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REVIEW

ZnO-Based Quantum Dots for Biosensing, Cancer Imaging and Therapy: An Overview

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Abstract

Cancer is the second leading cause of death globally. The earlier detection via targeted and sustained imaging for cancer diagnosis can significantly improve the situation. Tremendous efforts are currently underway to utilize unique properties of semiconducting nanocrystals or quantum dots (QDs) in biological imaging. Particularly, ZnO-based QDs are attractive because they are envisaged to enhance the penetration depth of light into the endogenous substance in view of being water dispersible. Besides, they offer numerous tunable features in terms of their optical behavior thereby leading to incredible scope in the areas like bio-imaging. Because of its high biocompatibility or poor cytotoxicity, ZnO QDs have slowly acquired a respectable place in bio-sensing, bio-imaging, and medication administration. Modified ZnO QDs via multiple approaches, such as doping, encapsulation, core–shell formation, surface functionalization and conjugation with polymer or other compounds, are suggested to be an effective carrier of drug at the target cells. Beginning from technological challenges, this overview presents recent developments on optical tuning and utilization of ZnO QDs for cancer imaging and their therapeutic potential.

Keywords Quantum dots · ZnO · Bio-imaging

Introduction

Diseases like cancer increase with the age of the population, urbanization, and industrialization. Cancer is the second leading cause of death globally, accounting for millions of deaths [1]. Although medical science has improved tremendously in recent decades, the early stage diagnosis and cure for cancer is still limited. Globally, in recent years, 7.6 million people died of cancer and the number is expected to increase more than tenfold in the next decade. According to WHO, 11.5 million people are expected to die by 2030. In many cases, malignant tumors are detected only in the advanced stage when chemotherapeutic drugs are most likely to be detrimental to the patient. In this regard, the earlier detection via targeted and sustained imaging for cancer diagnosis can significantly improve the situation.

Despite advancements in many areas of diagnostic radiology, detection, and imaging of human cancer remains inadequate. About six relevant imaging modalities are currently available to the medical practitioners to diagnose and treat human cancer: x-ray plain film and computed tomography (CT), ultrasound (US), magnetic resonance imaging (MRI), single-photon emission computed tomography (SPECT), PET, and optical imaging. Among them, only four (CT, MRI, SPECT, and PET) are capable of three dimensional (3-D) detection of cancer anywhere in human body [2]. The 3-D imaging modalities lack sensitivity and/or resolution that preclude their ability to solve important clinical problems in cancer screening and treatment because they were not designed to image small size and small number of cancer cells [2].

The recent advancements include a handheld device for breast cancer detection and use of MRI to enhance 3-D reconstruction of optical images. Addition of newer fluorescent contrast agents are envisaged to potentially enhance sensitivity and specificity. Any accessible tissue surface

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(e.g., skin, gastrointestinal tract, and cervix) is amenable to optical imaging, and there are variety of non-contrast optical imaging techniques, including diffuse reflectance, scattering spectroscopy, multi-wavelength spectroscopy, auto-fluorescence spectroscopy, and polarization spectroscopy [2, 3]. Majority of optical methods use relatively simple instrumentation to image-reflected excitation light, or fluorescence emission light, from a surface. Tissue reflectance imaging is high resolution and fast. However, in view of multiple light scattering effects, the sensitivity is limited and the scattering loss is a serious challenge to obtain high resolution imaging of affected area [2, 3]. There is an urgent need to enhance the emission efficiency along with tunable optical characteristics of imaging agents.

A significant effort is currently underway to utilize unique properties of semiconducting nanocrystals or quantum dots (QDs) in biological imaging because optical imaging based on traditional dyes [4, 5] has serious disadvantage of cell autofluorescence in the visible spectrum [6], which leads to the following effects, including but not limited to: (a) masking of signals from labeled organic dye molecules, (b) instability of organic dye under photoirradiation resulting in short observation times, (c) sensitivity of dyes to variation in pH, and (d) narrow excitation window and broad emission spectrum with a long tail at a red wavelength [5].

