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Achieving highly water-soluble and luminescent gold nanoclusters modified by β–cyclodextrin as multifunctional nanoprobe for biological applications

Yuyao Wang[a,1], Hongen Guo[b,1], Yixia Zhang[b], Feifei Tai[b], Yuxuan Wang[c], Qingchen Dong[b,*], Yu Nie[a,d,**], Qiang Zhao[e,***], Wai-Yeung Wong[b,f,****]

[a] Department of Biochemistry and Molecular Biology, Shanxi Medical University, Taiyuan 030001, China
[b] MOE Key Laboratory of Interface Science and Engineering in Advanced Materials and Research Center of Advanced Materials Science and Technology, Taiyuan University of Technology, 79 Yingze West Street, Taiyuan, 030024, China
[c] Department of Thoracic Surgery, Center for Mini-invasive Thoracic Surgery, Shanxi Dayi Hospital, Shanxi Academy of Medical Sciences, Taiyuan 030032, China
[d] State Key Laboratory of Cardiovascular Disease, Fuwai Hospital, National Center for Cardiovascular Disease, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100037, China
[e] Key Laboratory for Organic Electronics and Information Displays & Jiangsu Key Laboratory for Biosensors, Institute of Advanced Materials, Nanjing University of Posts and Telecommunications (NUPT), Nanjing, 210023, China
[f] Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Hung Hom, Hong Kong, China

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ABSTRACT

We designed and synthesized a highly water-soluble biological nanoprobe (Au-GS@β-CD) through the covalent bonding of β–cyclodextrin (β-CD) onto the surface of gold nanoclusters (NCs) (Au-GS). The morphology, composition and photophysical properties of as-prepared Au-GS and Au-GS@β-CD NCs were fully characterized. The maximum emission intensity at about 600 nm of Au-GS@β-CD NCs increased significantly as compared to Au-GS NCs, which is consistent with its effective absorption enhancement. The water solubility and biocompatibility of resultant Au-GS@β-CD NCs were also notably enhanced, which allow it to be selectively uptaken by gastric cancer cells (MGC-803) and exhibit red luminescence in the cells. Thus, the as-prepared Au-GS@β-CD NCs could be used as promising biological nanoprobes for diagnosis of gastric cancer cells. The successful loading of doxorubicin (DOX) also allows it to hold attractive ability of drug delivery. Moreover, both Au-GS and Au-GS@β-CD NCs are thermally responsive. Furthermore, the metal ions detection experiments indicate that both Au-GS NCs and Au-GS@β-CD NCs can selectively recognize Pb^{2+}, Al^{3+}, Cu^{2+}, Fe^{3+} and Ag^{+} ions through luminescence change. The detection limits of Pb^{2+} and Fe^{3+} are improved for Au-GS@β-CD NCs due to the synergistic effect of β-CD and Au NCs.

1. Introduction

The design and synthesis of luminescent gold nanoclusters (Au NCs) have received numerous attention due to their potential applications in cancer cell imaging and treatment, sensing and others [1–6]. The properties of Au NCs can be manipulated by various approaches through adjustment of the core size, the type of surface-attached ligands, the valence state of the Au atoms, and so on [7–11]. For example, Xie et al. reported the core-shell-structured Au^0/Au^I-thiolate NCs, which achieved strong luminescence through the aggregation-induced emission of Au^I-thiolate complexes on the core of Au^0 species [7]. Li et al. prepared a thermosensitive gold nanoparticles (NPs) smartly by attaching poly(*N*-isopropylacrylamide) (PPA) onto the surface of NPs, which hold potential use for stimuli-responsive application [8]. More importantly, numerous luminescent Au NCs have been explored as probes or sensors to recognize cancer cells, heavy metal ions (such as Fe^{3+}, Cr^{3+}, Cu^{2+}, Ag^{+}, Hg^{2+}, and Pb^{2+} ions), inorganic anions, *etc*. [12–17] For instance, Wei and co-workers reported a red-emitting Au NCs which can selectively and sensitively detect Fe^{2+} ions with a limit of detection of 0.2 ppm by using a bidendate ligand of

* Corresponding authors.
** Corresponding author. Department of Biochemistry and Molecular Biology, Shanxi Medical University, Taiyuan 030001, China.
*** Corresponding authors.
**** Corresponding author. MOE Key Laboratory of Interface Science and Engineering in Advanced Materials and Research Center of Advanced Materials Science and Technology, Taiyuan University of Technology, 79 Yingze West Street, Taiyuan, 030024, China.
E-mail addresses: dongqingchen@tyut.edu.cn (Q. Dong), nieyuniverse@126.com (Y. Nie), iamqzhao@njupt.edu.cn (Q. Zhao), wai-yeung.wong@polyu.edu.hk (W.-Y. Wong).
[1] These people contribute equally to this work.

