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Erythrocyte membrane bioinspired near-infrared persistent luminescence nanocarriers for *in vivo* long-circulating bioimaging and drug delivery

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ABSTRACT

Combination of biological entities with functional nanostructure would produce the excellent systemic drug-delivery vehicles that possess the ability to cross the biological barriers. Herein, from a biomimetic point of view, erythrocyte membrane bioinspired optical nanocarrier is fabricated by integrating Red blood cell (RBC) membrane vesicle with near-infrared persistent luminescence nanophosphors (PLNPs). The triple-doped zinc gallogermanate nanostructures with super-long near-infrared persistent luminescence (ZGGO) are used as optical emission center, mesoporous silica coated on the PLNPs (ZGGO@$mSiO_2$) is employed for drug delivery, and the RBC membrane vesicle is introduced for biomimetic functionalization to ensure the developed nanocarriers bypass macrophage uptake and systemic clearance. Owing to the coating of natural erythrocyte membrane along with membrane lipids and associated membrane proteins, the proposed bioinspired nanocarriers have exhibited cell-mimicking property. Retaining the applicability of PLNPs core that favored *in vitro* excitation, the developed RBC-ZGGO@$mSiO_2$ biomimetic nanocarriers have demonstrated intense fluorescence, super-long persistent luminescence, monodispersed nanosize, red light renewability, and excellent biocompatibility. *In vivo* mice bioimaging and biodistribution study demonstrate the erythrocyte membrane bioinspired nanoprobe loaded with doxorubicin as ideal nanocarriers for long-circulating bioimaging, *in situ* real-time monitoring and drug delivery. We believe the PLNPs-based biomimetic nanocarriers offer a promising nano-platform for diagnostics and therapeutics application.

1. Introduction

With the development of modern nanoscience and biotechnology, more and more artificial nanomaterials and nano-platforms have been used for bio-system regulation [1–6]. Learning from nature inspiration brings various artificial strategies for functional biomaterials design, such as structural biointerface materials, smart biointerface materials and chiral interface materials, widely applied in targeted bioimaging and drug-delivery [7–9]. Although significant progress has been already achieved, there still existed some limitations in practical applications, especially the insufficient biocompatibility and residence time *in vivo* [6]. Biological barriers and immune system protect the living body by regulating the trafficking, exchange and clearance of the systemically injected materials. Therefore, the important foundation for the development of high-performance novel drug-delivery nano-platforms for diagnostics and therapeutics is to ensure the developed nanocarrier bypass the systemic clearance and localize at the target tissue in sufficient quantities [10–12].

In the fast-growing of biochemical technology, bioinspired approaches emerged as an effective way for fabrication of highly sophisticated and rationally designed nanocarriers with long-circulating and monitorable drug delivery ability [13–19]. With the concept of bridging the gap between synthetic nanomaterials and biological entities, bioinspired methodology promotes the rise of biomimetic nanomaterials, which are capable of counteracting the extraordinary ability of living body to clear foreign materials [20–24]. The development of bottom-up approaches allowed the synthesis of biomimetic drug-delivery systems *via* surface functionalization using ligands and molecules able to bind the receptors

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of specific target cells, but inadequate in duplicating the complex protein makeup and cell membrane on a nanoscale substrate [25–28]. The recent proposed top-down biomimetic approaches involved natural cell membrane as the disguised coating for the nanoparticle and conferred the nanoparticle cell-like function for *in vivo* long-term bio-application [10–12,29,30]. Red blood cell (RBC) that is intrinsically biocompatible and nonimmunogenic has been successfully utilized as the biomimetic modifier for medical bioimaging and drug delivery with improved performance in terms of *in vivo* circulation time and therapeutics [21–23,31].

While designing the bioinspired nanocarriers for long-term *in vivo* bioimaging and drug-delivery, the synthetic nanoparticle core that acts as the signal indicator should provide monitorable signal with high sensitivity and resolution, and possess excellent photostability and biocompatibility [16]. Different functional nanomaterials, such as quantum dots (QDs) [32] and upconversion nanoparticles (UCNPs) [33,34], have been introduced as the optical nanoprobes for *in vivo* applications, which suffered from severe damage to organism, either from the nanoprobe itself or the excitation light source it needed, and limited sensitivity caused by the living tissue autofluorescence [35]. Near infrared (NIR) persistent luminescent nanophosphors (PLNPs), born with long-lasting afterglow and excellent biocompatibility, hold great potential as a new generation of nanoprobes for medical bioimaging [36–38]. The reported zinc gallogermanate structured PLNPs have demonstrated superior physiochemical features, including intense NIR emission (quantum yield ~10%), super-long afterglow (>90 h), monodispersed nano-size, and relative low toxicity [39]. The super-long persistent luminescence along with red light renewability of the tri-doped zinc gallogermanate PLNPs (ZGGO:Cr^{3+},Yb^{3+},Er^{3+}) is the important foundation for *in vivo* long-circulation bioimaging and drug-delivery. Besides, the easy surface modification of PLNPs nanoparticles qualifies the ZGGO PLNPs as ideal nano-platform for construction of nanocarriers [40–43].