QDs display a wide range of size-tunable colors that can be activated simultaneously using a single laser [7]. Thus, a single light source can be used to excite QDs with different emission wavelengths and obtain quantum effects that make crystals brilliantly fluorescent at specific wavelengths. Moreover, they are preferred over conventional organic fluorophores because their emission from visible to infrared wavelength and even into mid-infrared [8–12] can be tuned via optimization of size, composition. Additionally, near infrared (NIR) emitting QDs can be used to avoid interference from autofluorescence because cell, hemoglobin, and water have lower adsorption coefficient and scattering effects in NIR region (650–900 nm) [13]. While light is routinely used for intravital microscopy, imaging of deeper tissue (>500 μm) requires the use of NIR light [13]. Thus, semiconductor QDs are of significant interest for bioimaging and fluorescence labeling because they provide unrivaled cellular imaging.

The best available fluorophores for biological applications are CdSe encapsulated with a layer of ZnS [14, 15]. ZnS shells in CdSe/ZnS core–shell-shell nanocrystals develop almost flawlessly. The core–shell-shell nanocrystals have PL efficiency and photostability that are superior to those of CdSe/ZnS nanocrystals because of the excellent quality of the ZnS shell. The shape and luminescence polarization of the core–shell-shell nanocrystals may be engineered by the preferential development of the middle CdS shell in one crystallographic orientation [16]. There are, however, issues concerning reproducible synthesis and inorganic passivation and application to a broad range of pH. Furthermore, the potential cytotoxicity of heavy metals, Cd and Se is of serious concern. These QDs continue to be refined to achieve reproducible synthesis and inorganic passivation, by using capping strategies where organic surface ligands are replaced with a thiol group such as mercaptoacetic acid or mercaptopropionic acid [17–19]. The approach, although simple, reduces shelf-life of QDs to less than a week. Another drawback is that almost all carboxyl-terminated ligands limit dispersion to basic pH [14, 19]. Thus, identifying an effective cap from the view point of ligand-exchange efficiency remains a scientific art.

ZnO QDs: Choices and Challenges

Blood and other endogenous substances limit light penetration into tissue, and hemoglobin sometimes provides contrast that interferes with the detection, therefore, ZnO-based QDs are attractive because they are envisaged to enhance the penetration depth of light into the endogenous substance in view of being water dispersible [3, 20–22]. ZnO can slowly dissolve in both acidic (tumor micro-environment) and in strong basic conditions provided that the surface is in direct contact with solution. Furthermore, optical properties of ZnO nanomaterials can be tuned by doping with transition-metal and lanthanide ions, including Mn^{2+}, Cu^{2+}, Co^{2+}, Ni^{2+}, Ag^{+}, Pb^{2+}, Cr^{3+}, Eu^{3+}, Tb^{3+}, Sm^{3+}, and Er^{3+} [23].

There are constant efforts to develop a fundamental understanding on the physics of dopants on photoluminescence (PL) emission and the band gap, and simultaneously identify the best biocompatible dopant whose band gap can be conveniently tuned in the biological window. In most of the reports the objective of developing such nanoparticles (NPs) was accomplished by sol–gel methods. Sol–gel method is cost effective and wet chemical route which involves the development of an inorganic colloidal suspension namely 'sol' and gelation of the sol in a continuous liquid phase known as 'gel.' The obtained gel can further be converted into a three dimensional network structure. The generic method for synthesizing ZnO-based nanocrystals is depicted in Fig. 1. The sol–gel method can also be combined with green synthesis routes of QDs. Synthesis methods based on green chemistry are economical, non-toxic, and advantageous to the environment safety. In the past, green techniques that promoted environmental sustainability in the manufacturing of QDs were prioritized in the development of nanotechnology [24]. These processes use moderate reaction conditions and nontoxic precursors. Researchers and scientists have created QDs using many organisms, including plants, algae, bacteria, yeast, and fungus. In this overview, prime focus remains on sol–gel processed QDs.

