Gold Nanorod Core-mesoporous Silica Shell Nanodevice for Caner Targeting, Imaging and Controlled Drug Release

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Introduction: Gold nanorods (AuNRs) are an excellent material for biomedical applications, especially in photothermal therapy for cancer [Alkilany AM. Adv. Drug Deliv Rev. 2012; 64:190-199.]. In AuNR synthesis, the surfactant cetyltrimethyl ammonium bromide (CTAB) easily dissociate, resulting in severe cytotoxicity and low stability. Coating silica on AuNRs may solve the problems and also make it possible to conjugate targeting ligands to AuNRs. But the shape and thickness control and functionalization of silica shell pose challenges for silica deposition. The reported methods in literature for coating silica often lack reproducibility and require precise control of CTAB concentration in AuNR stock solution [Wu CL. Langmuir. 2009; 25:9441-46]. In this investigation, a facile method to synthesize AuNR with high uniformity and ease control of their dimensions was developed. For internalization of nanoparticles in cancer cells, the particle surface was modified with a ligand. The biological performance, including biocompatibility, cancer cell targeting and sensing was evaluated.

Methods: AuNRs were synthesized by a modified seed-mediated growth method using binary surfactants. To form mesoporous silica shell on AuNRs, highly diluted tetraethyl orthosilicate (TEOS) in ethanol was the precursor and surfactants adsorbed on AuNR surface were used. The amounts of TEOS/ethanol solution and CTAB were studied in forming the silica shell. To functionalize the surface of AuNR@$mSiO_2$ nanoparticles (NPs) with amino groups, AuNR@$mSiO_2$ NPs were refluxed in boiled ethanol containing (3-aminopropyl) triethoxysilane (APTES). Folic acid was then conjugated to amino groups on the silica shell. After removal of CTAB via refluxing in NH_3NO_3 and ethanol solution, anticancer drug doxorubicin hydrochloride (DOX) was loaded into mesopores of AuNR@$mSiO_2$ NPs. Drug release behaviors were subsequently studied. Hela cells were used for assessing the biological performance of the NPs, with MCF-7 cells being used for the control experiments.

Results: This investigation used binary surfactants (sodium oleate and CTAB) in the growth solution to tune the dimensions of AuNRs. The synthesized AuNRs showed high uniformity with 70 nm in length and 25 nm in diameter, having negligible impurities (e.g. spherical NPs). Previous studies hardly obtained a highly uniform silica coating and proper thickness. In this investigation, a modified method was used and through optimizing the process and concentration of reactants and surfactants, AuNR@$mSiO_2$ NPs had a silica coating with uniform and controllable thickness (Fig.1a). Mesopores in this coating were observed under TEM. Through amine functionalization and EDC/NHS catalysis, folic acid was conjugated to AuNR@$mSiO_2$ NPs (Fig.1b). After coating silica, the maximum longitudinal SPR wavelength red-shifted slightly but was still in the near-infrared region. Upon laser irradiation, AuNR@$mSiO_2$ suspensions exhibited temperature increases due to the photothermal effect of the AuNR core in AuNR@$mSiO_2$ NPs. The drug release from AuNR@$mSiO_2$ was also highly promoted under laser irradiation. These results indicated that AuNR@$mSiO_2$ NPs could not only serve as a good drug carrier but also provide an external stimulus-controlled drug release mechanism. Folate receptor (FR) commonly expresses on the surface of many human cancer cells such as cervical cancer cell (Hela cells). Folic acid displays high affinity for FR. Dark-field image of Hela cells after incubation with NPs is shown in Fig.2a. Hela cells were covered by strong yellow light scattered from FA-conjugated AuNR@mSiO2 NPs, as compared with weak red light from MCF-7 cells. The encapsulation of rhodamine 6G (a Raman reporter) in AuNR@$mSiO_2$ NPs which emitted red fluorescence had enabled fluorescent imaging to study the cellular uptake and targeting ability of these NPs. As shown in Fig.2b, strong red fluorescence in Hela cells could be clearly seen, indicating that some FA-conjugated AuNR@$mSiO_2$ NPs had crossed the cell membrane and entered the cytoplasm of Hela cells. In the control group, negligible fluorescent signals were shown in MCF-7 cells. These results indicated that the NPs could be specifically taken up by Hela cells as effective optical probes.

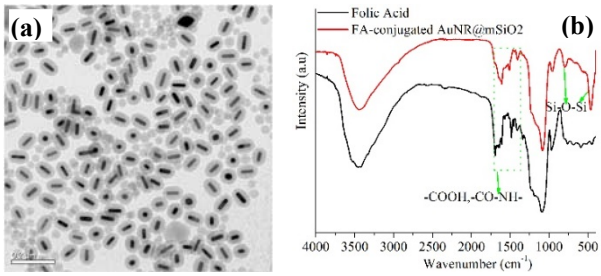

Fig. 1. AuNR@$mSiO_2$ NPs: (a) TEM image, (b) FTIR spectrum after folic acid conjugation.

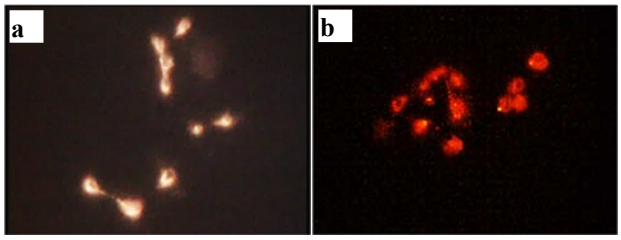

Fig. 2. *In vitro* results for Hela cells after incubation with functionalized AuNR@$mSiO_2$ NPs: (a) dark-field image, fluorescence image.

Conclusions: A facile method was developed to fabricate folic acid conjugated AuNR core-mesoporous silica shell (AuNR@mSiO2) NPs as multifunctional theranostics. *In vitro* release results showed that the nanodevice was an effective drug carrier and provided controlled drug release. *In vitro* biological results demonstrated that the nanodevice possessed good targeting and optical ability as effective probe for cancer detection.