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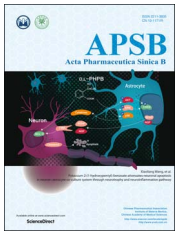

ORIGINAL ARTICLE

Biomimetic albumin-modified gold nanorods for photothermo-chemotherapy and macrophage polarization modulation

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Abstract Nanotechnology-based photothermal therapy has attracted great attention in the past decade. Nevertheless, photothermal therapy has some inherent drawbacks, such as the uneven heat production and limited laser penetration, often leading to insufficient treatment outcomes. Here, we developed a combination strategy to improve cancer therapy. The biomimetic albumin-modified gold nanorods (AuNRs) were prepared with incorporation of paclitaxel (PTX). This therapeutic system was characterized by several features. First, the albumin modification enhanced the biocompatibility and colloidal stability. Second, the surface-coated albumin promoted cellular uptake *via* the albumin-binding protein pathway. Third, PTX was incorporated *via* hydrophobic interaction between PTX and the albumin lipophilic domain. Fourth, the system can be used for combined photothermo-chemotherapy for yielding synergistic effects. The antitumor activity of the system was evaluated both *in vitro* and *in vivo* using the HCT116 colon cancer cell and tumor model. The combination therapy was found with an enhanced treatment efficiency and no obvious side effect. Most importantly, the thermal effect was also discovered with the ability to modulate the

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tumor microenvironments and suppress the macrophages polarization towards the M2 pro-tumor phenotype. It could be a mechanism for photothermal immunotherapy. The combination strategy and the system provide a potential method for cancer therapy.

1. Introduction

In the recent decade, photothermal treatment has attracted great attention as a promising avenue for cancer therapy, which makes use of the photothermal effect of the inorganic nanoparticles such as silica/gold nanoshells[1,2], gold nanorods[3,4], gold nanospheres[5,6], gold nanocages[7,8], gold nanostars[9,10], or carbon nanotubes[11,12]. These nanomaterials are administrated by intravenous or intra-tumor injection with subsequent irradiation of laser light to raise the temperature to kill the tumor cells. In photothermal treatments, the temperature in the tumor tissues where the blood vessels are deficient can be 5–8 degrees higher than the normal tissues, thus preferentially eradicating the cancer cells but sparing the healthy cells. Compared to the traditional cancer therapies, the photothermal treatment has great advantages, such as non-invasion, local action, and minor side effects.

Nevertheless, there are some limitations in photothermal treatment, too. For instance, the distribution of nanoparticles in the tumor is highly heterogeneous, and only a tiny fraction of the nanomaterials can reach the deep site of the tumors. In addition, laser beam energy is dramatically reduced after penetrating the tissues and it is at Gaussion distribution pattern, thereby leading to the insufficient photothermal effect deep inside the tumors.

A combination of photothermo-chemotherapy provides a promising method for improving the treatment efficacy[13–15]. The chemo-drugs can be encapsulated into the photothermal nanoparticles, and achieve the tumor targeting effect.

In this study, we developed a nano-system for photothermo-chemotherapy by loading a chemotherapy drug PTX to the albumin-modified AuNRs. Of note, albumin can serve as an efficient carrier of PTX *via* the strong interaction of the hydrophobic PTX binding with the hydrophobic domains of albumin. Another important function of albumin is its preferential uptake by the tumor cells. Albumin-binding proteins, *e.g.*, SPARC (secreted protein acidic and rich in cysteine), are the major pathway for albumin uptake by the tumor cells, which are greatly in need of albumin as a source of amino acids and energy to supply their rapid growth[16]. Therefore, the albumin-based nanoparticles can achieve enhanced tumor uptake *via* the biomimetic transportation mechanism of albumin-binding proteins (*e.g.*, SPARC)[17,18]. Therefore, it was expected that the PTX-loading, albumin-modified AuNRs could benefit from the albumin-mediated biomimetic intracellular delivery.

Thermo-immune responses have been demonstrated to be efficient for cancer therapy[19]. However, the mechanisms have not been understood yet. The tumor-associated macrophages (TAMs) are the major component in the tumor immune microenvironment. In this study, the photothermal effect on the TAMs was investigated.

2. Materials and methods

2.1. Materials

Tetrachloroauric (III) acid trihydrate and 11-mercaptoundecanoic acid (MUA) were purchased from J&K chemical Ltd. (Beijing, China). Bovine serum albumin (BSA) was obtained from RBC Life Sciences (Irving, USA) and PTX was from Melone Pharmaceutical Co., Ltd. (Dalian, China). Tris(hydroxyl methyl)aminomethane ($\geq$ 99.9%) was provided by Beyotime Institute of Biotechnology (Haimen, China). Anti-LC3B antibody was acquired from Cell Signaling Technology, Inc. (Danvers, USA). McCoy's 5A medium and 3-(4,5-dimethylthialzol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) were from Sigma–Aldrich (St. Louis, USA). 1-Ethyl,3-(3-dimethylaminopropyl)carbodiimide (EDC), *N*-hydroxysuccinimide (NHS), cetyl trimethyl ammonium bromide (CTAB), and other reagents were of analytical reagent grade, and purchased from Sinopharm Chemical Reagent Co., Ltd. (Shanghai, China).

2.2. Preparation of CTAB-AuNRs

AuNRs were synthesized by the seed-mediated growth method[20]. Briefly, the $HAuCl_4$ (0.5 mmol/L, 5 mL) aqueous solution was gently mixed with the CTAB solution (0.2 mol/L, 5 mL). Subsequently, with addition of the ice-cold $NaBH_4$ solution (10 mmol/L, 0.6 mL), the mixture was vigorously stirred for 2 min, and then kept at 28 °C for 3 h in darkness to generate the AuNR seeds.

CTAB (0.2 mol/L, 20 mL), silver nitrate (4 mmol/L, 0.8 mL), $HAuCl_4$ (1 mmol/L, 20 mL) were mixed in a flask. The solution was gently mixed, and ascorbic acid (80 mmol/L, 0.28 mL) was added. The mixture was turned from yellow to colorless. Immediately, the AuNR seeds (0.48 mL) were quickly added to the mixed solution above to initiate the growth of AuNRs. The reaction was maintained at 28 °C for 6 h in darkness, the CTAB-AuNRs were generated.

2.3. Preparation of MUA-AuNRs

The MUA-AuNRs were prepared by a round-trip ligand exchange method[21]. First, the CTAB-AuNRs were concentrated (2×10^{-8} –5×10^{-8} mol/L) by centrifugation. Dodecanethiol (DDT) was added to the CTAB-AuNRs aqueous solution to replace the CTAB. The thus-formed DDT-AuNRs were added to acetone. The organic phase was added to the solution of toluene and methanol (1:5). The DDT-AuNRs were collected using centrifugation, and the precipitation was resuspended in toluene by sonication. The DDT-AuNRs in toluene were added to 0.1 mol/L MUA

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