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AuNR@mSiO$_2$@Au Theranostics for Cancer SERS Detection and Combined Therapy

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Introduction: Currently, cancer is still a main cause for human deaths, generally due to late detection and low effectiveness of existing diagnostic and therapeutic technologies. Studies [Sailor MJ. Adv Mater. 2012;24:3779-3802.] are now conducted on developing theranostics which combine cancer diagnostic and therapeutic functions in single nanodevices. Multifunctional nanodevices, which integrate sensing, imaging and therapeutic modalities in a single nanostructure, are investigated for new theranostics. Although considerable efforts have been made, the smart combination of two or more distinct nanoparticles into a functional structure is still a major challenge. For theranostics, gold nanorods (AuNR) are attractive for a few reasons. Porous silica coating can form on AuNRs to improve their stability and biocompatibility and also to provide rich silanol group for attaching targeting ligands for cancer detection. Furthermore, porous silica is a good vehicle for drug delivery. It is well known that surface enhanced Raman scattering (SERS) is highly sensitive to the assembly state of Au nanostructure [Wang Y. Chem Rev. 2012;113:1391-1428.]. In this investigation, a core-shell structured theranostics which had an AuNR core and a mesoporous silica shell decorated with gold nanoparticles (AuNPs) was fabricated and studied. The nanodevice was expected to possess multifunctions for anticancer applications.

Methods: Core-shell structured AuNR@mSiO$_2$@Au NPs were made in a three-step process. First, AuNRs were synthesized using a seed-mediated growth method with binary surfactants. Second, AuNR@mSiO$_2$ NPs were produced using a sol-gel and surfactant-removal method while mesopores in silica shell were loaded with anticancer drug doxorubicin hydrochloride (DOX). Third, AuNPs (~5 nm in diameter) were assembled on surface of AuNR@mSiO$_2$ NPs to obtain AuNR@mSiO$_2$@Au NPs with a core@shell@shell structure. For cancer detection, rhodamine 6G (R6G, a Raman reporter) was embedded in NPs. Drug loading and release of this nanodevice were studied. The SERS activity of NPs was measured using Raman spectroscopy. The biological performance, including cancer cell targeting, *in vitro* SERS detection and photothermal therapy, was studied using Hela and MCF-7 cancer cells.

Results: As-synthesized AuNRs showed a monodispersed morphology (20 nm in diameter and 75 nm in length). TEM analysis showed that the silica shell of core-shell structured AuNR@mSiO$_2$ NPs had a thickness of around 25 nm. After removal of the template (surfactants adsorbed on the surface of AuNR), a mesoporous structure of the silica shell was created on AuNRs. Through conjugation with amino groups, AuNR@mSiO2 were positively charged, which facilitated the attachment of negatively charged Au NPs via electrostactic adsorption. Many AuNPs (~5 nm in diameter) were deposited on the surface of AuNR@mSiO$_2$ NPs (Fig.1a). These AuNPs would be hotspots which would enable high SERS activity for cancer detection. Fig.1b displays SERS spectra. The intensity of Raman signals of R6G were significantly enhanced when it was embedded in AuNR@mSiO2@Au NPs even at very low R6G concentration (10^{-5}M). The photothermal effect arising from the AuNR core of AuNR@mSiO$_2$@Au NPs was also studied. When irradiated with a 780 nm laser beam, AuNR@mSiO$_2$@Au immediately converted light to heat, increasing the temperature of AuNR@mSiO$_2$@Au suspensions. The temperature increase was up to 5 °C even at low NP concentration and low laser intensity. Drug release from AuNR@mSiO$_2$@Au was studied at 37°C with or without laser irradiation. Under laser irradiation, DOX release was activated, providing chemotherapy (Fig.2a). TEM analysis for Hela cells incubated with NPs showed that AuNR@mSiO$_2$@Au NPs were taken up by Hela cells, trapped in endosomes and maintained their original morphology, indicating the high specific targeting and integrity of NPs. Live/dead cell viability assay of cancers cells incubated with NPs and after laser irradiation showed that the NPs produced hyperthermia, resulting in extensive cancer cell death.

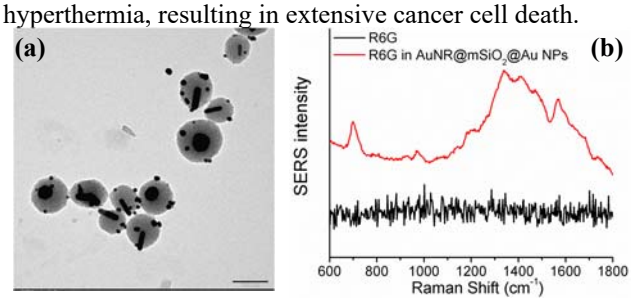

Fig. 1. Structure and property of AuNR@mSiO2@Au theranostics: (a) TEM image, (b) SERS spectra

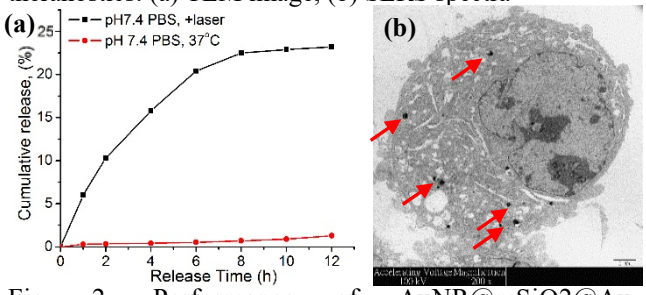

Fig. 2. Performance of AuNR@mSiO2@Au theranostics: (a) *In vitro* drug release from AuNR@mSiO$_2$@Au at 37°C, (b) Hela cells with internalized AuNR@mSiO$_2$@Au

Conclusions: Core-shell and multishell structured AuNR@mSiO$_2$@Au NPs as new theranostics were made. AuNPs on the outer surface of NPs would provide high-sensitivity SERS signals while AuNR core could generate photothermal effect. The stored drug was trigger-released under laser irradiation. The nanodevice exhibited good targeting ability and combined anti-cancer therapy.