Self-Synergistic Effect of Prussian Blue Nanoparticles for Cancer Therapy: Driving Photothermal Therapy and Reducing Hyperthermia-induced Side Effects

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Research

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Abstract

Backgrounds

Photothermal therapy (PTT) inducing localized hyperthermia to kill cancer cells has attracted wide attention in cancer therapy. The production of reactive oxygen species (ROS) during photothermal therapy (PTT) may cause irreversible damage to healthy tissues around the tumor. Simultaneously, hyperthermia can stimulate inflammatory response, thus promoting tumor recurrence and metastasis. How to reduce the undesired side effects remains to be an inevitable problem for the further development of photothermal therapy.

Results

The spherical mesoporous PBs with uniform size was prepared by an effective hydrothermal method. The yielded PBs exhibits good dispersion and stability in saline with an average hydrodynamic size of about 110 nm. The prepared PBs has a high photothermal conversion efficiency and photothermal stability. Meanwhile, PBs shows the intrinsic ROS scavenging properties (•OH, •OOH, and H_2O_2) in vitro. The antioxidant and anti-inflammatory effects of PBs have also been evaluated in vivo. Moreover, the toxicity assessment and endoplasmic reticulum (ER) stress-inducing ability show that PBs could not induce an inflammatory response. H&E-staining tissue of major organs show no significant damage, indicating that the good biocompatibility and safety of PBs in vivo. These intrinsic functions of PBs may achieve efficient PTT and simultaneously reduce the side effects induced by PTT.

Conclusion

The designed single-component PBs with intrinsic properties simultaneously drive their photothermal-antioxidant effect and photothermal-anti-inflammatory effect to overcome the problem of inflammatory response and heat stress-induced ROS during PTT. The discovery of the inherent function of PBs not only promotes the further clinical translation of PBs, but also promotes the further development of PTT.

Introduction

Photothermal therapy (PTT) utilizes photothermal conversion agents to generate localized hyperthermia to cause cancer cell death mainly via apoptosis and/or necrosis in the tumor, which can be served as a promising strategy for combating cancer.[1-3] Necrosis, the most common cellular response of cancer cells induced by PTT, destroys plasma membrane integrity to cause the release of damage-associated molecular patterns and inflammatory cytokines, such as tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6, IL-8, and IL-10.[4] The pre-survival genes in residual cancer cells can be activated by these inflammatory cytokines, thus inducing resistant to subsequent treatment.[5, 6] Furthermore, these inflammatory cytokines prime neutrophils (NEs) to migrate to the inflamed tumor. Inflammation with tumor-promoting effect plays key role in all stages of cancer. Inflammatory responses can simulate tumor regeneration and increase resistance to hinder the subsequent treatment.[7, 8] It has been reported

that heat stress (e.g. during PTT) can stimulate reactive oxygen species (ROS) production.[9, 10] In the course of the hyperthermia, superoxide anion is a by-product that generated from oxygen via one-electron reduction reaction. And the responding superoxide dismutase (SOD) 1 mRNA levels and SOD enzyme activity decrease by heat stress, causing the overproduction of ROS. In addition, hydrogen peroxide (H2O2) and hydroxyl radical are produced via superoxide detoxification by Mn-SOD and Fenton reaction, respectively.[9, 10] However, the overproduced ROS will exhibit detrimental influences on cells by causing protein denaturation, lipid peroxidation, and DNA injury，which will increase the risk of undesired side effects.[11] How to reduce the undesired side effects is an inevitable problem for the further development of PTT.

