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Regular Article

Fixed-diameter upconversion nanorods with controllable length and their interaction with cells

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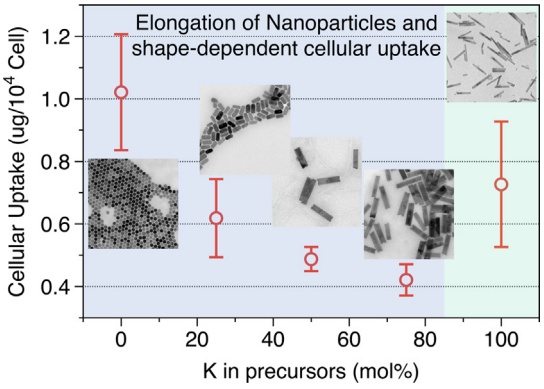
GRAPHICAL ABSTRACT



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ABSTRACT

A series of $NaYF_4$: Yb, Er upconversion nanorods with fixed diameter and controllable length were synthesized by the injection of sodium trifluoroacetate (CF_3COONa) mixed with potassium trifluoroacetate (CF_3COOK) precursor into a heated solution of ligand. We found that with the increased percentage of CF_3COOK, the length of resultant nanorods was increased from ~40 nm to ~200 nm whilst the diameter was kept in a narrow range of 37–42 nm. The elongation of nanorods was attributed to the specific absorption of sodium oleate on the prismatic facets, and the integration of potassium ions into the lattice as well. We further found that the elongated length affected the relative fluorescence intensity between red and green emission. More importantly, with fixed diameter, the cellular uptake of nanorods was found decreasing with the increase of their length. Meanwhile the decrease of diameter resulted in an increased cellular uptake. These results were attributed to both specific surface area and possibly varied contacting angle between nanorods and cell membrane. The current work not only suggested a synthetic method for the precise control of upconversion nanorods, but also shed light on the design of nanocrystals for cell-related biomedical applications.

1. Introduction

Morphology-controlled synthesis of nanocrystals has aroused tremendous attentions for years to get better optical, catalytic,

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magnetic, electronic and chemical properties [1–5]. In biomedical fields, the shape of nanomaterials has significant influences on their biophysical properties [6], especially on the nanomaterials-cells interaction that is of great importance not only for biological interests but also for nanodiagnosis and nanotherapy [7,8]. However, so far the reports showed inconsistent results for the influence of nanoparticle shape on their interaction with cells, especially the internalization. For example, Hao et. al. reported that mesoporous silica rods with aspect ratio of ~4 were more easily to be internalized by A347 human melanoma cells comparing with shorter nanorods with aspect ratio ~2, or spherical nanoparticles [9]. In contrast, Florez et al. showed a reversed correlation that nonspherical polymeric nanoparticles demonstrated lower uptake by mesenchymal stem cells and Hela cells than their spherical counterparts [10]. Even for the same nanomaterial, such as gold nanoparticles, there were contradictory findings in different reports. Some cases demonstrated that Au nanospheres showed much higher cellular uptake than Au nanorods in different cell lines [11,12]. Nevertheless, Kinnear et. al. [13] found that with a length scale of ~10–90 nm and aspect ratio less than 5, the shape of gold nanoparticles had little impact upon their internalization into either macrophages or epithelial cells. Conversely, nanorods with an aspect ratio above 5 were preferentially endocytosed by epithelial cells, whereas there was a lack of shape dependent uptake following exposure to macrophages *in vitro*. Thus, for the interaction between nanoparticles and cells, whether the shape-dependent principle exists and how it works on the internalization still remain unclear. It is therefore worthwhile to explore the shape control methods of each certain nanomaterial in favor of the study of the influence of shape on nanoparticle-cells interaction for biomedical applications, owing to that it may disclose the rationale in the design of nanoformulations.

As a promising nanomaterial in biomedical field, rare earth-doped upconversion nanoparticles (UCNs) have distinguished properties such as high efficient fluorescence, superior photostability, and deep penetration and low photodamage for biological tissues of the near-infrared excitation light [14]. In recent years, UCNs have attracted intensive attentions and found wide applications in cell and tissue labeling [15], deceases diagnosis [16], photodynamic therapy [17] and light-triggered drug release [18]. Great progress in the synthesis of UCNs has been achieved in that uniform and size-controlled UCNs could be maturely produced with spherical, hexagonal or rod-like shape. However, till now, the adjustment of the shape of UCNs came from the simultaneously change of length and diameter. For example, Lian et al. [19] obtained $NaCeF_4$ nanorods with changed length from 30 nm to 450 nm and the diameter varied from 20 nm to 80 nm in the meantime. Gau et al. [20] also synthesized rod-like β-$NaLuF_4$:Yb^{3+},Ln^{3+} (Ln^{3+} = Er^{3+},Tm^{3+} and Ho^{3+}) microstructures with length in 8–20 μm and diameter in 2–3.5 μm. As a result, the variation of properties could hardly be ascribed to their length, diameter, or size. Because of the difficulty in precise control of their shape, as an extremely promising nanomaterial for biomedical applications, how the shape of UCNs affects their interaction with cells still remains to be unravelled.

