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Near-infrared light-responsive nanoparticles with thermosensitive yolk-shell structure for multimodal imaging and chemo-photothermal therapy of tumor

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Abstract

Thermosensitive yolk-shell nanoparticles were developed as remote-controlled targeting drug delivery platform for multimodal imaging and combined therapy of cancer. The nanoparticles were fabricated using magnetic Fe_3O_4 nanoparticles as photothermal cores, thermo-responsive poly(N-isopropylacrylamide)-co-1-Vinyl-2-pyrrolidone p(NIPAM-co-NVP) as shells (Fe_3O_4-PNIPAM), with a hollow space between the two layers for loading of chemotherapeutic drug. The magnetic iron oxide nanoparticle cores could absorb and transform light to heat efficiently upon the irradiation of near infrared (NIR) laser, resulting in the shrink of the PNIPAM shell and the release of chemo-drugs. In vivo fluorescence/photoacoustic images demonstrated that Fe_3O_4-PNIPAM nanoparticles could accumulate in the tumor after intravenous injection. Upon the irradiation of the NIR laser, DOX-Fe_3O_4-PNIPAM nanoparticles exhibited outstanding synergistic effect. The tumor inhibition rate increased from 40.3% (DOX-Fe_3O_4-PNIPAM alone) and 65.2% (Fe_3O_4-PNIPAM +NIR) to 91.5%. The results demonstrated that the NIR-responsive nanocarrier offers a novel strategy for cancer theranostics and combined therapy of cancer.

Key words: Photoacoustic imaging; Magnetic iron oxide; Thermoresponsive; Photothermal therapy; Targeting drug delivery

Magnetic iron oxide nanoparticles have attracted extensive interest in biomedical field due to low toxicity, good biocompatibility and high stability in physiological environment. With the unique magnetic properties, magnetic nanoparticles have been widely applied in drug targeting and delivery,[1,2] diagnosis,[3,4] therapy.[5,6] Recently, magnetic iron oxide has been used as photosensitive agent for photothermal therapy (PTT). PTT is a newly emerging technique that employs NIR absorbing materials to mediate the conversion of near-infrared light into heat, and then leads to thermal ablation of cancer cells. Many endeavors have been devoted to the research of NIR absorbing materials such as gold-based nanomaterials,[7–10] carbon-based nanomaterials,[11–14] transition metal dichalcogenides (TMDCs),[15–17] and organic nanoparticles such as melanin,[18–20] Perylene-Diimide.[21] Compared with those NIR absorbing materials, magnetic iron oxide nanoparticles will be prominent photothermal agents due to well biocompatibility, low toxicity, targeting and magnetic resonance imaging. For instance, Chu et al studied the photothermal effect of the Fe_3O_4 nanoparticles with spherical, hexagonal and wire-like shapes for cancer therapy both in vitro and in vivo.[22] Chen et al reported that highly crystallized iron oxide nanoparticles coated

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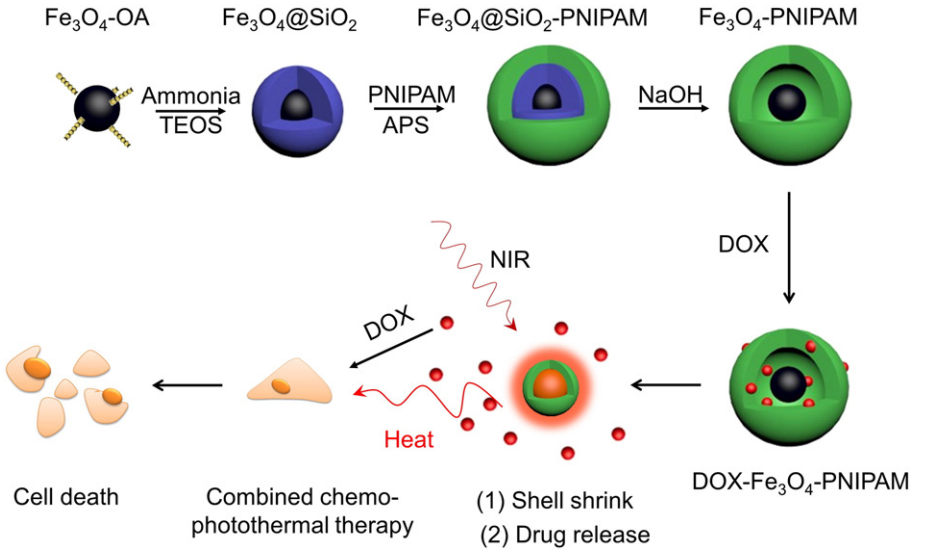