To circumvent this problem, photothermal-anti-inflammatory strategy may be of great significance for the management of aggressive cancers. Based on this strategy, anti-inflammatory prodrug pyrene-aspirin loaded on gold nanorod-encapsulated graphitic nanocapsule was constructed to achieve photothermal ablation of tumor and simultaneously alleviate PTT-triggered inflammation.[12] This photothermal-anti-inflammatory strategy overcomes the key shortcoming of traditional PTT (the trigger of proinflammatory cytokines during PTT). Alternatively, aiming at weakening the inflammatory response during PTT, a CO nanogenerator was constructed with partially oxidized in disulfide nanosheets, tumor targeting polymer (PEG-cRGD), and chemotherapeutic drug doxorubicin. In this system, CO was generated from CO_2 via the partially oxidized tin disulfide nanosheets-mediated photocatalytic reduction. This process not only increased the chemotherapeutic effect of doxorubicin, but also reduced the PTT-induced inflammation.[13] Also, this strategy may scavenge heat stress-induced ROS or their precursors, which protects normal or untreated cells from oxidative damage during PTT. Based on this concept, gold nanorods coated with platinum shell thickness (PtAuNRs) were designed as an efficient ROS scavenger and photothermal conversion agent. This PtAuNRs system showed high photothermal efficiency and ROS scavenging property, which could be employed to effectively treat cancer cells via hyperthermia with simultaneously reducing PTT-induced ROS during PTT.[14] However, only few researches focus on both inflammation and ROS during PTT. Furthermore, it is noteworthy that the reported systems with multi-components involved complicated synthetic process and high cost, which also leads more complex mechanism in vivo.[15]

Herein, based on the principle of "simpler is better", the concept of "self-synergistic effect of nanomaterials" is proposed, that is, single component nanodrugs take full use of their inherent characteristics to enhance each other's positive effects and/or reduce side effects. In this study, the concept of "self-synergistic effect of nanomaterials" is discussed with Prussian blue nanoparticles (PBs) as an example (Fig. **1**). PB showed good photothermal conversion, ROS scavenging, and anti-inflammatory cytokines properties. The intrinsic ROS scavenging property endows PB with the capacity of overcoming the bottleneck of heat stress-induced ROS during PB-mediated PTT. Simultaneously, the injected PB in blood circulation downregulated the inflammatory cytokines including IL-6 and TNF-α via their intrinsic anti-inflammatory properties (Fig. **1**). This efficient strategy integrates the photothermal-antioxidant and the photothermal-anti-inflammatory properties. The discovery of self-synergistic effect of PB promotes their further clinical translation. More importantly, the concept of self-synergistic effect

encourages scientist to further explore the intrinsic properties of nanomaterials for enhancing their positive effects and/or reducing side effects.

Materials And Methods

Preparation of PBs

$K_3[Fe(CN)_6]$ (495 mg), PVP□5 g□and HCl solution (1 M, 40 mL) were mixed in a glass bottle or reaction vessel under magnetic stirring for about 30 minutes to clarify the solution. After obtaining a clear solution, the vial was put into an electric oven at 80°C for 24 h. Then take it out for centrifugation and washed with deionized water several times, PBs were obtained. It was then re-dispersed and stored at room temperature with 0.9% saline for subsequent use.

Characterization of PBs

The microstructure of the nanoparticles was observed by JEM-2100F transmission electron microscope (TEM) and scanning transmission electron microscope (STEM). The concentration of materials was determined by inductively coupled plasma atomic emission spectroscopy (ICP-AES, Agilent Technologies, US). The hydrodynamic particle size of PBs was determined by dynamic laser scattering (DLS), on a Zeta sizer system (Nano ZS90, Malvern Instrument Ltd). The composition and crystal properties of samples was tested by X-ray diffraction (XRD) patterns on Rigaku D/MAX-2200PX X-ray diffraction system. Chemical status of the samples was characterized by X-ray photoelectron spectroscopy (XPS) on the ESCAlab250 instrument of Thermal Science Company. Fourier transform infrared spectroscopy (FTIR) was used for the analysis of chemical bonds. The UV- vis-NIR absorption spectrum was recorded by Shimadzu UV- 3600 ultraviolet-visible spectrophotometer.