In our previous work, Yb and Er codoped β-$NaYF_4$ as one kind of UCNs were synthesized by injecting sodium trifluoroacetate (CF_3COONa) into the surfactant solution of sodium oleate (NaOL) at elevated temperature [21]. Further study showed that by using potassium oleate (KOL) as a part of ligand, nanorods of Yb^{3+}, Er^{3+} codoped β-$NaYF_4$ could be obtained and also, both diameter and length would increase with the increase of KOL percentage [22]. The shape evolution was demonstrated to be originated from the doping of K^+ in UCNs lattice. In current work, we directly used potassium trifluoroacetate (CF_3COOK) mixed with sodium trifluoroacetate (CF_3COONa) as the precursor, and unexpectedly, the resultant UCNs showed a fixed diameter while the length was increased along with the increasing dosage of CF_3COOK. The mechanism related to the shape evolution was discussed by analyzing the in-process products of different CF_3COOK molar ratio. With such a shape evolution only in one dimension, it is possible to precisely evaluate the influence of scale of nanoparticles in one dimension on their shape-dependent properties of luminescence, cellular uptake and cytotoxicity, and thus may shed light on the design of nanocrystals for cell-related biomedical applications.

2. Experimental section

2.1. The synthesis

Yb^{3+}, Er^{3+} co-doped $NaYF_4$ upconversion nanoparticles were prepared following the hot injection process with modifications [21]. In brief, the precursor solution including CF_3COOK/CF_3COONa (total 1 mmol, in which the molar percentage of CF_3COOK was denoted in text), $(CF_3COO)_3Y$ (0.78 mmol), $(CF_3COO)_3Yb$ (0.20 mmol), $(CF_3COO)_3Er$ (0.02 mmol), 1-octadecene (2.5 ml), oleic acid (2.5 ml) by stirring at 100 °C under vacuum for about 1 h until the mixture became clear. The reaction solution containing sodium oleate (0.63 mmol), 1-octadecene (10 ml), and oleic acid (9.8 ml) were prepared under same condition before being heated to 290 °C with stirring under dry nitrogen. Then the precursor solution was injected into the reaction solution drop-wise. After the injection, the solution was heated to 330 °C quickly and kept reacting for 10 min. Next the solution was cooled down to room temperature before washing with chloroform and anhydrous ethanol for three times. The collected UCNs were dispersed in chloroform.

Before the study on their interaction with cells, the resultant hydrophobic UCNs (1 mg) were transferred to hydrophilic by stirring the UCNs/chloroform solution with 500 μl Lipofectamine Transfection Reagent (Lipo 2000, Invitrogen) diluted by water at 60 °C until the chloroform was removed completely.

2.2. Characterization

The size and morphology of the nanocrystals were observed with a JEOL JEM-2100 transmission electron microscope (TEM) operated at 200 kV, with which selected area electron diffraction (SAED) patterns were also obtained. The X-ray diffraction patterns were measured with a BRUKER AXS X-ray diffractometer equipped with Cu Kα radiation (k = 1.540 Å). The Na and K content in the as-obtained nanoparticles were measured by inductively coupled plasma atom emission spectrometer (ICP-AES, iCAP 6000 Radial, THERMO). Luminescence spectra were performed at room temperature on a luminescence spectrometer (Ventana VIS-NIR, Ocean Optics Co.) with an external 980 nm continuous laser diode (0–3 W) as the excitation source. The Zeta-potentials of the nanoparticles were measured with a Malvern Zetasizer ZS90 Analyzer.

2.3. Cellular interaction

To evaluate the effect of the cytotoxicity and cellular uptake of different shape UCNs, cells were seeded at 5000 cells/well in 96-well plates and incubated for 24 h. Then the culture medium was replaced by 100 μl fresh medium containing different concentrations of UCNs for another 24 h incubation, after which the UCNs remained in the medium were removed by washing with PBS. Then the fresh culture media with 10 μl Cell Counting Kit-8 (CCK-8, Sigma) was added and the cells were further incubated for 2 h before measuring the optical density (OD) at wavelengths of 450 nm using a microplate reader (Varioskan Flash, Thermo Scientific). Cell viability was determined by calculating $OD_{450\ test}/OD_{450\ control}$.