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Metal nanoshells as a contrast agent in near-infrared diffuse optical tomography

Changfeng Wu [1], Xiaoping Liang, Huabei Jiang *

Department of Biomedical Engineering, University of Florida, Gainesville, FL 32611, United States

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Abstract

The plasma resonance peak of metal nanoshells can be tuned to the near-infrared region (700–900 nm), making them have great potential in biological and biomedical applications. Gold nanoshells has been synthesized and characterized as a contrast agent for diffuse optical tomography. A unique advantage of the nanoshells is their tremendous absorptivity. Spectral measurements indicate that the absorption cross-section of each nanoshell is 40,000 times larger than that of an Indocyanine Green (ICG) molecule, suggesting that the nanoshells are a much more efficient absorption agent than ICG molecules. Tissue-like phantom experiments using the nanoshells were performed using our diffuse optical imaging system and absorption images were successfully obtained through a finite element based reconstruction algorithm.

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Keywords: Nanoshell; Optical imaging; Contrast agent

1. Introduction

Diffuse optical tomography (DOT) is a promising imaging modality for early detection of diseases such as breast cancer. The technique has the capability to produce quantitative images of tissue absorption and scattering [1,2], as well as fluorophore lifetime and quantum yield [3–5] if contrast agents are used. Near-infrared (NIR) radiation is generally chosen due to its non-ionizing characteristic and deep tissue penetration ability. In particular, this technique is able to extract both tissue structural maps and functional information such as hemoglobin, water content, and oxygen saturation [6–9].

The sensitivity of DOT depends on the contrast caused by the difference in local optical properties

* Corresponding author. Tel.: +1 352 392 7943; fax: +1 352 392 9791.
E-mail addresses: chfwu@clemson.edu (C. Wu), hjiang@bme.ufl.edu (H. Jiang).
[1] Tel.: +1 8646560409; fax: +1 8646566613.

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between tumor and normal tissues. Sometimes it is difficult to assess the significance of the absorption-derived intrinsic parameters because of other tissue optical-variations due to hormonal status [10–13], while the scattering contrast between tumor and normal tissues often is not very high [14,15]. Contrast agents can enhance detection sensitivity and provide additional diagnostic information for DOT, especially as new generations of contrast agents are designed to probe tissue malignancy at cellular and molecular levels [16–19]. Indocyanine Green (ICG) is the only contrast agent to date that has been approved by US Food and Drug Administration, and is commonly applied to clinical studies. As for other organic NIR dyes, the applications are often frustrated due to their intrinsic limitations such as chemical denaturation and photobleaching effects. Therefore, it is still desirable to develop alternative NIR materials that can provide higher tumor/background contrast.

In this regard, inorganic nanoparticles have advantages over conventional organic NIR dyes because of their tunable optical properties and high level of photostability. For example, semiconductor quantum dots have been successfully used for in vivo cancer targeting and imaging [20,21]. We are interested in another type of inorganic nanoparticles, gold nanoshells, which may have great potential in NIR optical imaging. In general, the intrinsic properties of a metal nanostructure can be tuned by controlling its size and shape. Recent studies by Halas and co-workers [22], for example, suggest that the surface plasmon peak of spherical gold nanoshells could be conveniently shifted to cover the spectral regime from 600 to 1200 nm, which are quite different from those of the solid counterparts. The strong absorption of gold nanoshells in the NIR region makes the materials ideal candidates for biological and biomedical studies and the application of the nanoshells as intense NIR absorber has been successfully demonstrated in thermal ablation of tumors [23].

In this paper, we describe the preparation of gold nanoshells and its application in diffuse optical imaging. A spectral comparison indicated that the nanoshells synthesized are a more efficient absorption agent than ICG. Tissue-like phantoms were carried out to confirm the potential use of the nanoshells for cancer detection using a multi-channel diffuse optical imaging system coupled with a finite element based reconstruction algorithm.

2. Materials and methods

2.1. Synthesis of gold nanoshells

Gold nanoshells were prepared through a template-engaged replacement reaction, where nanoscale hollow structures of metals were generated by reacting solutions of appropriate salt solutions with solid templates of a more reactive metal. The procedure used in this paper was derived from that described elsewhere with some modifications [24,25]. Silver nanoparticles were first synthesized according to the method of Creighton [26], and then reacted with gold chloride solution to form gold nanoshells. In a typical synthesis, 0.15 mL of silver nitrate solution ($AgNO_3$, 0.2 M) and 0.15 mL of citric acid solution ($C_6H_8O_7 \cdot H_2O$, 0.2 M) were added to 100 mL deionized water, and mixed thoroughly. 2 mL of sodium borohydride solution (H_4BNa, 0.01 M) was then added to the mixed solution. The solution became dark immediately and then lightened over a few hours to a brilliant yellow. Magnetic stirring (at a rate of $\sim$500 rpm) was maintained throughout the synthesis.

A 50 mL aliquot of the as-obtained dispersion of silver nanoparticles was then refluxed for 5 min before a specific volume of hydrogen tetrachloroaurate solution ($HAuCl_4$, 1 mM) aqueous solution was added dropwise. The mixture was refluxed for another 10 min until its color became stable. Vigorous magnetic stirring was maintained in the entire process. As the solution was cooled to room temperature, white solids (AgCl precipitates) were found to settle at the bottom of the container. The supernatant solution containing gold nanoshells was separated for characterization and usage in optical imaging. All the chemical reagents mentioned above were purchased from ACROS Organics (Morris Plains, NJ).

The samples for transmission electron microscopy (TEM) observations were prepared by