Photothermal Performance of PBs

The photothermal performance of PB aqueous solution with different Fe concentrations was studied by monitoring the temperature changes under an 808nm high-power multimode pump laser (Shanghai Connect Fiber Optics Company). Pure water was chosen as the control. The real-time temperature changes and thermal images of the irradiated aqueous dispersion were recorded by an FLIR thermal camera (FLIR Thermal CAM E40) and FLIR Examiner software. In addition, the temperature increase of PBs aqueous solution (100 μg mL^{-1} and 200 μg mL^{-1}) irradiated by 808 nm laser at different power intensities (0.2, 0.4, 0.8, and 1.0 W cm^{-2}) was tested. To evaluate the stability of PBs after irradiation, PBs aqueous solutions (100 μg mL^{-1}) were irradiated by 808 nm laser for 5 times and 10 min, and then collected for DLS and UV- vis-NIR absorption spectrum observation.

In vitro scavenging effects of PBs on ROS

The TiO_2/UV system was used to test the scavenging effect of PBs on •OH. Electron spin resonance (ESR, Bruker EMX spectrometer) was used to detect •OH generation in a form of spin adduct DMPO/•OH. TiO_2

suspensions was exposure under UV light (340 nm) to produces •OH, different concentrations of PBs (12.5, 25, 50, 100 μg mL^{-1}) were added into 0.1 mg mL^{-1} TiO2 (P25, Degussa Huls Corporation, Germany) and 50 mM DMPO. ESR spectra were recorded after 5 min exposure to UV light. To verify the superoxide anion (•OOH) scavenging ability of PBs, xanthine and xanthine oxidase (XOD) were mixed in buffer solutions (pH5.0) to generate •OOH, then DMPO was used to trap the •OOH in the form of spin adduct DMPO/•OOH. The CAT-like activity assay of PBs was proved by detecting the oxygen production with an oxygen electrode on Multi-Parameter Analyzer (DZS-708, Cany, China). 1.5 mL H_2O_2 solution (10 mM) was added to 13.5 mL PBs solution (100 μg mL^{-1}) under neutral conditions. The generated O_2 solubility (unit: mg L^{-1}) was measured at different reaction time.

In vivo serum biochemistry and routine blood test

Balb/c mice were intravenously administrated with 200 μL PBs (0 mg mL^{-1}, 2 mg mL^{-1}, 4 mg mL^{-1}). After 24 h, mice were anesthetized to obtain spleen, heart, lung, liver, kidney and blood. The spleen, heart, lung, liver and kidney were stained with H&E. The blood serum seperated from the collected blood were prepared for serum biochemistry parameters analysis including alanine aminotransferase (ALT) and aspartate transaminase (AST). The blood routine test was measured by a Sysmex XS-800i automated hematology analyzer. The levels of IL-6 and TNF-α were measured by using enzyme-linked immunosorbent assay (ELISA) kit (Anogen-Yesbiotech, Canada). Three independent experiments were carried out.

Immune cells in the liver and spleen

Fresh liver and spleen tissue were accepted aseptically and then placed in pre-cooling PBs and washed in a 70 μm-mesh nylon mesh placed in 2 mL of precooled 1640 medium. We obtained the lymphocyt suspension by centrifugation and suspension. Then the lymphocyt suspension was transferred to the centrifuge tube. After adding 10 times volume of 1640 medium and washed once, the supernatant was discarded. PE-CD3, FITC-CD4 and Percp/cy5.5-CD8 were used to stain the $CD^{3+}T$, $CD^{4+}T$, and $CD^{8+}T$ cells, respectively (eBioscience Inc, San Diego, CA, USA). Flow cytometry was selected to analyze the percentage of $CD^{3+}T$, $CD^{4+}T$, and $CD^{8+}T$ cells.

