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808 nm light triggered black TiO_2 nanoparticles for killing of bladder cancer cells

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ABSTRACT

The black TiO_2 nanoparticles are synthesized via a facile calcination method combined with an in-situ controllable solid-state reaction approach. The results indicate that the photocatalyst with a narrow band gap of ~2.32 eV extends the photoresponse to visible light and near infrared region. And thus more reactive oxygen species can be obtained to induce the cell-killing under 808 nm light triggering. The as-obtained black TiO_2 nanoparticles exhibiting low toxicity, good biocompatibility and high anticancer effect in vitro, is demonstrated as efficient photosensitizers for phototherapy to kill the bladder cancer cells. These findings suggest that the facile synthetic black TiO_2 nanomaterials will have broad application in biomedicine.

1. Introduction

Titanium dioxide (TiO_2) is one of the most promising semiconductor photocatalyst materials for its environmental benignity [1], chemical stability [2], low cost [3] and non-toxicity [4]. It has been widely used in the field of photocatalysis [5], dye sensitized solar cell [6], self-cleaning coating [7], cosmetic [8], food [9], and biomedicine [10]. It is well-known that the crystal structure of TiO_2 greatly affects its photocatalytic activity [11]. Generally, anatase phase shows the best photocatalytic activity among the four TiO_2 crystal phases, containing anatase, rutile, brookite, and monoclinic TiO_2 (B) [12,13]. Compared to a single crystal phase, dual-phase TiO_2 photocatalysts has a higher photocatalytic activity owning to the synergistic effect between them. For example, commercial P25 (71% anatase and 29% rutile), has been proven to be an exceptionally excellent photocatalyst [14] for pollutants photodegradation.

Over the past few decades, phototherapy including photothermal therapy (PTT) and photodynamic therapy (PDT) [15–17] has drawn wide attention as a powerful cancer treatment technology for its convenience [18] and minimal invasiveness [19]. The principle of phototherapy is that photogenerated reactive oxygen species (ROS) can react with cancer cell membranes and interiors, leading to the death of the cancer cells [20–22] based on both apoptosis and neurosis [23–26]. According to previous reports, as an inorganic photosensitizer (PS), TiO_2 has historically been utilized in UV photodynamic therapy for cancer treatment [27–29] in biomedicine. Based on the theory of UV light-triggered radical production, TiO_2 for cancer PDT have attracted much attention over the last two decades [30]. However, due to the overheating [31], very shallow penetration depth [32] and toxicity of UV light [33], cancer PDT with TiO_2 meets obstacles that further hinder its preclinical research and clinical application. Thus, many researchers [34–36] have tried to change the excitation wavelength of TiO_2 from UV to visible light by doping [37] or surface modification [38]. Although these advances have solved this problem to some extent, the results are not satisfactory. As the excitation source, visible light circumvents the overheating issues and the mutagenic problems [39] of UV excitation, but it still does not provide optimal penetration depth compared with near infrared (NIR) light, which can reaches a minimum absorbance for all biomolecules. Therefore, near infrared light mediated PDT has attracted much attention [40] for cancer treatment. It is urgently needed to seek an enhanced visible and NIR light absorption PDT agent.

Recently, Mao et al. [41] reported that hydrogenated black titania with a narrow band gap (~1.54 eV) exhibited enhanced visible light

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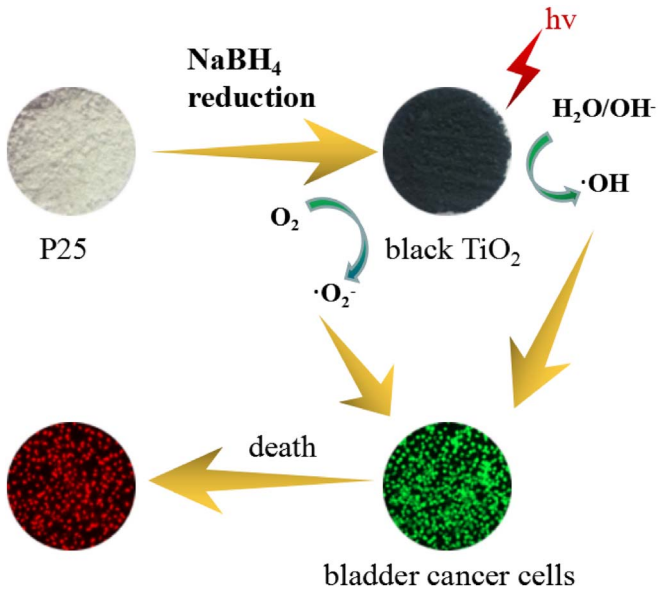
and NIR absorption and had attracted substantial interest for its potential application in the fields of photocatalysis, sustainable energy sources and fuel cells. Subsequently, black TiO_2 nanoparticles (NPs) have been proved to have high conversion efficiency and can be used for cancer phototherapy [42]. Therefore, constructing the combinational PTT and PDT nanoplatform-triggered [43,44] by a near infrared light laser based on black TiO_2 for the synergistic effect on cancer treatment is desirable but great challenging.

