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Effects of surface modification of quantum dots on viability and migration of triple-negative breast cancer cells

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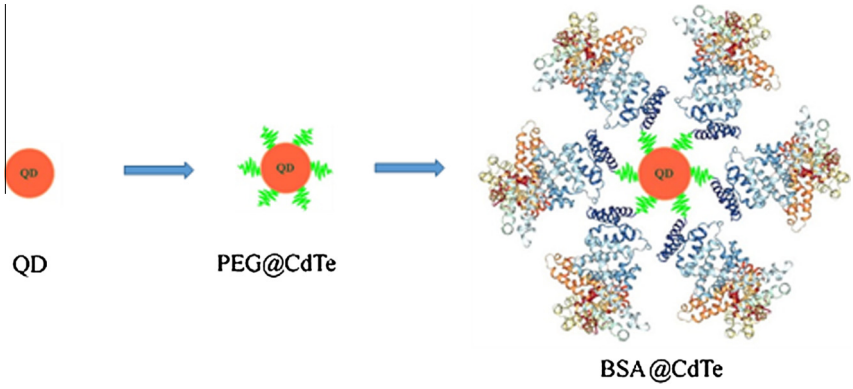
GRAPHICAL ABSTRACT



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ABSTRACT

Triple-negative breast cancer (BC) shows strong metastasis and has a bad prognosis. There are few effective approaches until date to detect BC cells at an early stage. Quantum dots (QDs) are one of the most promising nanomaterials for the detection of BC cells. QDs are usually modified with some functional molecules, such as PEG and BSA, to decrease or possibly eliminate their toxicity. Although a large number of studies have investigated the cytotoxicity of QDs, the effects of surface modification of QDs on biological behaviors of triple-negative BC cells remain unclear. In this work, QDs were prepared using the hydrothermal method and chemically modified with PEG and BSA. The optical performance of QDs was recorded with a digital camera. Their absorption and fluorescence (FL) properties were analyzed by UV–Vis spectrometer and FL spectrophotometer, respectively. The effects of QDs and surface modification on viability and migration were principally investigated. The possible mechanism was primarily analyzed. The results show that QDs exhibit excellent optical performance under ultraviolet irradiation. Surface modification slightly reduces the photon count reaching the QDs surface. Moreover, surface modification results in a blue-shift of FL peak of QDs, which is ascribed to the change in surface chemical environment because of PEG and BSA modifications. In addition, QDs, PEG coated QDs (PEG@CdTe) and BSA coated QDs (BSA@CdTe) can reduce viability and inhibit migration of BC cells. The inhibition effects are time- and concentration-dependent. In addition, PEG and BSA modified QDs exhibit lower inhibition effects on BC cells, as compared with unmodified QDs. In this process, Reactive oxygen species (ROS) does not appear to play an important role, and other pathways should be

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considered. This work provides experimental support and useful clinical guidance for QDs-applications in BC detection.

1. Introduction

Breast cancer (BC) is one of the most common malignant tumors in females in both developed and developing countries [1]. The incidence of BC increases each year, with new cases reaching about 1.7 million annually worldwide, and over 500 thousand women die because of metastasis and recurrence of BC every year in the whole world [2]. Triple-negative BC accounts for about 12–17% of BC cases, which displays a lack of expression of human epidermal growth factor receptor 2 (HER-2), progesterone receptor (PR), and estrogen receptor (ER) in immunohistochemistry [3]. Triple-negative BC has a bad prognosis and cannot be treated with endocrine and targeting therapy [4]. Numerous literatures report that the triple-negative BC exhibits high recurrence and metastasis [5,6].

In fact, overall curability of early BC is almost 100%, and the number of advanced BC cases is only about 20% [7]. Therefore, early diagnosis and therapy are especially important for BC, which can manifest increased curability and life quality of BC patients. Although a couple of technologies for the diagnosis of BC exist [8,9], none are effective for diagnosis at an early stage.

Nanotechnology is one of the most promising technologies to realize diagnosis of early BC. Among numerous emerging nanomaterials, QDs are the most promising nanoparticles, with tunable optical and electronic properties, depending on their size and composition [10–12]. Therefore, they have high potential in many fields, such as solar cell, proteomics [13,14], metal detection [15], biosensing [16], and drug analysis [17,18]. Compared with traditional organic fluorophores, QDs have a broad excitation band, superior fluorescent intensity, and excellent optical stability [19,20]. Thus, researchers studied the detection of BC cells using QDs and obtained exciting results [21,22].

