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Core-interlayer-shell Fe_3O_4@mSiO$_2$@lipid-PEG-methotrexate nanoparticle for multimodal imaging and multistage targeted chemo-photodynamic therapy

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ABSTRACT

Multimodal imaging-guided multistage targeted synergistic combination therapy possesses many advantages including increased tumoricidal effect, reduced toxicity, and retarded drug resistance. Herein, we have elaborately developed a core-interlayer-shell structure Fe_3O_4@mSiO$_2$@lipid-PEG-methotrexatenanoparticle(FMLM), in which the Fe_3O_4 core could be used for magnet-stimulate-response drug release, magnetic resonance imaging, and early-phase magnet targeting ability; the mSiO$_2$ layer could encapsulate anticancer drug doxorubicin (Dox) for chemotherapy; and the protective shell of lipid-PEG and lipid-PEG-methotrexate offered later-phase specific cellular targeting ability, good water dispersibility, and loading of photosensitizer zinc phthalocyanine (ZnPc) for simultaneous near-infrared fluorescence imaging and photodynamic therapy. Both *in vitro* and *in vivo* studies indicated that the both Dox and ZnPc-loaded FMLM (Dox/ZnPc-FMLM) exhibited the enhanced tumor accumulation, increased cellular uptake, improved anticancer activity, and weaked side effects compared with Dox/ZnPc-Fe_3O_4@mSiO$_2$@lipid-PEG nanoparticle (Dox/ZnPc-FML) and free drug. For the first time, magnet targeting cooperative with methotrexate macromolecular prodrug targeting is successfully exploited to develop a promising versatile theranostic nanoplatform for dual-modal fluorescence and magnetic resonance imaging-guided combined chemo-photodynamic cancer therapy.

1. Introduction

Imaging-guided therapy is a critical tool used in cancer treatment (Xie et al., 2010; Zhang et al., 2016). So far most of the theranostic systems focused on single-modality theranostic nanocarrier, which only combined a single-modality diagnostic agent with a therapeutic agent. However, cancer is a complex outcome of multiple signaling pathways, multiple cellular processes and multiple stages (Vogelstein et al., 2013). For cancer treatment, the multiple-modality imaging and therapy is much more effective than the individual treatment (Doane and Burda, 2012). But simultaneously integrating two or more imaging and therapeutic modalities into a multimodality theranostic system is still a great challenge.

Recently years, photodynamic therapy (PDT) has been introduced as a desirable treatment in clinical multimodality theranostic studies. PDT depend on oxygen species (ROS) generated from the photosensitizer to damage and kill the lesion cells, which can be selectively excited by specific light (Sharman et al., 1999). As a representative second-generation photosensitizer, Zinc phthalocyanine (ZnPc) has the disadvantages such as water insolubility, unfavorable pharmacokinetics, and inadequate accumulation in target tissues, which have hindered its clinical applicability (Broekgaarden et al., 2014; Hou et al., 2015; Shi et al., 2013). As a potential tool, nanocarriers bring hope to solve these problems.

Among various multifunctional nanocarriers, organic/inorganic hybrid nanoparticles have attracted the attention due to its unique advantages, such as precise early diagnosis of the diseases and effective treatment *via* smart delivery of therapeutic agent. Magnetic mesoporous silica nanoparticles, Fe_3O_4@mSiO$_2$ (FM),