TUNEL Assay

The TUNEL assay was used to specifically detect the fragmented genomic DNA usually caused by sequential activation of caspases and endonucleases during apoptosis.Dewaxing, tissue rehydration, and staining were carried out according to the recommended procedures of the fluorescence-conjugated TUNEL kit manufacturer (Roche, Mannheim, Germany). For counting the total number of cells in tissue samples, DAPI was added before mounting the coverslips to stain the nuclei. Images were captured with a fluorescence microscope (Olympus BX61W1with Fluoview FV1000 software, Japan), and then analyzed using the ImagePro software. Three different image areas of at least 500 cells were counted to determine the apoptosis rate. Histopathological Examination. The histopathological analysis was performed

following standard procedures. Briefly, the organ tissues were fixed overnight in 10% neutral-buffered formalin, embedded in paraffin blocks, cut into 4-μm sections, and mounted onto glass slides. After hematoxylin and eosin (H&E) staining, the pathological changes in the tissues were observed under an optical microscope (Leica DM4000M, Germany) by a well-trained pathologist.

In vivo scavenging ROS and inhibiting inflammationeffects of PBs

The mice were divided into three groups: (1) control group, (2) LPS group, and (3) PBs+LPS group. PBs were injected into mice by tail vein. The inflammatory model was established by injection of LPS on the seventh day. After 24 hours of LPS injection, the serum samples and liver tissues were taken. Hematological changes and inflammatory cytokines were detected. Then, the ROS in liver was detected by flow cytometry. The liver tissues were stained by Hematoxylin-eosin (H&E) for observing the structure and morphology, TdT-mediated dUTP nickend labeling (TUNEL) for observing the cells apoptosis and necrosis.

In vivo photothermal therapeutic efficacy of PBs

Female BALB/c nude mice (4-6 weeks) were purchased from Animal experiment Center of Shanghai sixth people's Hospital (Animal Welfare Ethics acceptance number No: DWLL2019-0309 Animal Experiment Registration number No: DWSY2018-035).All the animal procedures were performed under the protocol approved by the Institutional Animal Care and Use Committee of Shanghai Jiao Tong University Medical College. All the animal experimental operations were in compliance with the National Guidelines for Animal Protection. Implantation of 4T1 xenograft tumor in mice. To put it simply, 4T1 cells (1×10^6 cells per mouse) were suspended in 100 μL of PBS and injected into the right hip of mice to establish animal tumor xenografts. The mice can be treated when the tumor volume reached 100 mm^3. They were divided into 4 groups (n = 5 in each group), as follows: (1) control group, (2) 808 nm laser group, (3) PB+Laser group (intravenous injection, dose of 5 mg kg^{-1}) and (4) PB+Laser group (intratumoral injection, dose of 1.25 mg kg^{-1}). After 24 hours of intravenous or intratumoral injection, photothermal therapy was performed with 808 nm laser irradiation (1.0 W cm^{-2} ,10 min). Thermal infrared camera was used to monitor the temperature rise in real time. The tumor size and body weight of mice were measured every two days during the observation period after treatment. Tumor volume was calculated by the following equation: $width^2 \times length \times 0.5$. After 24 hours of PTT treatment, blood samples were taken from mice to measure inflammatory cytokines IL-6 and TNF in serum. After that, Tumors were dissected and stained by Hematoxylin-eosin (H&E) for observing the structure and morphology of cancer cells and Ki-67 antibody staining for determining cancer cells growth state. According to the standard animal protocol, euthanized should be carried out once the mice tumors volume larger than 1000 mm^3.

Statistical Analysis

All the data were presented as mean ± standard deviation (SD), and the significance between groups were conducted with Student’s two-tailed t test (*, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$).