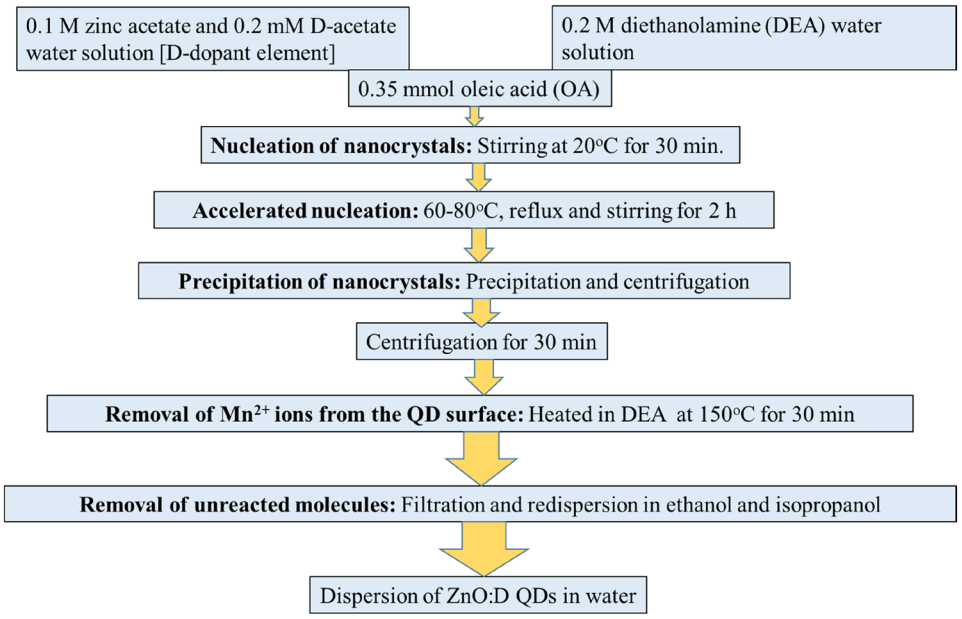

Fig. 1 Flowchart showing the route (sol-gel) for the preparation of doped (Mn) ZnO nanoparticles and quantum dots

In the case of Ca-doped ZnO thin film, [25] the blue-shift in the optical band gap in nanocrystalline $Zn_{1-x}Ca_xO$ was observed to increase from 3.38 to 3.81 eV with the increase in Ca concentration from $x = 0$ to $x = 0.15$ for the first time. This reflected a 12.72% increase in band gap of ZnO. In another instance, Ni increased the lattice parameters, impacting band edges, and consequently changed the band gap [26]. Intriguingly, the dislocation density and band gap followed a similar trend, which led us to conclude that dislocations can be controlled by doping, and the band gap tuned. A more recent study [27] concerning doping of ZnO with Sr, suggested an increase of band gap from 3.281 to 3.30 eV. The change in the absorption energy levels shifted the absorption edge to higher energies (blue shift) resulting in band gap broadening. The UV emission peak corresponding to the band gap also witnessed a blue-shift. A similar effect was observed with Ca [28] and Mn. The experimental studies were corroborated with theoretical calculations using effective mass model, which is based on quantum confinement effects [29]. Hence, it is plausible to conclude that the band gap in doped-ZnO systems is governed by three major factors notably dislocations, sp-d exchange interaction, and carrier concentration. The aforementioned observations and understanding can help us to select a suitable dopant for the ZnO matrix to achieve desired optical features.

