Biomaterials 34 (2013) 3390–3401

Contents lists available at SciVerse ScienceDirect

Biomaterials

journal homepage: www.elsevier.com/locate/biomaterials

A Gd-doped Mg-Al-LDH/Au nanocomposite for CT/MR bimodal imagings and simultaneous drug delivery

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ARTICLE INFO

Article history:
Received 29 December 2012
Accepted 16 January 2013
Available online 4 February 2013

Keywords:
Layered double hydroxides (LDHs)
CT imaging
MR imaging
Dual-modality imaging
Intracellular anti-cancer drug delivery

ABSTRACT

The early diagnosis and simultaneous drug delivery monitored by non-invasive visualization are highly challenging but clinical-relevant for the diagnostics and therapy monitoring of serious diseases such as cancers. Herein, a Gd-doped layered double hydroxide (LDH)/Au nanocomposite has been developed as both a drug carrier and a diagnostic agent. The obtained nanocomposite shows high non-anionic anti-cancer drug DOX loading capacity and an interesting pH-responsive release profile of loaded DOX. The nanocomposite was found to be able to efficiently transport DOX into the cancer cell, release the DOX in the acidic cytoplasm and then cause death of cancer cells. Meanwhile, the nanocomposite demonstrates better *in vitro* CT and T_1-weighted MR imaging capabilities than the commercial MRI and CT contrast agents and favorable *in vivo* CT and T_1-weighted MR imaging performance. After being modified with heparin, the nanocomposite also demonstrates effective CT and MR imagings of tumors by intravenous administration in tumor-bearing mice. Furthermore, the nanocomposite shows negligible cytotoxicity and no detectable tissue damage on mice after injection of high dosage of nanocomposite. In conclusion, the synthetic nanocomposite is expected to be a potential theranostic agent for bimodal imagings of cancers and anti-cancer drug delivery as well.

1. Introduction

During the past decades, remarkable progress has been achieved in developing nanotechnology platforms for early cancer diagnosis or therapy [1–4]. Among them, the integration of two or more strategies in one system has attracted great interests of many researchers and also become a representative challenge in biomedicine [5–7]. When drugs and imaging agents are integrated into the same compartments, *e.g.*, carriers such as nanoparticles, the biodistributions of nanoparticles or drugs and their accumulation at the target sites can be confirmed and monitored non-invasively by bioimaging under *in vivo* conditions [8]. In addition, the combination between/among different imaging modalities, such as MRI/CT [9,10], PET/CT [11] and PET/MRI [12], can provide more reliable and accurate information for the detection and positioning of disease sites than a single modality. Therefore, based on the detailed and accurate imaging information provided by multimodal imagings, the drug delivery and cancer therapy processes can be well monitored non-invasively once the drug carriers can also act as imaging agents, which is expected to further optimize the efficacy of both early disease diagnosis and therapeutic treatment [13,14].

Nanoparticles (NPs) could be used to integrate more than one kind of imaging or therapeutic functions, which makes them promising multi-functional nanoplatforms for both diagnosis and therapy [5–7,15]. The nanoplatforms can be constructed by either organic materials (liposomes, polymeric micelles, dendrimers, *etc*) [16–18], inorganic ones (iron oxide, gold, mesoporous silica, *etc*) [19–22], or organic inorganic hybrid materials [23], among which, inorganic nanoplatforms for the diagnosis and simultaneous therapy have been widely studied presently owing to their high chemical and biological stability, easy modification and high loading of drugs, *etc* [19–22,24]. However, the research for multi-functional inorganic nanoplatforms is still at its tentative stage, and new nanoplatforms with unique and smart characteristics are expected to provide more and better options for more personalized treatment programs [25].

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0142-9612/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.biomaterials.2013.01.070

Layered double hydroxides (LDHs), consisting of stacked positively charged brucite-type octahedral metal hydroxide layers with anions and water molecules occupying the interlayer space [26–28], are currently attracting intense research interests as nano-carriers for delivering drugs and bio-active molecules due to their unique structure, low-to-negligible toxicity, favorable biocompatibility, high anionic exchange capacity, tunable particle sizes, *etc* [29–34]. Many anionic drugs (such as methotrexate, ibuprofen and 5-fluorocytosine) [35–37], fluorescent molecules (sulforhodamine B) [38] and genes [28] could be easily intercalated into the space between the layers of LDHs. In addition, LDHs could be doped with functional ions in their crystal structure or be modified with functional groups or NPs (*e.g.*, Fe_3O_4, Au and Ag NPs) on the surface [35,36,39–41]. More importantly, as compared with widely investigated inert and negatively charged silica-based drug carriers [14,24], the LDH-based nanoplatforms are featured with a pH-controlled release profile of the cargo and slow but pH-dependent degradation under physiological conditions [42–44]. In the meantime, LDHs also have the very unique clathrin-mediated endocytosis mechanism and positive surface charge, which make the LDH's approach and adhesion to cells a quick process and facilitate cellular drug delivery of LDHs without further modifications [45–48]. Therefore, LDHs will be one of the most potential ideal inorganic carrier candidates for drug delivery and simultaneous bioimaging by, without much difficulty, integrating more than one kind of functional ingredients such as imaging or therapeutic agents. In spite of all the abovementioned advantages of LDHs and their high probability as imageable nano-carriers, however and to our surprise, no literature reports on the LDH-based multi-functional platform for multimodal imaging and simultaneous drug delivery can be found to date.

