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The effect of oil-water partition coefficient on the distribution and cellular uptake of liposome-encapsulated gold nanoparticles

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ABSTRACT

The shape, size, and surface features of nanoparticles greatly influence the structure and properties of resulting hybrid nanosystems. In this work, gold nanoparticles (GNPs) were modified via S-Au covalent bonding by glycol monomethyl ether thioctate with poly(ethylene glycol) methyl ether of different molecular weights (i.e., 350, 550, and 750 Da). These modified GNPs (i.e., GNP350, GNP550, and GNP750) showed different oil-water partition coefficients (K_p), as detected using inductively coupled plasma-atomic emission spectroscopy. The different K_p values of the gold conjugates (i.e., 13.98, 2.11, and 0.036 for GNP350, GNP550, and GNP750, respectively) resulted in different conjugate localization within liposomes, as observed by transmission electron microscopy. In addition, the cellular uptake of hybrid liposomes co-encapsulating gold conjugates and Nile red was evaluated using intracellular fluorescence intensity. The results indicated that precise GNP localization in the hydrophilic or hydrophobic liposome cavity could be achieved by regulating the GNP oil-water partition coefficient via surface modification; such localization could further affect the properties and functions of hybrid liposomes, including their cellular uptake profiles. This study furthers the understanding not only of the interaction between liposomes and inorganic nanoparticles but also of adjusting liposome-gold hybrid nanostructure properties via the surface chemistry of gold materials.

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1. Introduction

During recent decades, liposomes have been widely used in the biotechnology and pharmaceutical industries to create robust biomembrane drug delivery systems (DDSs) [1,2] due to their versatile drug-loading properties. To form new hybrid systems, liposomes have been used to encapsulate various substances, including hydrophilic and hydrophobic small molecules, biomacromolecules, e.g., nucleic acids, proteins, and peptides, and metals or transition metal crystals at the nanoscale [3].

Various types of gold nanoparticles (GNPs) have been encapsulated by or adsorbed onto organic vehicles to mark and observe the structure, movement, and change of these organic nanomaterials both in vitro and in vivo [4–10]. In particular, liposome-gold nanoparticle (Lip-GNP) complexes have attracted a significant amount of attention. Much research emphasis has been placed on preparing GNPs [11,12] using liposomes as a template, evaluating the effects of nanogold on liposome membrane fluidity and fusion [13–15], inducing the release of drugs from thermosensitive gold-loaded liposomes using light [16–20], and improving the performance of hybrid systems using the advantages of GNP delivery [21,22].

Although liposomes have been successfully applied in the fields of nanomedicine and theranostics [23,24], the detailed relationships and interactions between liposomes and their cargo, especially nanoparticles, are not yet completely understood. All current investigations are based on the model in which the phospholipid bilayer is defined as the intermediate structure in the vesicle formation process [3]. The general understanding of drug localization in liposomes is that lipophilic and hydrophilic molecules are encapsulated by and remain in the lipid bilayer and the aqueous liposomal core, respectively [25,26]. However, no further supporting evidence that demonstrates or illustrates this reasonable assumption has been reported. In addition, differences

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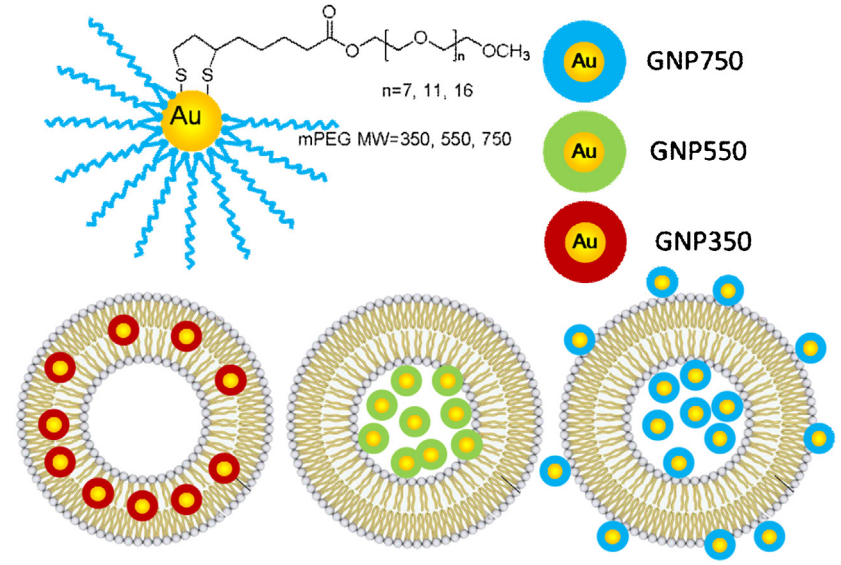

Fig. 1. A schematic diagram of the prepared GNPs with different hydrophilic and hydrophobic natures and their distribution within liposomes. (For interpretation of the references to colour in the text, the reader is referred to the web version of this article.)

in the hydrophilicity of the core and surface of liposomes are also currently unclear. Understanding the fundamental nature of liposomes and other organic vehicles is critical to better utilize the advantages of such theranostic systems.