Herein, from a biomimetic point of view, erythrocyte membrane bioinspired optical nanocarriers were fabricated by integrating RBC membrane vesicle with near-infrared persistent luminescence nanophosphors. With the goal of both therapeutics and diagnostics *in vivo*, the triple-doped zinc gallogermanate nanostructure with super-long near-infrared persistent luminescence ($Zn_{1.25}Ga_{1.5}Ge_{0.25}O_4$:$Cr^{3+}$,$Yb^{3+}$,$Er^{3+}$) was leveraged as optical emission center, the biocompatible mesoporous silica coated on the PLNPs (ZGGO@$mSiO_2$) was employed for drug delivery, and the biodegradable RBC membrane vesicle was introduced for biomimetic functionalization to ensure the developed nanocarriers bypass macrophage uptake and systemic clearance. As illustrated in Fig. 1, ZGGO PLNPs were prepared by the modified bi-phase solventthermal process along with subsequent calcination. Afterward, mesoporous silica was coated on the PLNPs surface by using CTAB as structure-directing agent to form the drug-delivery carrier (ZGGO@$mSiO_2$). For biomimetic functionalization, erythrocyte membrane vesicle was separated from RBC, and integrated with ZGGO@$mSiO_2$ *via* fusion, thus obtained the erythrocyte membrane bioinspired PLNPs nanocarriers (RBC-ZGGO@$mSiO_2$). Owing to the coating of natural erythrocyte membrane along with membrane lipids and associated membrane proteins, the proposed bioinspired nanocarriers demonstrated cell-mimicking property. Doxorubicin (Dox) was employed as the anticancer drug model. Retaining the applicability of PLNPs core that favored *in vitro* excitation, the developed erythrocyte membrane camouflaged ZGGO@$mSiO_2$ biomimetic nanocarriers have exhibited intense fluorescence, super-long persistent luminescence, monodispersed nanosize, red light renewability, excellent biocompatibility, and long-circulating bioimaging and concomitant drug-delivery.

2. Results and discussion

2.1. Preparation and characterization of the RBC-PLNPs nanocarriers

The rare-earth elements co-doped zinc gallogermanates persistent luminescence nanophosphors were prepared *via* the bi-phase solventthermal method in combination with short time calcination in air and post hydrothermal procedure, referring to the previous reports [39]. In the triple-doped ZGGO nanostructure, zinc gallogermanates provided the host matrix, the doped $Yb^{3+}$and Er^{3+} acted as the defect centers, while the Cr^{3+} was the common NIR emitter. The as-prepared ZGGO PLNPs possess a bright NIR persistent luminescence centered at 700 nm with the maximum excitation around 260 nm and red LED rechargeable features (Fig. 2A). Through the comparison with the reported Zn_2GeO_4 phase of PDF = 25–1018 and $ZnGa_2O_4$ phase of PDF = 25–1240, XRD analysis revealed the obtained ZGGO powder gave a XRD pattern of a pure spinel phase zinc gallogermanate crystalline structure that is consistent with the reported results (Fig. 2B). The triple-doped ZGGO nanostructures showed remarkable super-long afterglow (over 20 days) property (Fig. S1), and the luminescence can be re-activated by red LED light (650 ± 10 nm) no matter the UV pre-irradiation was given or not, which verified the potential of application of the ZGGO PLNPs as the long-term *in vivo* bioimaging and

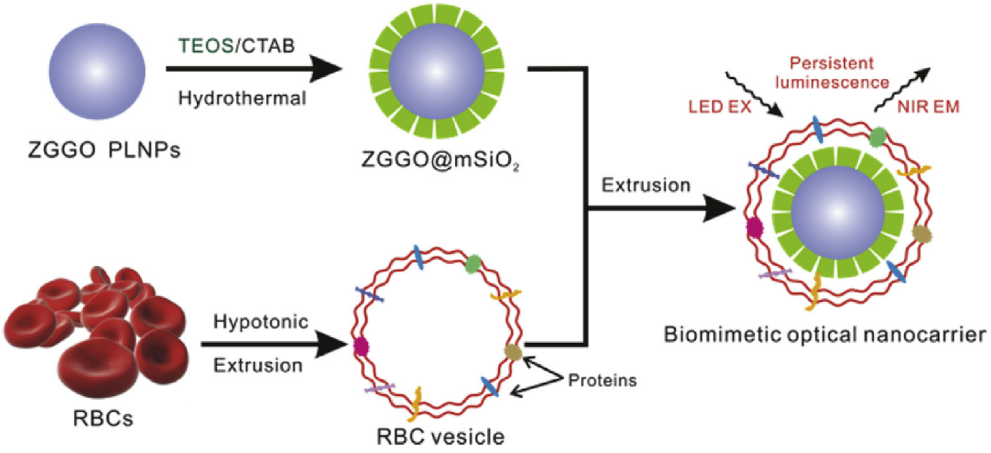

Fig. 1. Schematic illustration of the fabrication of the erythrocyte membrane bioinspired PLNPs nanocarrier for *in vivo* bioimaging and drug delivery.