Herein, we report the successful chemical synthesis, CT and MR imaging performance and interesting pH-responsive anti-cancer drug delivery of Gd-doped LDH/Au (LDH-Gd/Au) nanocomposite (Fig. 1). The advantage of the LDH-based multi-functional system here over other nano-systems is that the imaging agent components, such as Gd^{3+} and Au NPs, can be easily and effectively introduced into LDH based on its unique structure, which is expected to be capable of acting as a contrast agent for bio-imaging. To do this, Gd^{3+} ions as the magnetic resonance imaging (MRI) contrast agent was doped into metal hydroxide crystalline layers of Mg-Al-LDH *via* coprecipitation method by which lanthanide ions can be incorporated in LDH lattice [36]. The Au NPs as CT contrast agent were incorporated in nanocomposite by depositing $Au(OH)_3$ on the surface of LDH-Gd under alkaline condition followed by the reduction with $NaBH_4$. The obtained LDH-Gd/Au nanocomposite has high surface area and pore volume due to the acid corrosion of LDH during preparation, and therefore, it can absorb, with a high capacity, the most commonly prescribed and clinically approved non-anionic anti-cancer drug doxorubicine (designated as DOX) by hydrogen bonding interaction, and a pH-responsive drug release feature is expected based on the properties of DOX itself [49]. To our knowledge, this is the first report in which LDH is used as carrier for loading drug DOX, which is a useful extension for only a limited number of anti-cancer drugs (usually anionic drugs) loaded in LDH-based carriers [42]. Thanks to the high specific surface area and the layered structure of LDH-Gd/Au, the high probability of water molecule access to the gadolinium ions doped in the LDH layer lattice and consequent significant water molecule relaxivity enhancement can be expected, which is essentially beneficial in enhancing MR imaging. Furthermore, the synthesized Au NPs in LDH-Gd/Au nanocomposite are very small and favorable to CT imaging [50]. In this paper, the feasibilities of LDH-Gd/Au nanocomposite as a multi-functional bio-platform for anti-cancer drug delivery and simultaneous bimodal CT/MR imaging are investigated in details.

2. Experimental section

2.1. Materials

Gadolinium(III) oxide and hydrogen tetrachloroaurate (III) trihydrate were purchased from Acros Organics (USA). Magnesium nitrate hexahydrate, aluminum nitrate nonahydrate, sodium nitrate, nitric acid (65%–68%), sodium hydroxide and ethanol were all purchased from Sinopharm Chemical Reagent Co., China. Gadolinium nitrate was prepared by dissolving the corresponding Gadolinium(III) oxide (Acros) in nitric acid solution at elevated temperature and then evaporating the water completely. All the other chemical reagents were of analytical grade and used directly without further purification. Deionized water was used in all experiments.

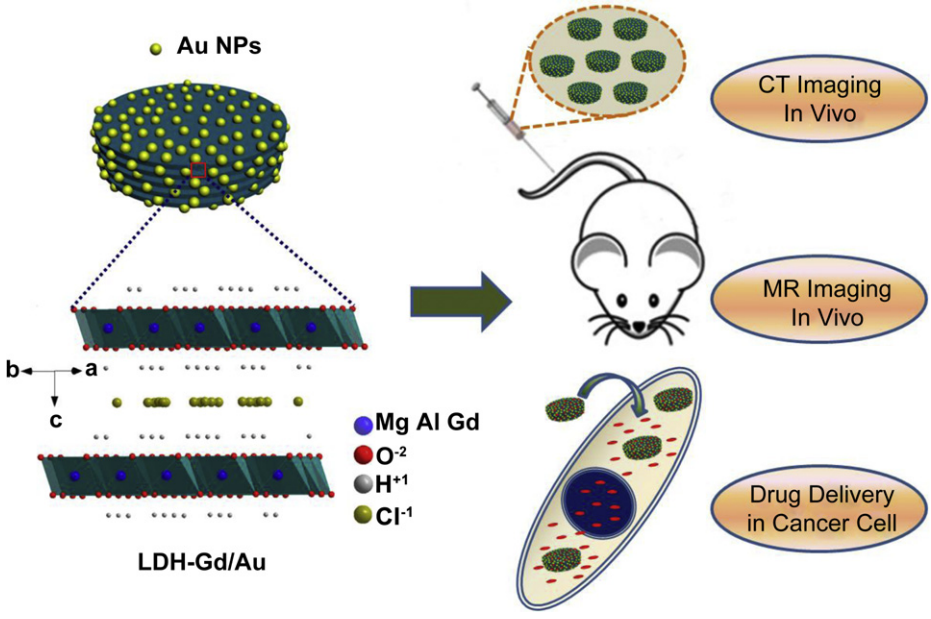

Fig. 1. Schematic illustration of the LDH-Gd/Au nanocomposite as a multi-functional platform for dual modal CT-MR imaging and anti-cancer drug delivery.