The enhancement of PL emission intensity is another important aspect which must be monitored for the material to be useful for bioimaging and biosensing. Undoped and Ag-doped ZnO nanocrystalline thin films were deposited using the sol–gel spin-coating method [30]. The emission intensity of UV peak was enhanced seven times by Ag doping in ZnO thin film. Because of the increase of Ag acceptors, the free holes concentration increased which leads to a stronger free-to-bound PL resulting in UV emission intensity enhancement. These observations conceptually confirm that PL emission intensity and wavelength shift can both be obtained using an appropriate dopant. The increase of emission intensity is important where weak signal strength constitutes a major challenge, particularly in the physiological environment. Based on the aforementioned studies with different dopants, ZnO with a band gap of 3.1 eV at room temperature provides a unique opportunity to tune the photoluminescence from green-yellow to orange-red (NIR) emission range via size and doping effects.

Silica being one of the abundant biominerals found in nature and inspired by the complexity of naturally evolved shells, such as diatoms, silica and silicate materials have been exploited in bioaugmentation as protective coatings for biological systems. The PL intensity of ZnO-based QDs was enhanced by immobilizing them on thiol-functionalized silica nanospheres of ~ 100–120 nm followed by encapsulation with a very thin silica shell to obtain higher physical stability [31]. Hence, the embedding of QDs on silica nanospheres is beneficial for amplifying the PL intensity, biocompatibility, and chemical stability. Thus, the unique optical properties (e.g., photoluminescence in the near-infrared (NIR) region and narrow bandgap) clearly suggest that ZnO-based materials are excellent candidates for biosensing and bioimaging. In addition, ZnO-based materials are easy to be biofunctionalized and exhibit low cytotoxicity, making them ideal candidates for interfacing with biological systems.

However, the synthesis of luminescent ZnO-based NPs with good solubility in water is a challenge because the visible fluorescence of ZnO arises mainly from its defects, which are destroyed by water molecules. But, the chemically active surface of ZnO is rich in –OH group, an advantage

which can be exploited by functionalizing the surface with oleic acid (OA) together with diethanolamine (DEA) [32–34].

A second challenge concerns the processing of chemically pure and compositionally well-defined ZnO at room temperature, particularly from the perspective of bio-applications. Several methods like hydrothermal and microwave assisted synthesis have been attempted, but controlling the purity, particle size and morphology, surface defects and optical properties remain a challenge.

ZnO QDs in Biosensing, Cancer Imaging and Therapy

Luminescent and semiconductor behavior of ZnO QDs and anti-tumor characteristic of its chief constituent Zn make ZnO one of the most investigated materials for its applications in sensing, imaging, and synergistic therapy of cancer. Sol–gel synthesized ZnO nanoprobes as a platform for sensitive bioassays indicate that they can be used as an alternative fluoroprobe for cancer cell targeting and sensing applications [35]. Even though sensing properties of ZnO QDs are wider and applied to many other domains, here a glimpse over their sensing behavior in biological arena is presented along with the potential as a biomarker for cancer cells.

Biosensing

According to the analyte employed, ZnO-based biosensors can be divided into multiple categories such as immunosensors, nucleic acid biosensors, and aptamer-based biosensors [36]. In addition, ZnO nanostructures can be used to detect biomolecules like glucose, cholesterol, urea, and uric acid. There are continuous efforts to spark more interest in advancing biosensor research for medical diagnosis [37]. Here, a discussion on applications of ZnO QDs as suitable biosensors using fluorescence and photoelectrochemical (PEC) process is presented considering one specific study for each. In a study, an elementary precipitation method was used to synthesize ZnO QDs. ZnO QDs guiding layer facilitated immobilization of uricase and showed high sensitivity, and reproducibility. A three electrode based electrochemical biosensor was successfully fabricated for uric acid analysis. Biosensor showed a wide linear range of detection 1–10 mM, which covers the physiological range present in urine samples [38]. A recent study shows that ZnO QDs homogenously dispersed in a solution act as fluorescent probe for the detection of cysteine in different solutions such as bovine serum albumin and tap water. The developed fluorescent probe exhibited a highly selective and sensitive response to the detection of cysteine. Also, the proposed fluorescent probe demonstrated a larger Stokes shift value (236 nm) [39]. The PEC process is a promising low-cost method for converting chemical energy into electrical signal under light irradiation and applied potential. PEC biosensing has received a lot of attention due to its ability to detect biomolecules via photocurrents generated when biomolecules are oxidized [40]. Interestingly, the coated graphene oxide nanosheets on the surface of Cu-doped ZnO QDs could expedite the charge transfer and ameliorate the photocorrosion. The dopant copper into ZnO QDs could enhance the absorption of visible light by tuning the band gap of ZnO QDs, thereby increasing the photocurrent under visible irradiation. Under optimal conditions, the developed PEC biosensing platform exhibited good analytical performance with a linear range of 50–10,000 fM thrombin and a limit of detection of 29 fM. Such strategy can offer a new horizon in developing bridge-connected graphene-coated ZnO nanomaterials and novel signal amplification mechanism for the development of PEC biosensors [41].