Figure 1. Schematic illustration of the preparation of Fe_3O_4-PNIPAM yolk-shell nanocomposites and NIR-trigger drug release.

with a polysiloxane-containing copolymer could be used as effective mediators for photothermal therapy.[23] We had constructed carboxymethyl chitosan (CMCTS) stabilized Fe_3O_4 nanoparticles with extremely low toxicity for in vivo tumor ablation.[24]

For cancer therapy, traditional chemotherapy suffers from several drawbacks such as poor solubility, non-specificity and adverse side effect. Smart drug delivery systems which are stimuli-responsive, such as thermosensitive microgels, provide the great potential of specific treatment of cancer. With the external heating, the hybrids shrink and lead to the site-specific release of the loaded chemotherapeutic drug in tumor. As one of the most common temperature-sensitive matrix, poly(N-isopropylacrylamide) (PNIPAM) exhibits good biocompatibility and suitable lower critical solution temperature (LCST).[25] Below this critical temperature (T_C), the chains swell and the drug can be loaded. When above the T_C, the chains undergo collapse and the drug is discharged.

Herein, we fabricated yolk-shell structured particles based on Fe_3O_4 particles and stimuli-sensitive poly(N-isopropylacrylamide)-co-1-Vinyl-2-pyrrolidone (p(NIPAM-co-NVP)) matrix. Fe_3O_4-p(NIPAM-co-NVP) (defined as Fe_3O_4-PNIPAM) yolk-shell particles with photothermal and thermo-responsive properties were useful in imaging and chemo-photothermal therapy of tumor. The structure of the particles was schematically illustrated in Figure 1. Thermoresponsive Fe_3O_4@PNIPAM particles have been reported recently.[26,27] However, the reported thermoresponsive particles were prepared by coating PNIPAM directly onto the surface of the Fe_3O_4 instead of yolk-shell structure which could increase the loading capacity of drug by the interstitial space between the outer shell and the inner core. The prepared nanocomposites exhibited favorable magnetic property and outstanding NIR optical absorbance, and thus offered the contrasts in magnetic resonance imaging (MRI) and multispectral optoacoustic tomography (MSOT) imaging. Upon the irradiation of NIR laser, drug release obviously enhanced. Synergistic anticancer effect was observed both in vitro and vivo experiment, indicating the potential of the nanocomposites for specific therapy of cancer.

Methods (refer to the supplementary information for details)

Yolk-shell structured Fe_3O_4-PNIPAM nanoparticles were synthesized and characterized. In vivo experiments were performed in compliance with the Jiangsu University Animal Study Committee's requirements for the care and use of laboratory animals in research.

Results

Synthesis, characterization and thermosensitive property of nanocomposite

As illustrated in the transmission electronic microscopy (TEM), the Fe_3O_4 nanoparticles had a uniform size with an average diameter of ~25 nm (Figure 2, *A*, S1). When silica layer was introduced onto the Fe_3O_4 to form Fe_3O_4@SiO_2 nanoparticles, these nanoparticles remained uniform shapes with the mean diameter of ~65 nm (Figure 2, *B*, S1). The Fe_3O_4@SiO_2 particles coated with thermosensitive layer had been confirmed by TEM image (Figure 2, *C*). Thermosensitive layer thickness was about 50 nm (Figure 2, *C*, S1). Figure 2, *D* revealed a noticeable yolk-shell structure after SiO_2 layer was etched. The formation the nanoparticles can also be verified by thermo-gravimetric analysis (TGA). As shown in Figure S2a, the weight loss of ~45% mainly attributed to the decomposition of oleic acid on the surface of Fe_3O_4. With the coating of SiO_2, the weight loss decreased to about 25%. Then over 40% of weight loss was found after the introduction of p(NIPAM-co-NVP). The etching of SiO_2 further increased the weight loss to about 55%. The TGA results indicate the successful construction of the yolk-shell structure.

Fe_3O_4-p(NIPAM-co-NVP) (defined as Fe_3O_4-PNIPAM) yolk-shell particles showed the absorption at NIR region (700 ~ 850 nm). Drug-loaded particles (DOX-Fe_3O_4-PNIPAM) displayed a UV–vis absorption peak at 490 nm, which was the characteristic of free DOX (Figure 3, *A*). The thermosensitive