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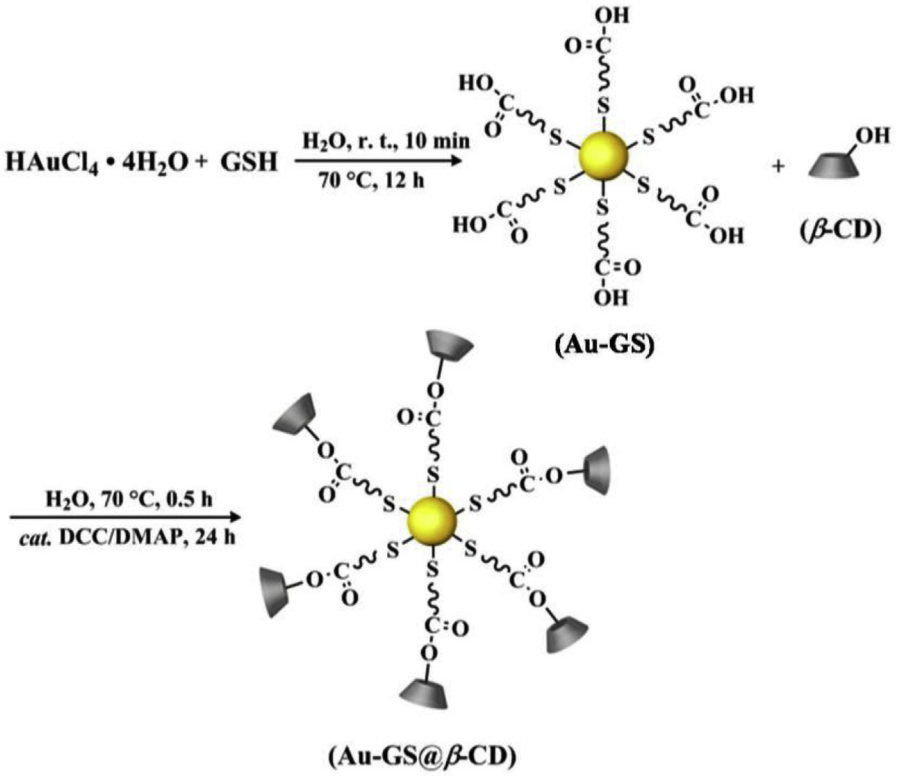

Scheme 1. Synthetic routes of **Au-GS** and **Au-GS@β-CD** NCs.

dihydrolipoic acid (DHLA) to stabilize the Au NCs [12].

Moreover, biological imaging application of the Au NCs is very appealing due to their excellent photostability, large Stokes shift and environmental friendliness [18,19]. Nevertheless, the biocompatibility of this type of materials is unsatisfactory and has limited their practical application due to their poor water solubility [19]. Thus, further modification is particularly needed to address this crucial issue. As the integration of diagnosis and therapy abilities together is extremely important in biomedicine in the future, suitable modification of materials should be considered [20]. It is well known that, cyclodextrins (CDs) are naturally occurring cyclic oligosaccharides consisting of six to eight gluocose units with "inner-outer" amphiphilic character, i.e. lipophilic central cavities and a hydrophilic outer surface [21]. Therefore, they can protect drugs from physical, chemical and enzymatic degradation, as well as to solubilize hydrophobic drugs, which allow them to be widely used as drug-delivery agents [22–26]. Therefore, using CDs to modify the surface of luminescent Au NCs via covalent bond interaction is likely to endow attractive drug delivery ability and at the same time to improve the hydrophilicity of the Au NCs. For example, Kim et al. reported that β-cyclodextrin-covered gold NPs as drug pocket through noncovalent encapsulation of anti-cancer drug (β-Lapachone) with anti-epidermal growth factor receptor (anti-EGFR) antibody as targeting ligands can effectively deliver the anti-cancer drug into A549 human lung cancer cells and MCF human breast cancer cells [27]. It is worth noting that, in this work, sulfydrylized β-CD (SH-CD) was synthesized first and then used directly for the generation of gold NPs. As discussed above, the surface attached ligands can significantly influence the optical and chemical properties of the resulting Au NCs or NPs. Therefore, by adopting a novel synthetic strategy, we here demonstrate the development of a highly water-soluble biological nanoprobe through the covalent bonding of β-CD onto the surface of presynthesized gold nanoclusters (Au-GS@β-CD), which possesses excellent photophysical property and cytocompatibility. More importantly, temperature sensing, metal ions detection and *in vitro* gastric cancer cells imaging experiments were also performed and discussed in detail. Finally, the drug loading ability of the surface attached β-CD was examined for potential theranostic application.

2. Experimental

2.1. Materials

All the solvents and chemicals that were used in the synthetic route were of reagent grades. The following materials were purchased from Energy Chemical Co.: ethanol, hydrogen tetrachloroaurate ($HAuCl_4{\cdot}4H_2O$), glutathione (GSH), β–cyclodextrin (β–CD), 4-dimethylaminopyridine (DMAP), N,N′-dicyclohexylcarbodiimide (DCC), diphenyl ether, oleylamine, cetyltrimethyl ammonium bromide (CTAB) and doxorubicin (DOX). Fetal bovine serum, phosphate buffer saline (PBS), 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2-H-tetrazolium bromide (MTT), paraformaldehyde and formazan were purchased from Nanjing micro-world biology technology Co. Ltd. The gastric mucosal and gastric cancer cells were available in the Cell Bank of Type Culture Collection of Chinese Academy of Sciences. All the reagents were used as received without further purification. Ultrapure water was used in all the experiments.

2.2. Synthesis of Au-GS NCs

Au-GS NCs were prepared through the reduction of $HAuCl_4{\cdot}4H_2O$ with GSH. Briefly, in a 100 mL one-neck round bottom flask, $HAuCl_4{\cdot}4H_2O$ (0.50 mmol, 0.22 g) and GSH (0.50 mmol, 0.149 g) were added to 30 mL ultrapure water. The mixture was stirred at room temperature for 5 min, and then continuously stirred for 12 h at 70 °C. After the reaction was completed, 30 mL ethanol was added to precipitate out the product, which was filtered and dried to give rise to Au-GS NCs as a brown powder (0.2 g, 58%) [7].