Identifying the cancer at the early stage is also one of the major challenges. Current diagnostic approaches are not sensitive enough to recognize cancer biomarkers at primary stages of the disease; therefore, more practical, efficient, and cheaper techniques are urgently required [42–44].

Due to their distinct physicochemical characteristics, ZnO QDs are among the most suitable nanomaterials for usage as sensitive tags for identifying different forms of cancer. With exceptional accuracy, QDs-based probes that are coupled with the appropriate targeted molecules, interact with biological systems to identify chemical changes in biology [45, 46]. For precise des-carboxy-prothrombin (DCP) evaluation in the detection of liver cancer, researchers have created a screen-printed DCP immunosensor employing ZnO QDs [45].

Choline and its associated compounds are said to be elevated at greater levels in breast cancer cases. Therefore, it may be quite interesting to find choline in cancer cells utilizing a nano-interfaced electrochemical biosensor. Recently, a functional electrode for electrochemical detection made of glassy carbon and a ZnO QDs interface was discovered [47].

By boosting the loading of active catalysts and enabling chemicals to diffuse more quickly, nanopore architectures enhance analytical performance [48]. The most stable material is thought to be nano-porous ZnO because of its cross-linked structure and resistance to biodegradation [49]. ZnO nanofibers may also have their conductivity, distribution, form, and size altered for their use in creating biosensors by changing the composition of the components used in production. Electro-spun mesoporous ZnO nanofibers were created for the detection of breast cancer, and anti-epidermal growth factor was conjugated as a biomarker [42].

ZnO-nanosheets made using the sol–gel method have the proven ability to detect malignancies. A yellow-orange light was produced by the cells after being exposed to

ZnO-nanosheets for 20 min prior to imaging, showing that the ZnO nanostructures had effectively accessed the cells' nanofibers for use in creating biosensors [50].

Cancer Imaging

Ethanol-dispersed ZnO QD can display in vitro bioimaging potential. A simple and inexpensive synthesis route, carried out under normal conditions (room temperature, atmospheric pressure, neutral pH) of ZnO QD was based on the protonation of amines with water. Such QDs (average diameter 4.5 nm) showed a wide and strong UV emission peak centered at 385 nm under UV excitation wavelength of 325 nm. It was observed that when the surface of the ZnO nanoclusters was covered with amine/PVP, forming a ZnO @ amine/PVP core shell, an unexpected blue fluorescent signal was generated within the environment of bacteria and cancer cells. Such observation raised the possibility that ZnO QDs can be used for fluorescence bioimaging [51]. Capping of QDs with suitable agent is another promising scheme which can make QDs suitable for bioimaging. It was noticed that other oxides such as TiO_2 and SiO_2 were effective in shifting the emission peak to the visible range with high intensity. In a study performed with optimum capping thickness 0.5 nm on ZnO–TiO_2 QDs showed good bio-imaging capability on plant cells. Quantum yields of the pure ZnO and TiO_2 capped ZnO were measured and compared to commercial fluorescence materials. The capped QDs revealed huge imaging potential [52].