Results And Discussion

Characterization and intrinsic properties of PBs

PBs were obtained with the raw materials of polyvinylpyrrolidone (PVP), $K_3[Fe(CN)_6]$, and hydrochloric acid via an efficient hydrothermal strategy. Scanning electron microscope (SEM) (Fig. **2**a) and transmission electron microscopy (TEM) images (Fig. **2**b, and Fig. S1) display the robust spherical morphology, uniform size and well dispersibility of PBs. The average hydrodynamic size of PBs is about 110 nm (Fig. **2**c). The ultraviolet-visible-infrared (UV-vis-NIR) absorbance spectrum of PBs reveals a wide absorption in the near infrared region (Fig. **2**d), and the absorption peak at 700 nm can be attributed to the intermetallic charge-transfer band from Fe^{II} to Fe^{III} in the structure of PBs. X-ray diffraction data (Fig. **2**e) shows that the characteristic peaks of the prepared PBs are well-match with those of $Fe_4[Fe(CN)_6]_3$ (JCPDS# 73-0687). The peaks of $Fe2p^{3/2}$ (712.4 eV) and $Fe2p^{1/2}$ (720.8 eV) match to Fe^{III} in $Fe_4[Fe(CN)_6]_3$, and the peak at 708.0 eV represents the existence of $Fe2p^{3/2}$ in $[Fe(CN)_6]^{4-}$ (Fig. **2**f). Fourier transform infrared spectroscopy (Fig. S2) displays a characteristic peak around 2,085 cm^{-1} of Fe^{II}-CN-Fe^{III}. N_2 absorption–desorption results shows that the specific surface area of PBs is 114.8 m^2 g^{-1} and the average pore diameter is 12 nm (Fig. **2**g). We detailly evaluated the photothermal conversion properties of PBs at the wavelength of 808 nm. The increasing temperature profile of PBs is dependent on concentration of PBs (Fig. **2**h, i and Fig. S3), laser power intensity (Fig. 2j, and Fig. S4), and irradiation time (Fig. **2**h-j, and Fig. S3, 4). In addition, the prepared PBs show good photothermal stability (Fig. **2**k) and high photothermal conversion efficiency (Fig. S5), demonstrating the good photothermal conversion properties of the prepared PBs. These results are also consistent with the reported research of PBs as a photothermal conversion agent.[16-18]

The prepared PBs own good dispersibility and stability in water and saline (Fig. S6), and the UV-vis-NIR absorbance spectra of PB dispersions remains stable before and after irradiation for 10 min and 30 min by 808 nm laser irradiation (Fig. S7).There is no obvious changes of the absorption peak and hydrodynamic diameter of PBs in water and saline at different temperatures for at least seven days (Fig. **3**a-d), indicating well dispersed in water and saline and with a good stability, easy to preserve in vitro. Then, we selected •OH, •OOH, and H_2O_2 as represented ROS models to investigate the ROS scavenging properties of PBs. The prepared PBs efficiently scavenged •OH generating from TiO_2/UV system (Fig. **3**e), •OOH generating from xanthine/xanthine oxidase system (Fig. **3**f), and H_2O_2 (Fig. **3**g). PBs show concentration-dependent profile of scavenging •OH, •OOH, and H_2O_2.

The toxicity and endoplasmic reticulum (ER) stress-inducing ability of the prepared PBs

According to the US Environmental Protection Agency and National Research Council, toxicity testing for cellular responses or adverse outcome pathways (AOP) to evaluate adverse health effects are the preferred toxicity testing strategies in the 21st century.**[31]** Therefore, we used a mouse model to investigate the toxicity and ER stress-inducing ability of the prepared PBs.[19] Mice were administered

