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Responsive fluorescent Bi_2O_3@PVA hybrid nanogels for temperature-sensing, dual-modal imaging, and drug delivery

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ABSTRACT

The polymer-inorganic hybrid nanogels with temperature-responsive characteristic are of considerable current interest to many fields ranging from fundamental biomaterials science to bionanomedicine. This paper reports the preparation of temperature-responsive hybrid nanogels by immobilization of Bi_2O_3 quantum dots (QDs) in the interior of a nanogel of poly(vinyl alcohol) (PVA). Unlike conventional temperature-responsive hybrid nanogels with the responsive features deriving from the temperature-responsive polymers (e.g. PNIPAMs or non-linear PEGs), we demonstrate that QDs can work cooperatively with the gel networks of PVA, an unconventional responsive polymer, to enable the temperature-induced volume phase transition of the designed Bi_2O_3@PVA hybrid nanogels. Building on the rationales, Bi_2O_3@PVA hybrid nanogels can adapt to a surrounding fluids of different temperatures over the physiologically important range of 37–40 °C, convert the disruptions in homeostasis of environmental temperature into high-sensitive fluorescent signals, enter into the mouse melanoma B16F10 cells for dark-field and fluorescence dual-modal imaging, and regulate the release of a model anticancer drug temozolomide. The unconventional strategy that can broaden the design scheme of temperature-responsive hybrid nanogels for theranostic action should enhance our ability to address the complexity of biological systems.

1. Introduction

Responsive hybrid nanogels, comprising quantum dots (QDs) immobilized in a polymer nanogel, have recently attracted intensive interest [1–13]. While QDs exhibit unique optical and electronic properties including wideband excitation, phenomenal photostability, and high quantum yield [14,15], responsive hybrid nanogels can undergo volume phase transition in response to external stimuli [16,17], such as an increase in local temperature (1–5 °C) on the pathological zones because of the enhanced metabolic activity [18–20], to modify the physicochemical microenvironment of the QDs immobilized inside, making QDs responsive to the change in environmental temperature. The controllable properties of the temperature-responsive hybrid nanogels may lead the way to multiple functionalities, such as chemical and biochemical sensing [2–5], controlled drug delivery [6–8], and intelligent labeling and cellular imaging [8–11]. The ability of a single hybrid nanogel to perform simultaneously diagnosis and therapy is often cited as an advantageous characteristic of the nanoplatform that cannot be achieved with the conventionally individual constituents [9–13]. Clearly, the theranostic action of the hybrid nanogels is directly controlled by one's ability to harness the reversible temperature-induced volume phase transition onto the hybrid nanogels. However, at present only the temperature-responsive polymers, most of which are poly(*N*-isopropylacrylamide) derivatives (PNIPAMs) and the non-linear poly(ethylene glycol) (non-linear PEGs), have been employed to construct the temperature-responsive hybrid nanogels. The temperature-induced volume phase transition and thus the temperature-responsive functionalities of those hybrid nanogels principally rely on the phase behavior of the

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temperature-responsive polymers [4,11]. Although considerable research efforts have been put into various fields, unfortunately, no report of any temperature-responsive hybrid nanogels on the basis of other polymers has appeared in the literature.

In this work, we describe the use of an unconventional responsive polymer, poly(vinyl alcohol) (PVA), as a model to construct temperature-responsive hybrid nanogels. Different from many vinyl polymers, the commercial PVA is not prepared by polymerization of the corresponding monomer. PVA instead is prepared by hydrolysis of poly(vinyl acetate) to remove acetate groups. It is reported that partially (~80%) hydrolyzed PVA has a maximum solubility in water at ~18 °C, which is related to the conformational changes of the polymer [21]. A recent NMR study by El-Aasser's group hinted that the highly (~99%) hydrolyzed PVA can undergo molecular conformation changes at ~27 °C (the lowest temperature) [22]. Nonetheless, the change in temperature would not cause cloudiness of the solution. Thus, PVA is more frequently considered as a water-soluble polymer with cost effectiveness, innocuousness, and outstanding biocompatibility that can be made to ophthalmic solutions, cell scaffolds, and artificial organs [23,24]. PVA is also widely used as a surface modifier or steric stabilizer in synthesizing QDs and other inorganic nanocrystals, through interaction of the many –OH groups with the growing crystallites [25–27]. Recently, our group reported the morphology-controlled synthesis of Bi_2S_3@PVA hybrid nanostructures [28]. It is found that a series of nanostructures of controllable tubal, branched, actinomorphic, and dendritic morphologies can be obtained by simply controlling the exposure time of the reaction system to a ^{60}Co γ-ray source, which is used to induce the reaction.