The anticancer, antibacterial, antioxidant, antidiabetic, and anti-inflammatory properties of ZnO NPs, as well as drug transport and bioimaging applications, have sparked interest in their processing and biological applications. In addition, ZnO NPs have been found to cause cytotoxicity in a range of cancer cells. Zinc (Zn^{2+}), a component of ZnO, is commonly acknowledged as a necessary micronutrient for humans and is thus safe to use. Fluorescence imaging, on the other hand, among molecular imaging techniques, has the advantages of low cost, great sensitivity, and excellent spatial resolution. ZnO QDs have good photodynamic characteristics and could be useful in photoluminescence imaging. Because of its high biocompatibility, ZnO QDs are commonly utilized in bioimaging and medication administration. An illustration given in Fig. 2, shows the biological applications of ZnO QDs, particularly in three major domains. Many scientists are working to increase ZnO QDs' stability and water solubility [53].

ZnO QDs have large exciton binding energy. High-efficiency stimulated emission fluorescence can be easily achieved at room temperature, and different particle sizes can achieve different fluorescent colors [54]. They are good candidates for imaging agent due to their excellent photoluminescence properties and low toxicity; however, studies have shown that ZnO QDs degrade rapidly in biological acid medium. To overcome this limitation of biological application, generally two strategies are adopted. In the first one, ZnO-based QDs are incorporated in lipidic nanocapsules aiming to protect the QDs from biological degradation. In the second one, core/shell conjugated to ZnO QDs are used that exhibit pronounced near-infrared fluorescence and good colloidal stability in different pH ranges [55].

Aqueous stable luminescent ZnO QDs conjugated to folic acid (FA) can target some specific cancer cells with overexpressed FA receptors on the membranes and thus differentiate the MCF-7 cancer cells from the normal 293 T cells. The nanoparticle uptaking experiments using confocal laser microscopy confirm the specificity of ZnO-FA QDs toward the FA-receptor overexpressed cancer cells, which have potential for diagnosing cancers in vitro [56].

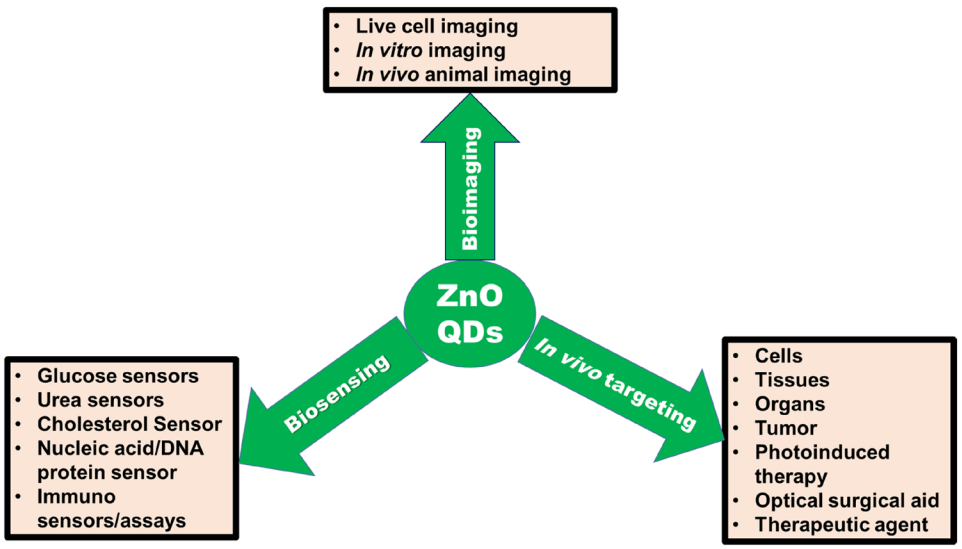

Fig. 2 Potential applications of ZnO QDs in major three bio-related areas; biosensing, bioimaging, and in vivo targeting