with a single intravenous injection of PBs. The effects on body weight, marker gene expression, hematology, inflammation, and histopathology were conducted in detail. There are no significant changes in the body weight of the mice after intravenous injection of PBs (data not shown). Most of PBs were captured by reticuloendothelial system (RES)-related organs such as the spleen and liver, consistent with previous reports.[17, 20] The effects of PBs on the expression of AOP markers were performed using reverse transcription-polymerase chain reaction (RT-PCR). Fig. **4**a-f represents the effects of PB-induced ER stress responses and inflammations on different tissues. No significant upregulations of the spliced form of X-box binding protein 1 (xbp-1s) are observed (Fig. **4**a). The CCAAT-enhancer-binding protein homologous protein (chop) and binding immunoglobulin protein (bip) gene exhibit similar trends in various tissues, and are overexpressed in the spleen after exposure to a high concentration of PBs (Fig. **4**b,c). No obvious changes in the levels of TNF-α and interleukin (IL)-1β are observed in any of the tested tissues (Fig. **4**d,e), indicating that the PBs could not induce an inflammatory response. In addition, there are no obvious changes in the expression levels of AOP marker proteins after 24 h treatment of mice with PBs (Fig. **4**f). To study the immune response in the blood, liver, and spleen after PBs injection, the frequencies of important effector cell types (CD3+, CD3+CD8+, and CD3+CD4+ T cells) were carefully measured. The frequencies of CD3+, CD3+CD8+, and CD3+CD4+ T cells indicate no significant changes in the blood, liver, and spleen after PBs injection (Fig. **4**g-i , Fig. S8-S10). The above results indicated the prepared PBs own good in vivo biosafety.

The ROS scavenging effect and anti-inflammatory effect of PBs in vivo

Furthermore, we used a Lipopolysaccharide (LPS)-induced mouse model of inflammation to investigate the key effect of PBs in modulating inflammation and oxidative stress. The animals were divided into three groups: (1) Control group; (2) LPS-induced inflammatory group; and (3) PB+LPS-induced inflammatory group. Compared to the Control group, LPS induced the increases of ROS, inflammatory cytokine expression, and apoptosis in the liver and spleen, indicating successful construction of the inflammation mouse model (Fig. **5**). The alanine aminotransferase (ALT) and aspartate amino transferase (AST) were significantly decreased after treatment with PBs, demonstrating that PBs possessed the potential to protect hepatocytes from damage (Fig. **5**a,b). It is known that the overproduction of ROS during inflammation can induce damage of proteins, lipids, and DNA. The PBs showed strong scavenging capability against LPS-induced increased ROS in the liver and spleen, showing no significant differences with the Control group (Fig. **5**c-f). The number of TUNEL-positive cells of liver and spleen quantified from Fig. **5**g-j were distinctly decreased with PBs compared to the LPS group, suggesting that the PBs may protect the liver and spleen from LPS-induced damage. By hematoxylin and eosin (H&E) staining, the focal nuclear pyknosis, inflammatory cell infiltration, and even bile stasis could be observed in the livers of mice treated with LPS, demonstrating the successful stimulation of acute hepatitis. While with PBs treatment, the livers displayed markedly decreased histological alterations (Fig. S11). Furthermore, the expression of inflammatory cytokines IL-6 and TNF-α distinctly reduced after PBs treatment (Fig. **5**k,l). The intrinsic ROS scavenging capability and anti-inflammatory effect of PBs may reduce PB-mediated PTT-induced side effect during PTT for cancer.