Although QD-application in the detection of BC cells is an exciting progress, researchers were concerned regarding the cytotoxicity of this promising nanomaterial [23,24]. In the biological environment, QDs may release Cd^{2+} leading to further toxic effects on the cells [25]. In recent years, surface modification was confirmed as an effective method to decrease QD cytotoxicity [26,27]. In fact, surface modification has been widely studied in surface engineering field of nanomaterials. Prof. Huang and co-workers used chemically reduced bovine serum albumin (dBSA) to modify CdTe QD. They found that a shell-like complex structure $CdTe_x(dBSA)_{1-x}$ formed on the surface of CdTe "core", resulting in enhancement of PL intensity and a blue-shift of the PL peak [28]. Prof. Li and his team anchored molecularly imprinted polymer (MIP) on the surface of dBSA-modified QD, using a surface molecular imprinting process. dBSA was used not only to modify the surface defects of the CdTe QDs, but also as assistant monomer to create effective recognition sites. Under optimum conditions, the linear range for lysozyme (Lyz) concentration was from 1.4×10^{-8} to 8.5×10^{-6} M, and the detection limit was 6.8 nM [29]. Prof. Zhao et al. used BSA to modify the surface of QD. Under optimal conditions, BSA@CdTe could detect silver (I) in the range of 0.08–10.66 μM, and the detection limit was 0.01 μM [30].

In cytotoxicity research, Prof. Bhatia and his co-workers found that CdSe-core QDs were indeed acutely toxic under certain conditions. The cytotoxicity of QDs was modulated by processing parameters during synthesis, exposure to ultraviolet light, and surface coating [31]. Huang et al. evaluated the cytotoxicity of a series of thiol-stabilized CdTe, core-shell structured CdTe/CdS, and core-shell-shell structured QDs, using K562 and HEK293 cell lines as models. Their investigation clearly showed that the cytotoxicity of QD can be modulated through elaborate surface modifications [32]. Despite a significant surge in the number of studies on the cytotoxicity of QDs, there is currently limited knowledge regarding their effects on triple-negative BC cells. Several systemic experiments are required before QDs can be applied in the clinic.

In this study, we synthesized QDs and chemically modified their surfaces with PEG and BSA. Triple-negative BC MBA-MD-231 cells were chosen as target cells. The effects of QDs, with and without surface modifications, on cell viability and migration were principally investigated. The results demonstrated that QDs could decrease viability and migration capability of BC cells. Surface modification with PEG and BSA reduced this inhibition effect. In this process, ROS, probably, did not play a critical role. This work provides valuable experimental support and technological foundation for application of QDs in BC detection.

2. Experimental section

2.1. Reagents

All chemical reagents used in this work were of analytical grade, without further purification. $CdCl_2{\cdot}2.5H_2O$ and NaH_4B were purchased from No. 3 Chemical Reagent Plant of Tianjin (China). Te powder was obtained from Jinke Fine Chemical Research Institute of Tianjin (China). 3-mercaptopropionic acid (MPA) was provided by Shanghai Tixiaicheng Chemical Industry Development Co., Ltd (China). PEG was purchased from JenKem Technology Company of China. N-(3-Dimethyl aminopropyl)-N′-ethycarbodiimide hydrochloride (EDC) was obtained from Fluka Company, N-Hydroxysulfosuccinimide sodium salt (sulfo-NHS) was provided by Sigma-Aldrich, and BSA was a product of Gibco Biocompany. [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide] (MTT) was purchased from Sigma; ROS kit was obtained from Beijing Fanbo Biochemical Company.

2.2. QD preparation

In this work, QDs were synthesized using a facile chemical route as described in our previously published paper and elsewhere [33,34]. Briefly, aqueous QD solution was synthesized by adding a freshly prepared NaHTe solution to N_2 saturated $CdCl_2$ in the presence of MPA as a stabilizing agent. The CdTe QD precursor solution was transferred into Teflon-lined autoclaves, and maintained at 160 °C, 170 °C, or 180 °C. After reaction, the autoclaves were naturally cooled to room temperature.

2.3. QDs bioconjugation with PEG and BSA

The bioconjugation procedure of QDs with PEG and BSA was similar as described elsewhere [35,36]. EDC was used in the presence of sulfo-NHS to activate the carboxylates on the QD surface to form an intermediate sulfo-NHS ester. Then, PEG was added to the mixture. The QD modified with PEG was named PEG@CdTe. After the unreacted reactants were separated, PEG@CdTe was re-dissolved in the reaction buffer. BSA was added into the mixture