Cancer Therapy

In addition to bioimaging, ZnO QDs have been used as a platform for intracellular delivery of an anticancer medication that is targeted and pH responsive. As a cheap nanomaterial with low toxicity, ZnO QDs have shown great potential for application in bioimaging [57–59]. Because the unprotected ZnO QDs are decomposed completely at pH 5 in aqueous solution, these materials can be employed as nanocarriers for drug delivery. In most of the cases, QDs are modified to serve efficiently as drug carrier. Major five strategies are noticed in literature; doping, encapsulation, core–shell formation, surface functionalization and conjugation with polymer or other compounds. Some of the practical and effective modification strategies which could demonstrate high potential as drug carrier and in vivo targeting are discussed below.

By conjugating FA to the surface of ZnO–NH_2 QDs via an amidation process, the cancer-targeting property is achieved. Doxorubicin (DOX), a popular medicine for cancer treatment, is then successfully loaded onto the FA functionalized ZnO QDs, taking advantage of the drug's strong proclivity to forming metal complexes. A drug release profile, confocal microscopy, and a cell-cytotoxicity assay all have confirmed that drug-loaded ZnO-FA QDs are stable at physiological pH but quickly disintegrate in the mildly acidic intracellular environment of cancer cells. In comparison to typical drug nanovectors, ZnO-FA QDs have high therapeutic action once they reach their target location; thus, coupled DOX and ZnO QDs may be more effective than either alone. As a result, this method provides a useful ZnO QDs-based nanovector that may be used to target, diagnose, and treat cancer cells all at the same time [60].The cytotoxicity of ZnO QDs in HeLa cervical cancer cells reveals a dose-dependent increase in reactive oxygen species and a decrease in mitochondria membrane potential [61].

The ultrasmall size (≈ 3 nm) of acid-decomposable, luminous aminated ZnO QDs demonstrate their potential as nanocarriers. The addition of dicarboxyl-terminated poly(ethylene glycol) (PEG) to NH_2–ZnO QDs stabilizes them in physiological fluid. Furthermore, hyaluronic acid (HA) is coupled to ZnO QDs to allow cancer cells to specifically bind to the overexpressed glycoprotein CD44. Doxorubicin (DOX) molecules are successfully loaded onto PEG functionalized ZnO QDs via covalent contacts and the development of a metal–DOX complex. After absorption by cancer cells, the pH-sensitive ZnO QDs dissolved to Zn^{2+} in acidic endosomes/lysosomes, triggering dissociation of the metal–drug complex and regulated DOX release. As a result of combining the anticancer effects of Zn^{2+} with DOX, a synergistic therapy can be achieved [62]. Figure 3 shows the schematic diagram of the ZnO QD-based pH-responsive drug delivery system.