In this work, we designed and prepared a family of modified GNPs protected by poly(ethylene glycol) methyl ether (mPEG)-appended dihydrolipoic acid ligands (DHLA-mPEG350, 550, and 750) (Fig. 1). Different oil-water partition coefficients (K_p), which affect the hydrophilic or hydrophobic nature of GNPs, could be obtained and controlled by adjusting the molecular weight (MW) of mPEG. The modified GNPs showed different localization behaviors in the three-dimensional structure of the liposomes and exerted different effects on the cellular uptake of hybrid liposomes encapsulating hydrophobic molecules, e.g., Nile red (NR). These results further the understanding of not only interactions between organic vehicles and inorganic nanoparticles but also how to finely control the properties of organic-inorganic hybrid nanostructures by adjusting GNP surface chemistry.

2. Materials and methods

2.1. Materials and instrumentation

Hydrogen tetrachloroaurate hydrate ($HAuCl_4{\cdot}3H_2O$) was obtained from Shanghai Chemical Reagent Company (Shanghai, China). mPEG (average MWs of 350, 550, and 750 Da), thioctic acid (TA), *N*,*N*'-dicyclohexylcarbodiimide (DCC), and 4-(*N*,*N*-dimethylamino)pyridine (DMAP) were of analytical grade and were used as received from Sigma-Aldrich Ltd. (USA). Soy lecithin (SPC, S100) was obtained from GmbH Lipoid (Ludwigshafen, Germany). Cholesterol was purchased from Shanghai Huixing Biochemical Reagent Co., Ltd. (China). Unless otherwise stated, all starting materials were obtained from commercial suppliers and used without further purification. All aqueous solutions were prepared using deionized water (>18 MΩ, Purelab Classic Corp., USA).

UV–vis spectra were recorded on a UV-2401 PC UV/vis spectrophotometer (Shimadzu, USA). Transmission electron microscopy (TEM) images of different GNP-mPEG conjugates, blank liposomes, and Lip-GNP complexes were analyzed using a JEM-2100 TEM instrument with an acceleration voltage of 200 kV (JEOL JEM, Japan). The fluorescence emission spectra of NR-containing samples were measured using an RF-5301 PC spectrofluorophotometer (Shimadzu, USA). The hydrodynamic diameters and zeta potentials were obtained using a zeta potential analyzer (ZetaPlus, Brookhaven Instruments Corporation, USA). The octanol-water partition coefficient of the GNP-mPEG conjugates was determined using inductively coupled plasma-atomic emission spectroscopy (ICP-AES, Optima 5300 DV, PerkinElmer Inc., USA).

2.2. Preparation of GNP-mPEG conjugates

2.2.1. Synthesis of TA-mPEG and DHLA-mPEG

A general method was followed for the synthesis of bidentate thiol motifs by reacting mPEG with TA followed by the ring opening of the dithiolane moiety using sodium borohydride ($NaBH_4$) reduction. The synthesis of TA-mPEG750 is described below as an example.

TA-mPEG750: In brief, TA (1.298 g, 6.3 mmol), mPEG750 (2.94 g, 3.92 mmol), DMAP (0.122 g, 1 mmol), and dichloromethane (CH_2Cl_2, 20 mL) were placed in a flask and degassed with a stream of N_2 for 30 min. The reaction mixture was cooled to 0 °C in an ice bath, and a solution of DCC (0.979 g, 4.7 mmol) in CH_2Cl_2 (20 mL) was added dropwise. The reaction mixture was stirred at 0 °C for 1 h, subsequently warmed to room temperature and stirred for 24 h.

The precipitate was filtered, and the solvent was evaporated. The residue was mixed with a saturated sodium bicarbonate solution and extracted with ethyl acetate until the TA-mPEG750 was completely extracted from the aqueous layer. The combined organic layers were dried over anhydrous sodium sulfate and filtered, and the solvent was evaporated. The crude product was subjected to chromatography on silica gel eluted with CH_2Cl_2:methanol (60:1), and 3.5 g of pale-yellow oil was obtained (95.2%). The final products were characterized using ^1H and ^{13}C NMR.

TA-mPEG350: ^1H NMR ($CDCl_3$, 500 MHz): δ 1.48 (m, 2H), 1.66 (m, 4H), 1.92 (m, 1H), 2.00 (s, 1H), 2.36 (t, 2H), 2.46 (m, 1H), 3.18 (m, 2H), 3.37 (s, 3H), 3.50–3.80 (m, 33H), 4.22 (t, 2H). ^{13}C NMR ($CDCl_3$, 500 MHz): δ 24.31, 28.37, 33.62, 34.27, 38.16, 39.89, 55.99, 58.67, 63.13, 68.85, 70.19, 70.27, 71.64, 173.02.

TA-mPEG550: ^1H NMR ($CDCl_3$, 500 MHz): δ 1.48 (m, 2H), 1.66 (m, 4H), 1.92 (m, 1H), 2.00 (s, 1H), 2.36 (t, 2H), 2.46 (m, 1H), 3.18 (m,

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