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Novel gadopentetic acid-doped silica nanoparticles conjugated with YPSMA-1 targeting prostate cancer for MR imaging: an *in vitro* study

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ABSTRACT

The early diagnosis of prostate cancer (PCa) is particularly important for reducing its high mortality rate. With the development of molecular magnetic resonance imaging (MRI), early diagnosis via non-invasive imaging has become possible. In this study, gadopentetic acid (GA)-doped silica (Gd@SiO_2) was first synthesized by a reverse microemulsion method, and amino and carboxyl groups were then successively introduced onto the surface of this Gd@SiO_2. After these steps, a monoclonal antibody (YPSMA-1) to prostate-specific membrane antigen (PSMA) was conjugated with carboxyl-modified Gd@SiO_2 (Gd@SiO_2-COOH) nanoparticles (NPs) by the carbodiimide method. Gd@SiO_2-Ab NPs were thus obtained as specific MR contrast agents for PCa-targeted imaging. Transmission electron microscopy showed that the Gd@SiO_2-Ab NPs exhibited a dispersed spherical morphology with a relatively uniform size distribution. The Gd@SiO_2-Ab NPs showed high stability and high the longitudinal relaxation rate (r_1). Cell-targeting experiments *in vitro* demonstrated the high potential of the synthesized NPs to target PSMA receptor-positive PCa cells. *In vitro* cytotoxicity assays showed that the Gd@SiO_2-Ab NPs exhibited good biological safety. These results suggest that the synthesized Gd@SiO_2-Ab NPs have great potential as specific MR contrast agents for PSMA receptor-positive PCa cells.

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1. Introduction

Prostate cancer (PCa) is one of the most common malignancies in men. Due to the high mortality rate of PCa in the United States and China [1,2], its early diagnosis is particularly important. Magnetic resonance imaging (MRI) is a potentially useful tool for the non-invasive diagnosis of PCa owing to its high resolution in soft tissue. However, the early diagnosis of PCa as well as the differential diagnosis of PCa and chronic prostatitis are difficult by conventional MRI [3,4]. Currently commonly used in clinical settings, MR contrast agents do not localize to specific targets to enable molecular diagnosis and treatment [5]. A novel carrier of MR contrast agents with targeting ability is necessary to non-invasively and specifically diagnose PCa at an early stage.

Commonly used carriers include carbon nanotubes, polymeric micelles, liposomes and silica nanoparticles (NPs). As nanocarriers, silica NPs have many advantages, including a high colloidal stability, a tunable particle size for efficient cellular uptake, and transparency to light and magnetism [6]. Additionally, there have been numerous studies on the biocompatibility and low toxicity of silica [7,8]. The surface of silica contains many active hydroxyl groups [9], which can be functionalized with multiple groups [10].

Recently, the combination of silica NPs with superparamagnetic metal oxides as negative MR contrast agents has been investigated intensively [11,12]. However, the combination of silica with Gd(III) compounds (T_1 contrast agents) requires further exploration [13]. Most previous studies have used the Stöber method to synthesize Gd-doped mesoporous silica NPs (Gd-MSNs). In addition, Gd-MSNs have been synthesized by the addition of an ionic form of gadolinium ($GdCl_3$) or Gd_2O_3 in some studies [14,15]. However, Gd^{3+} ions were easily released and caused toxic reactions [16]. To obtain Gd-containing NPs with a higher r_1, higher stability and smaller size, we first constructed gadopentetic acid (GA)-doped silica

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($Gd@SiO_2$) as a positive MR contrast agent by the reverse microemulsion method in this study. GA is a complex of Gd and a chelating agent [17]; thus, toxicity is avoided because Gd^{3+} ions are not easily released.

PSMA is a type II integral membrane protein that is thought to be highly specific for prostate cancer cells [18] and is not secreted, unlike other prostate-restricted molecules [19]. PSMA is highly expressed in PCa but only expressed at low levels in normal prostate and other tissues [20]; therefore, PSMA is an ideal target protein because of the high frequency and high homogeneity of PSMA expression in PCa cells [21]. Although PSMA-mediated nanocarriers have been explored for the targeted imaging and treatment of PCa, previous reports have mainly focused on radionuclide-labeled PSMA ligands for nuclear medicine imaging and treatment [22], as well as silica-coated Fe_3O_4 NPs conjugated with J591 mAb as a negative MR contrast agent [23]. To the best of our knowledge, the use of silica-coated GA conjugated with an antibody as a positive MR contrast agent for the targeted imaging of PCa has not been reported in the literature.

