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Facile synthesis of folic acid-conjugated fluorapatite nanocrystals for targeted cancer cell fluorescence imaging

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ABSTRACT

Bioluminescent calcium fluorapatite nanocrystals (TCaFAp:Eu) with controlled morphology were fabricated through an easy one-step method and found to have excellent water dispersibility and biocompatibility. Further modification of conjugation with both optical imaging and cell targeting capabilities provided useful nanoprobes for highly sensitive biorecognition applications, which was realized by grafting folic acid onto the surface of TCaFAp:Eu. The uptake of designed TCaFAp:Eu-FA by HepG2 cancer cells was verified by confocal laser scanning microscopy after 30 min, whereas the uptake of TCaFAp:Eu-FA by MCF-7 cells did not work, indicating that the prepared nanoprobe effectively targeted the imaging of cancer cells with over-expression of folate receptor.

1. Introduction

In modern tumor medicine, the development of diagnostic and therapeutic is not possible without the development of molecular imaging and employ of resultful targeting moleculars [1]. Over the past decades, many imaging techniques such as computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), single-photon emission computed tomography (SPECT), and other techniques are well refined and widely explored in diagnostic imaging [2]. Fluorescence analysis is a sensitive analytical method for noninvasive cancer cell detection and bioimaging [3].

Furthermore, among the conventional imaging modalities, fluorescence imaging is one of the most noninvasive diagnostic approach because of its natural ideal characteristics, such as extraordinary sensitivity similar to nuclear imaging, does not use radioisotopes or X-rays, cost-effective, and especially has distinguished spatial resolution [4].

Several luminescent nanomaterials, such as quantum dots [5], nanostructures doped with organic dyes [6], and lanthanide-based nanoparticles have been applied as optical probes. Lanthanide-based nanoparticles have attracted particular interest because of their sharp emission bands, unique long luminescence lifetime, and insensitivity to photobleaching [7]. As a bioprobe, biocompatibility is a common characteristic considered in the design of lanthanide-based nanoparticles for biological applications. In recent years, apatite crystals such as hydroxyapatite and fluorapatite, gained interest because of their structural similarity to bone mineral [8]. Lanthanide ions possess a radius similar to that of Ca^{2+} ions and a high affinity to PO_4^{3-} ions, which ensure the compatibility of the host materials for lanthanide doping. The luminescence properties of europium-doped apatites have also been witnessed, with narrow emission peaks and long luminescence lifetimes [9]. Herein, fluorapatite has been selected as the doping matrix because fluoride ions can contribute materials with low phonon energies, thereby increasing the probability of lanthanide fluorescence transitions [10]. However, many lanthanide-based fluorapatites with agglutination or hydrophobicity limited the usefulness of these nanoparticles for in vivo imaging [11].

Therefore, well-dispersed europium-based luminescent calcium fluorapatite nanocrystals (TCaFAp:Eu) with good dispersion stability was developed by a simple method using SiO_2 as template in this research. The conjugation with both optical imaging and cell targeting capabilities can serve as useful bifunctional probes for remarkable sensitive biorecognition applications. This report pre-

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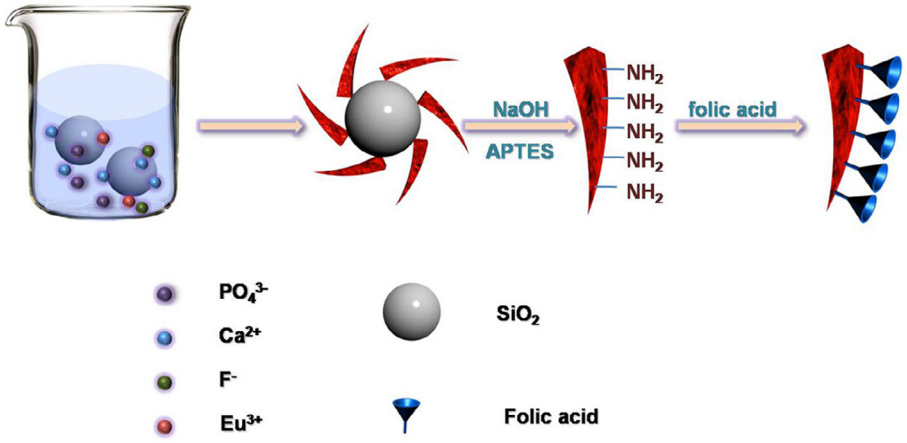

Fig. 1. Schematic view of synthetic method of TCaFAp:Eu-FA nanocomposite.