Self-synergistic effect of PBs in the PTT for cancer

Taking consideration of the problem of inflammatory response and heat stress-induced ROS during PTT, PBs can take advantage of these three intrinsic properties including photothermal conversion property, ROS scavenging capability, and anti-inflammatory effect, to promote their positive effects (PTT for tumor) and reduce side effects (inflammatory response and heat stress-induced ROS during PTT). We revealed the self-synergistic effect of PBs in the tumor therapy. As shown in Fig. **6**a and Fig.S12 , PBs increased the temperature of tumor high enough for ablation via either intravenous administration or intratumor administration. The growth-curve of tumor volume with time in each group (Fig. **6**b**)** and the corresponding H&E and tumor sections Ki-67 antibody staining (Fig. **6**e**)** demonstrated the prepared PBs achieved the good photothermal therapeutic efficacy under laser irradiation. There were no obvious pathologic changes among the H&E staining of major organs and no significant weight changes in various groups, indicating good therapeutic biosafety (Fig. S13,14). Importantly, the expression of inflammatory cytokines IL-6 and TNF-α in the group of “PBs+Laser (i.t.)” were much higher than those of the Control group and “PBs+Laser (i.v.)” group after 24 h treatment. However, there were no significant difference of the expression of inflammatory cytokines IL-6 and TNF-α between the Control group and “PBs+Laser (i.v.)” group (Fig. **6**c,d). After laser irradiation for tumor, the designed PBs drove their good PTT to induce cancer cell death via apoptosis or necrosis. In the group of “PBs+Laser (i.v.)”, the injected PBs via intravenous administration alleviated the expression of inflammatory cytokines IL-6 and TNF-α in serum during PTT. However, the injected PBs via intratumor administration could not stop the increasing expression of inflammatory cytokines IL-6 and TNF-α in serum during PTT (Fig. **6**c-e). Time-dependent body-weight curves of 4T1 tumor-bearing nude mice showed no significant difference in various groups (Fig. S13). In addition, H&E staining tissue of major organs from 4T1-bearing nude mice after various treatments displayed no obvious change, indicating the safety of this prepared PBs and PTT (Fig. S14). These two in vivo animal experiments including LPS-induced animal model and xenograft tumor model for PTT well defined the self-synergistic effect of PBs. This proposed concept of self-synergistic effect provides an efficient strategy for promoting their positive effects and/or reducing side effects, simultaneously, and encourages scientists to focus on the intrinsic performance of materials, rather than combining multiple complex components into one system. Most importantly, the intrinsic properties of nanosystem (PBs) own self-synergistic effect for enhanced therapeutic efficacy and/or reduced side effect, promoting their further clinical translation.

Conclusions

In summary, we presented a novel ‘self-synergistic effect’ concept that single-component nano-system utilize their intrinsic properties to promote positive effects of treatment and/or reduce side effects simultaneously. The designed PB with intrinsic properties (good photothermal conversion property, ROS scavenging capability, and anti-inflammatory effect) drive their self-synergistic effect to achieve PTT for tumor, and simultaneously alleviate PTT-induced inflammatory response, and reduce PTT-triggered reactive oxygen species. This efficient strategy overcomes the problem of inflammatory response and heat stress-induced ROS during PTT. The discovery of self-synergistic effect of PB may promote their

further clinical translation. More importantly, the concept of self-synergistic may open a new perspective in exploring the intrinsic properties of materials for enhancing their positive effects and reducing side effects, so as to be better used in the treatment of tumor or other biomedical fields.

Declarations

Authors' contributions

YZ, XC and JW conceived and designed research; XX and WG performed experiments, analyzed data, prepared figures; JH analyzed data and prepared figures; XX and WG drafted manuscript; YZ and XC edited and revised manuscript; YZ, XC and JW approved final version of manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets and materials used in the study are available from the corresponding author.

Ethics approval and consent to participate

All the animal procedures were performed under the protocol approved by the Institutional Animal Care and Use Committee of Shanghai Jiao Tong University Medical College. All the animal experimental operations were in compliance with the National Guidelines for Animal Protection.

Consent for publication

All authors have approved the manuscript be submitted.

Competing interests

The authors declare no competing interests.

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Figures

Figure 1

Schematic illustration of self-synergistic effect of PB. Self-synergistic effect of nanomaterials: single-component nanomaterials utilize their intrinsic properties to enhance each other's positive effects and/or reduce side effects, and the intrinsic properties of nanosystem own synergistic effect for enhanced therapeutic efficacy and/or reduced side effect. PBs can drive their anti-inflammatory effect to downregulate the inflammatory cytokines including IL-6 and TNF-α. In addition, PBs can utilize their antioxidant effect to translate harmful ROS (such as •OH, •OOH, and H_2O_2) into harmless H_2O and O_2 efficiently. Furthermore, PBs can be activated their photothermal effect to achieve PTT for tumor by laser irradiation. The designed single-component PBs with intrinsic properties simultaneously drive their photothermal-antioxidant effect and photothermal-anti-inflammatory effect to overcome the problem of inflammatory response and heat stress-induced ROS during PTT for the first time.

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