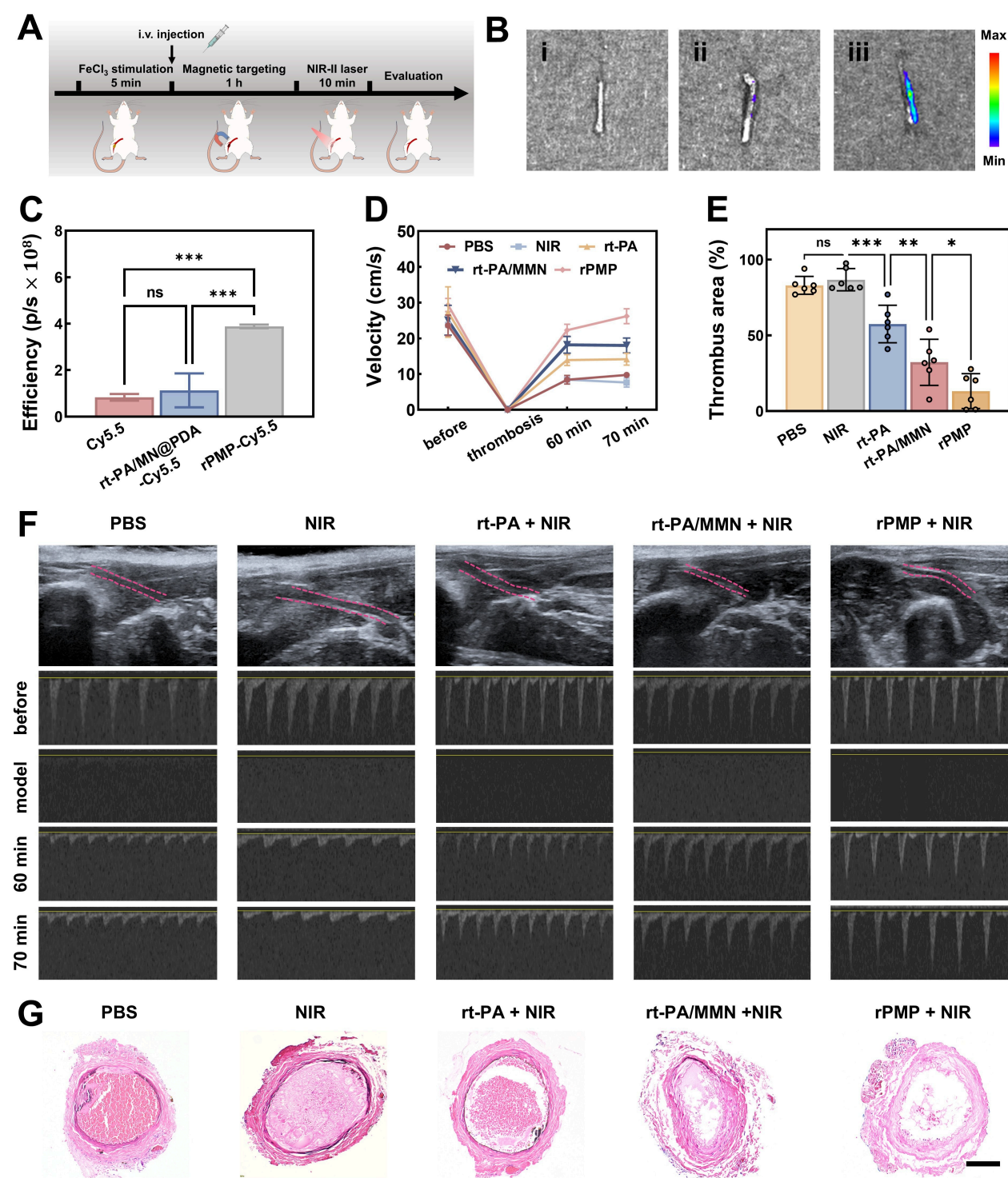


Figure 5

Thrombolysis effect of rPMP *in vivo*. (A) Schematic illustration of the animal experimental procedure. (B) *In vivo* targeting assessment of different samples (i: Cy5.5, ii: rt-PA/MN@PDA-Cy5.5, iii: rPMP-Cy5.5). (C) Quantitative analysis of fluorescence intensity of the femoral artery after treatment for 60 min (scale bar: 100 μ m) (n = 3). (D) Doppler ultrasound blood flow velocity analysis of the femoral artery after FeCl₃ induction and different treatments (n = 3). (E) Quantitative analysis of the thrombolysis effect (n = 6). (F) Doppler ultrasound blood flow imaging of the rat femoral artery after FeCl₃ induction and different treatments, including PBS, NIR, rt-PA + NIR, rt-PA/MMN + NIR, and rPMP + NIR. (G) H&E staining of the femoral arteries subjected to various treatments. Data is presented as mean $\pm$ SD. **P < 0.01, ***P < 0.001, ****P < 0.0001.