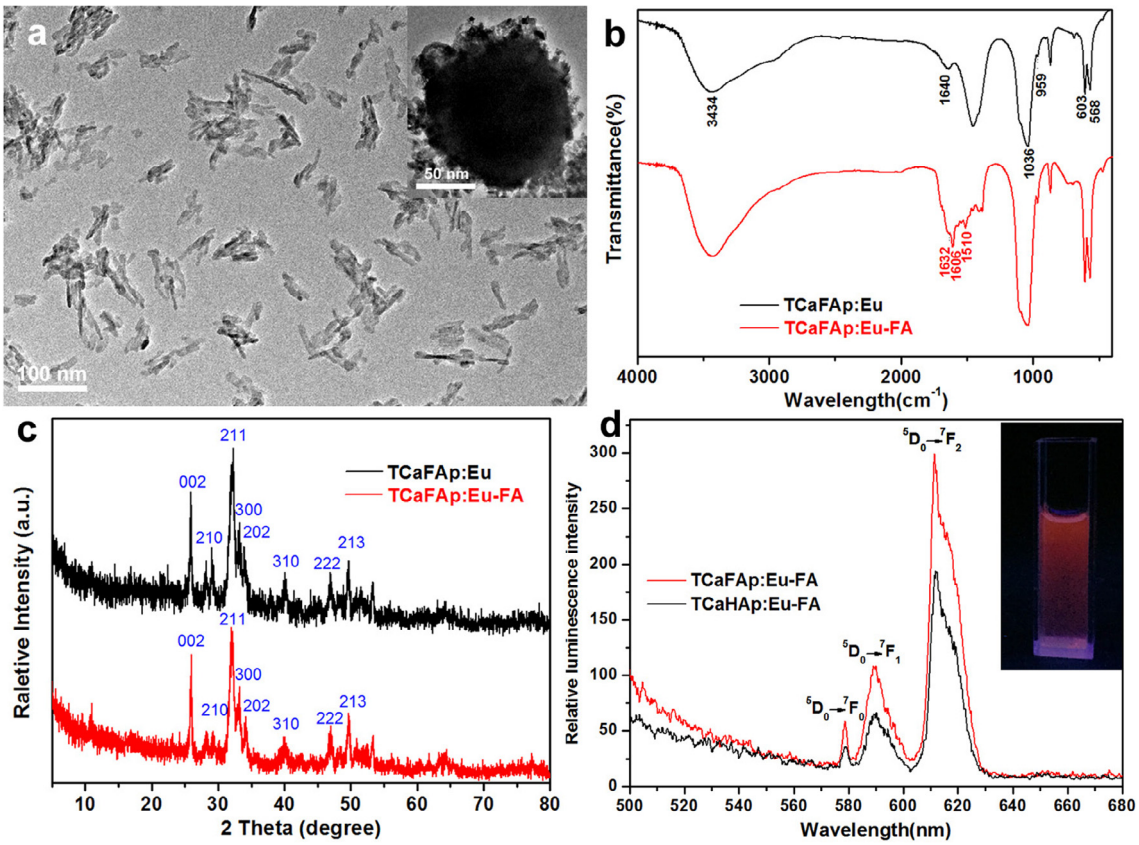

Fig. 2. (a) TEM image of TCaFAp:Eu nanocrystals, inset: TEM image of SiO_2@CaFAp:Eu; (b) FTIR spectra and (c) PXRD patterns of TCaFAp:Eu and TCaFAp:Eu-FA nanocomposites; (d) emission spectra of TCaHAp:Eu-FA and TCaFAp:Eu-FA nanocomposites, inset: fluorescent image of TCaFAp:Eu-FA.

sented the preparation and applicability of folic acid (FA) modified TCaFAp:Eu as a functional tumor identified nanocomposite; this study was inspired by folate receptors (FRs) used as a useful target for tumor-specific identification [12]. The expression level of folate receptors was significantly higher especially for lung cancer patients [13] (Fig. 1).

2. Experimental

The TCaFAp:Eu nanoparticles were presented based on modifying our previous synthetic method [14]. The obtained TCaFAp:Eu nanoparticles were isolated by successive centrifugation, washed with ultrapure water until neutral and then dried in the air. FA (20 μg) was then sonicated in DMSO (20 mL); EDC (10 μg) and NHS (10 μg) were added to activate the carboxylic acid groups of FA according to literature. Amino-functionalized TCaFAp:Eu nanoparticles were first synthesized for modification by FA. The TCaFAp:Eu-NH_2 nanoparticles were added to the activated FA solution, after which the mixture was stirred for 24 h at room temperature. The nanocomposite was recovered by centrifugation, washed with ultrapure water and ethanol, and dried in vacuo. The obtained TCaFAp:Eu-FA nanocomposite was used for evaluation