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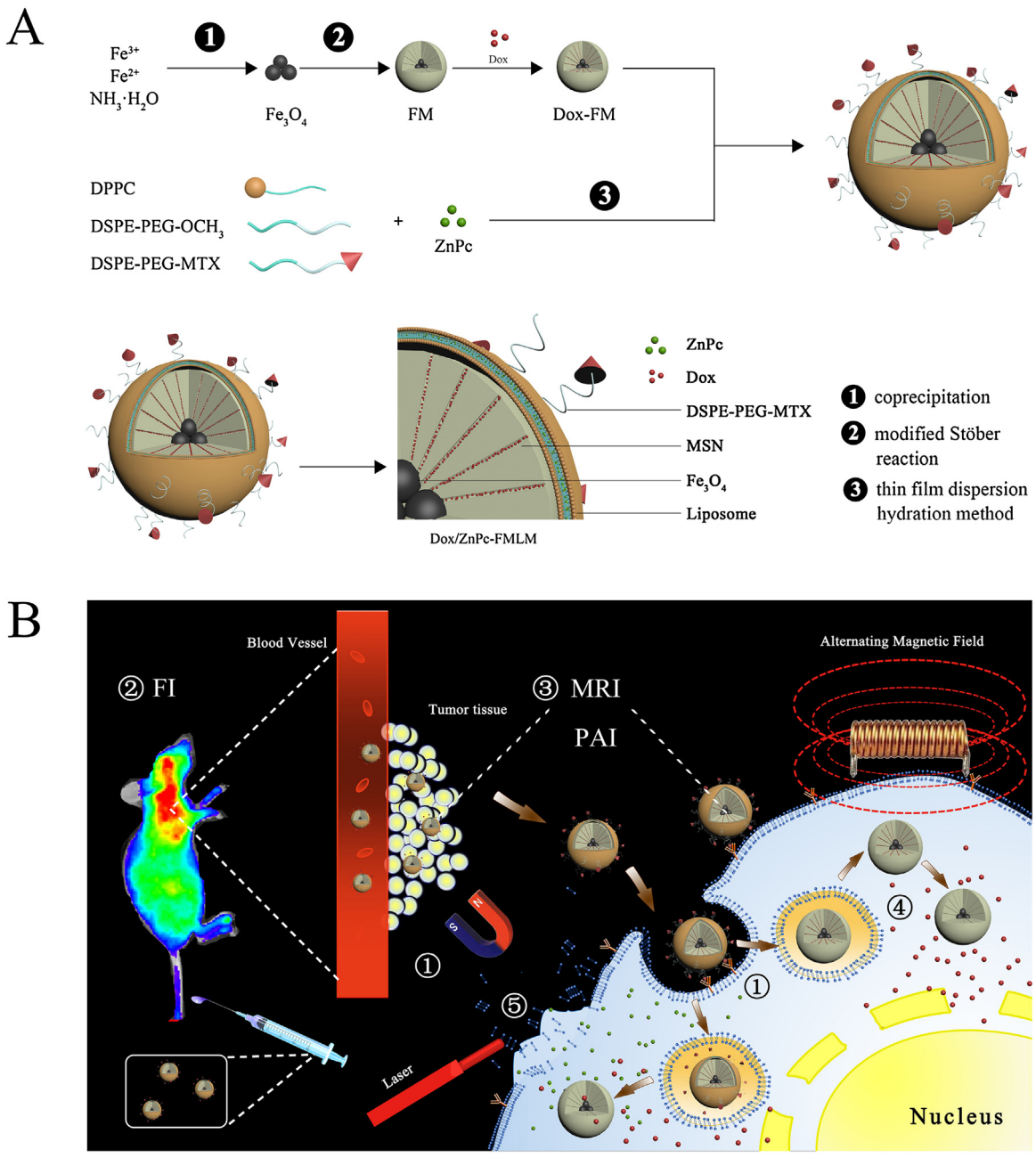
as inorganic nanocarriers that combine the advantages of superparamagnetic monodisperse nanocrystals and mesoporous silica nanoparticles, have attract considerable interest in the field of magnetic resonance imaging (MRI), hyperthermia, and drug delivery. In addition, magnetic targeted drug delivery and MRI were relied on uperparamagnetic part. While mesoporous silica part has been utilized as the carrier for the delivery of special drugs, owing to their ordered mesoporous arrangement, high specific surface area (high drug loading capacity), large pore volume, tunable pore size, good biocompatibility in human body, and modifiable inner/outer surface (Tang et al., 2012; Wang et al., 2015).

In this study, we innovatively fabricated the doxorubicin (Dox) and ZnPc-loaded Fe_3O_4@mSiO_2@lipid-PEG-methotrexate nanoparticle (Dox/ZnPc-FMLM). Firstly, FM was designed to effectively encapsulate Dox, then a thin layer of methotrexate (MTX)-conjugated PEGylated liposome as gatekeeper was covered onto the Dox-loaded FM, which can selectively target and kill tumor tissues and cancer cells overexpressing folate receptors, further to improve the specific tumor targeting and enhance the selective cellular internalization through ligand-receptor interactions. Finally, photosensitizer ZnPc was encapsulated into the bilayer membrane of liposomes (Scheme 1A). In this way, both Dox and ZnPc could achieve synergistic multistage targeting efficiency



Scheme 1. (A) Schematic representations of synthesis and drug loading of FMLM. (B) Schematic illustrations of the FMLM on multimodal theranostic and synergistic photodynamic and chemo-cancer therapy. ① Multistage targeting strategy of FMLM depends on early-phase magnet targeting cooperated with late-phase active cellular targeting by folate receptor-mediated endocytosis; ② Dox/ZnPc-FMLM used as self-fluorescencetracker by ZnPc in fluorescence imaging; ③ FMLM used as both MRI contrast agent and PAI agent in multimodal diagnosis platform; ④ The encapsulated Dox was released in the acidic tumor environment in a pH-responsive and magnet-stimulate-response manner, magnetic vibration resulted in increasing Dox release with the help of AMF; ⑤ Photodynamic therapy of Dox/ZnPc-FMLM irradiated by 630 nm laser irradiation.