Herein, we report temperature-responsive hybrid nanogels (~163 nm), denoted as Bi_2O_3@PVA, by immobilization of Bi_2O_3 QDs (~18 nm) in the interior of PVA nanogel (Fig. 1). The reported use of Bi_2O_3 in Injectable Bone Substitute to improve contrast performance for minimal invasive surgery [29] and as a bioactive root canal dressing or filling material [30] have highlighted the promising biocompatibility of the Bi_2O_3@PVA hybrid nanogels for biomedical applications. We demonstrate that the stable, radio-opaque [31,32] and fluorescent Bi_2O_3 QDs can not only act as an optical code, more importantly, but also work cooperatively with PVA gel network chains to enable the reversible temperature-induced volume phase transition of the Bi_2O_3@PVA hybrid nanogels. The temperature-response of the newly designed hybrid nanogels is generally comparable, and in some cases, superior to the ones based on a PNIPAMs/non-linear PEGs nanogel immobilized with QDs. The immediate advantage of such a QD-activated temperature-response is that the designed Bi_2O_3@PVA hybrid nanogels can exhibit a quite high-resolution fluorescent signal in response to environmental temperature, in comparison with previous developed arts with CdTe or other QDs physically restricted in the temperature-responsive PNIPAM-/non-linear PEG-based nanogels [2–5]. Building on the rationales, besides the obvious interest for high-sensitive fluorescent temperature-sensing using a single nanoplatform solution, tests are also carried out to demonstrate that the multidisciplinary design can allow Bi_2O_3@PVA hybrid nanogels to integrate another two important functionalities of widespread interest: dark-field and fluroescence dual-modal imaging, and biologically (an increase in local temperature) [18–20] controlled release of anticancer drug, so that contributions toward a paradigm for theranostic action can be envisaged.

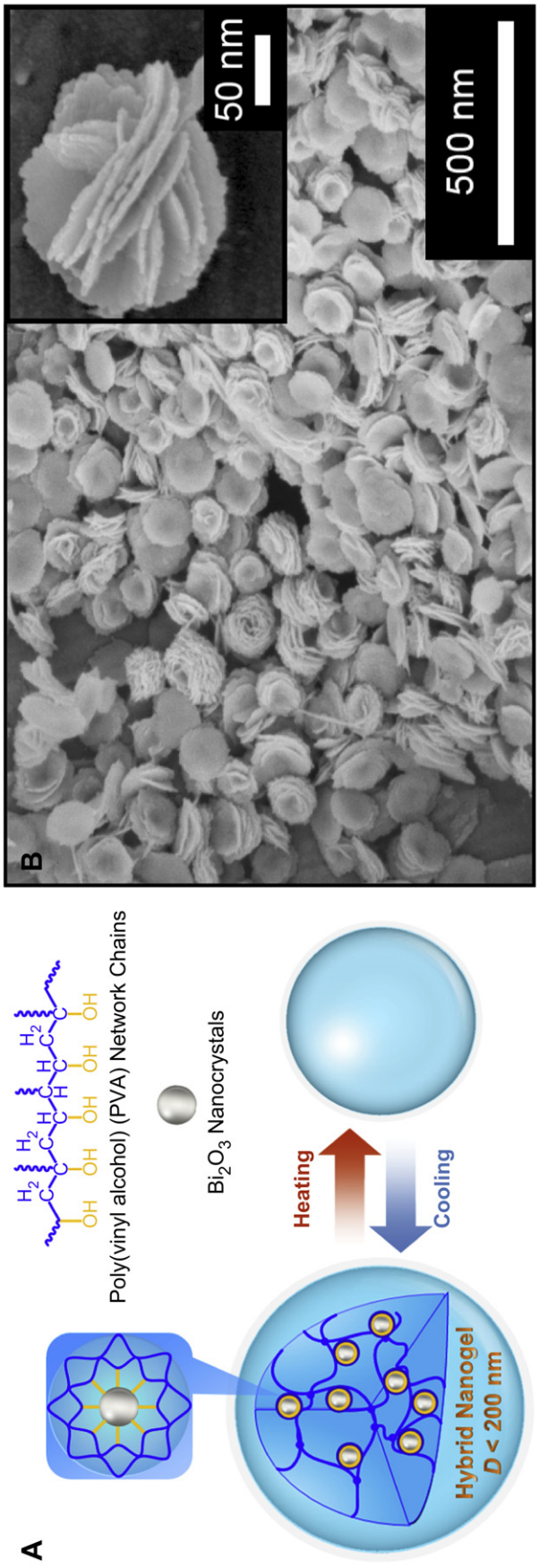

Fig. 1. (A) Model of the temperature-responsive Bi_2O_3@PVA hybrid nanogels. (B) Typical SEM image of Bi_2O_3@PVA hybrid nanogels.