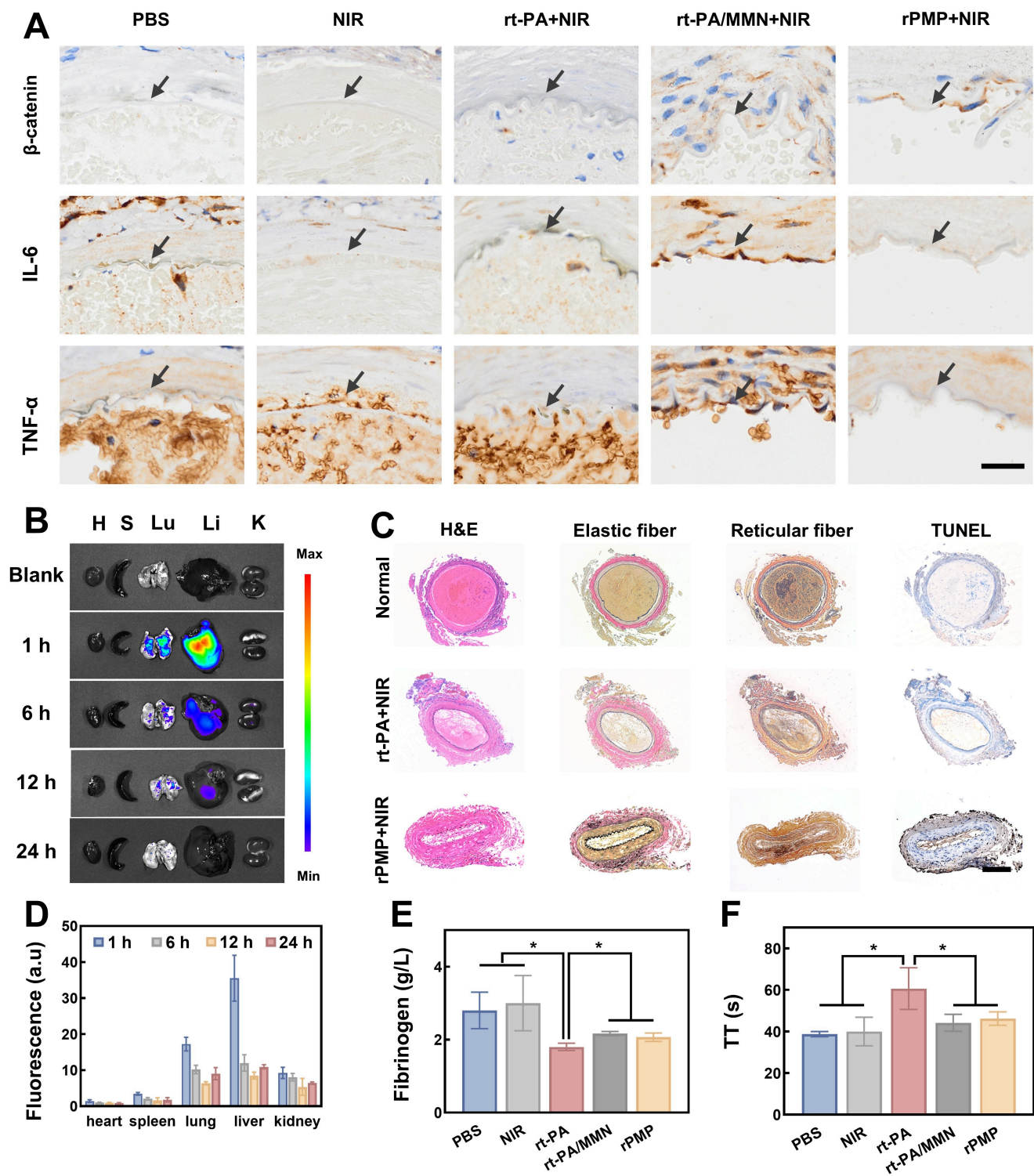


Figure 6

In vivo anti-inflammation and biosafety evaluation of rPMP. (A) Immunohistology staining of β -catenin, IL-6, and TNF- α expression in the femoral artery after treatments (scale bar: 25 μ m). (B) Fluorescence image of the distribution of rPMP in the major organs. (C) Histology of blood vessels after different treatments (scale bar: 200 μ m). (D) Fluorescence intensity from organ imaging at different times (n = 3).

(E-F) Fibrinogen concentration and TT in thrombosis rats (n = 3). Data is presented as mean $\pm$ SD. **P < 0.01, ***P < 0.001, ****P < 0.0001.

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