In this study, GA-doped silica was first fabricated by an inverse microemulsion method and then subjected to the successive introduction of amino and carboxyl groups to the surface of $Gd@SiO_2$; YPSMA-1 reacted with carboxyl groups on the surface of $Gd@SiO_2$-COOH that had been activated with 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide/*N*-hydroxysuccinimide (EDC/NHS) coupling reagents to obtain $Gd@SiO_2$-Ab (Fig. 1A). The characteristics, toxicity, and PCa cell-targeting ability of the $Gd@SiO_2$-Ab NPs were then studied *in vitro*. Our aim was to prepare novel GA-doped silica NPs that are conjugated with YPSMA-1 as a positive MR contrast agent to specifically detect PSMA receptor-positive PCa.

2. Materials and methods

2.1. Materials

Triton X-100 (TX-100), n-hexyl alcohol and cyclohexane were purchased from Alfa Aesar (Ward Hill, MA, USA). GA, 3-aminopropyltrimethoxysilane (APTES), tetraethyl orthosilicate (TEOS), EDC, NHS and 2-N-morpholino-ethanesulfonic acid (MES) were purchased from Sigma-Aldrich (St. Louis, MO, USA). Tetrahydrofuran, succinic anhydride, acetone, anhydrous ethanol (99.5%) and ammonia solution (25–28%) were purchased from Chuandong Chemical Co., Ltd., (Chongqing, China). Cell Counting Kit-8 (CCK-8), fetal bovine serum (FBS) and trypsin were purchased from Wuhan Boster Biological Technology, Ltd., (Hubei, China). Anti-PSMA antibody (YPSMA-1), goat anti-mouse IgG and goat anti-mouse IgG H&L (FITC) were provided by Abcam (Cambridge, UK). Deionized water was provided by a Milli-Q system from Millipore (Millipore, USA). Gd-DTPA (Magnevist®) was provided by the Consun Pharmaceutical Group, Ltd., (Guangdong, China). All chemicals were of reagent grade and used without further processing.

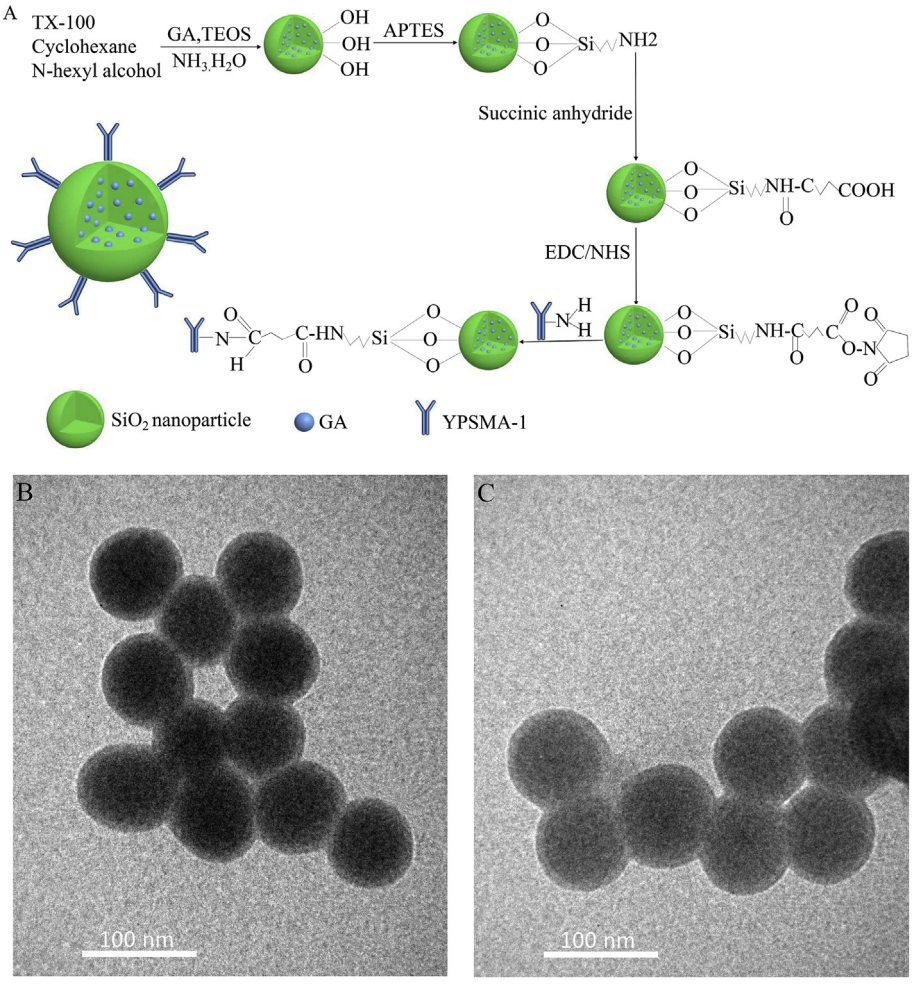

Fig. 1. Illustration of $Gd@SiO_2$-Ab synthesis strategy (A). TEM images of $Gd@SiO_2$ (B) and $Gd@SiO_2$-Ab (C).

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