Bladder cancer is the fourth and eleventh most common cancer among men and women [45]. Commonly, it could be clinically divided into three categories, namely non-muscle-invasive bladder cancer (NMIBC), muscle-invasive bladder cancer (MIBC) and metastatic bladder cancer [46]. Among them, the NMIBC accounted for ~80%. The current standard therapy for NMIBC is complete transurethral resection of the bladder tumor (TURBT) followed by adjuvant intravesical therapy with Bacillus Calmette-Guérin (BCG) or less commonly with mitomycin, valrubicin, gemcitabine, or thiotepa [47–49], designed to reduce recurrence and prevent progression to a more advanced stage [50,51]. However, multiple recurrences and rapid progression easily occur after initial TURBT. It has been reported that approximately 25% of these patients with NMIBC progress to MIBC and metastatic bladder cancer [52,53]. It thus appears that the current situation for bladder cancer therapy is still unsatisfactory and needs to be improved and innovated. Recently, PDT as the rising star has been an attractive alternative modality in the treatment of bladder cancer for the fact that it is minimally invasive [54], relatively tumor selective [55], and possesses low risk [56] for development of resistance [57]. As the intravesical cavity can be easily observed through an endoscope, which is beneficial for intravesical photosensitizer application and good light penetration in cancer cells during irradiation [58]. As mentioned at the beginning of this section, much attention has been generated to TiO_2 for cancer PDT on the basis of the theory of UV light-triggered radical production [59,60] over the last two decades. Nevertheless, several limited issues set back its preclinical research and clinical application, including the overheating, very shallow penetration depth and toxicity of UV light [61]. Combined with the merits of black TiO_2 material, it may be good candidate for a near infrared light triggered PDT on bladder cancer cells.

Given all the circumstances mentioned above, we report the successful construction of black TiO_2 nanomaterials combined with a near infrared light triggered PDT on bladder cancer cells (Scheme 1). In this work, black TiO_2 NPs are successfully synthesized via a facile calcination method combined with an in-situ controllable solid-state reaction approach. The obtained black TiO_2 NPs with a narrow band gap (~2.32 eV) exhibits visible and near infrared light absorption. Finally, the cytotoxicity and therapy effects of black TiO_2 NPs are relative systemically evaluated in vitro. These results demonstrate that black TiO_2 NPs are efficient as photosensitizer for PTT and PDT possessing low toxicity, good biocompatibility, high penetration depth and favorable anticancer effect in vitro. These findings suggest that the facile synthetic black TiO_2 NPs will have broad application prospect in biomedicine.



Scheme 1. Illustration of 808 nm light triggered black TiO_2 nanoparticles for killing of bladder cancer cells.

2. Materials and methods

2.1. Materials

Titanium dioxide (P25, 71% anatase and 29% rutile) powder was purchased from Degussa Co. Ltd., Germany. Ethylenediamine (EN), and absolute ethanol (EtOH), were purchased from Tianjin Kermel Chemical Reagent Co. LTD, China. Sodium boron hydride ($NaBH_4$, 98%) was purchased from Aladdin Reagent Company, China. All reagents used in the experiments were analytical grade and employed without further purification, and the deionized (DI) water was used throughout this study.

2.2. Synthesis

1.0 g of the TiO_2 powder (denoted as TP) was dispersed in 50 mL of DI water under magnetic stirring for 30 min. While still stirring, 7 mL of EN were slowly added dropwise to the solution till the pH ~ 11. Thereafter, the mixture was transferred into a 100 mL flask with three necks connecting the condenser tube and maintained at 95 °C for 48 h. After naturally cooling down to room temperature, the resulting solution was collected, rinsed with DI water for several times and dried at 60 °C for 24 h. Subsequently, the obtained powder was calcined for 2 h at 700 °C with a heating rate of 3 °C min^{-1} (denoted as TP-700).

0.5 g of prepared sample was mixed with 0.5 g of $NaBH_4$ at room temperature for 30 min thoroughly. Then the mixtures were transferred into porcelain boats, and placed in a tubular furnace to anneal at 350 °C for 1 h under the Ar atmosphere. After naturally cooling to room temperature, the black TiO_2 NPs were obtained (denoted as b-TP-700) and washed with deionized water three times to remove unreacted $NaBH_4$. For comparison, the TP without calcined was also synthesized under the same condition with adding $NaBH_4$ (denoted as b-TP).

2.3. Characterization

X-ray diffraction (XRD) was collected on a Bruker D 8 Advance diffractometer by using Cu Kα radiation source (λ = 1.5406 Å). Raman spectra were obtained by using a Jobin Yvon HR 800 micro-Raman spectrometer in the range of 100 to 1000 cm^{-1} at 457.9 nm. X-ray photoelectron spectroscopy (XPS) measurements were conducted on a PHI-5700 ESCA instrument with Al-Kα X-ray source. All binding energies were calibrated with surface adventitious carbon of 284.6 eV. Transmission electron microscopy (TEM) was observed with a JEM-2100 electron microscope (JEOL, Japan). Surface area determination was performed by the Brunauer-Emmett-Teller (BET) method with an AUTOSORB-1 (Quantachrome Instruments) nitrogen adsorption apparatus. Pore size distributions were obtained using the Barrett-Joyner-Halenda (BJH) method from the adsorption branch of the isotherm. UV–Vis diffuse refection spectra (UV–vis DRS) were recorded on a UV–vis spectrophotometer (Lambda 950, PerkinElmer), with an integrating sphere attachment.