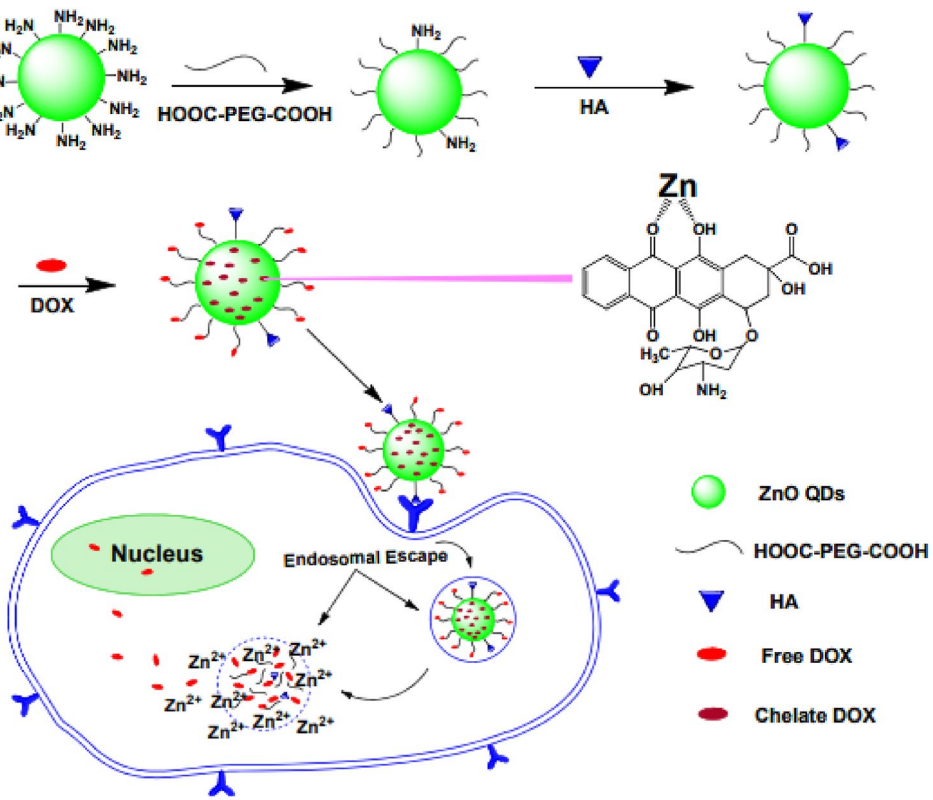

Fig. 3 Schematic diagram of the ZnO QD-based pH-responsive drug delivery system. PEG and HA combine with the ZnO QDs; Then, DOX is loaded to HA–ZnO–PEG and transported to the tumor cells. The pH-sensitive ZnO QDs are dissolved to Zn^{2+} in acidic endosome or lysosome, which trigger the dissociation of the metal–drug complex and a controlled DOX release. Adopted with permission from Ref. [62]

Rare earth elements due to their unique emission capability can be a help in the diagnosis and treatment of cancer cells [63]. A multifunctional ZnO-Gd-DOX nanoplatform was studied on mice tumors in vivo and could demonstrate several advantages such as complete biodegradability in the acidic environment of tumors and their excellent pH responsiveness ensuring the specificity of drug delivery to cancer cells, stability in aqueous solution due to the polymer shells, excess carboxyl groups coordinated with many Gd^{3+} ions, which render an outstanding relaxivity for MRI, combination of highly luminescent ZnO QDs and DOX benefiting the imaging in vivo, better therapeutic efficacy than DOX and no detectable toxic side effects to mice etc. [64].

A pH-responsive nano-drug delivery system based on ZnO QDs was developed using zwitterionic poly(carboxybetaine methacrylate) (PCBMA) and poly(2-(dimethylamino) ethyl methacrylate) (PDMAEMA) for controlled release of drugs [65]. These compounds were introduced to modify ZnO QDs, which had enhanced water stability, blood circulation time, and endocytosis. ZnO@P(CBMA-co-DMAEMA) loaded with DOX could achieve lysosomal acid degradation and release of DOX after endocytosis by tumor cells, resulting in synergistic treatment of cancer. Here, anticancer effect of both Zn^{2+} as well as DOX was seen to be pivotal. [65].

Blue-light emitting ZnO QDs combined with biodegradable chitosan (N-acetylglucosamine) have revealed efficacy for tumor-targeted drug delivery. Chitosan enhanced the stability of the QDs because of the hydrophilicity and its cationic charge and a long-term fluorescence stability could be noticed for the design of drug release carrier [66].

Hollow mesoporous silica spheres (HMSS) having a hierarchical mesoporous structure can offer covalent attachment of ZnO QDs to themselves. Outer surface of HMSS serves as gate-protector. The controlled release of the drug from the ZnO-gated HMSS delivery system could be realized by the dissolution of ZnO QDs upon a decrease in pH and cleavage of the di-sulfide bonds, which indicated that the pH- and redox-responsive controlled release of the drugs could be synergistically stimulated by tumor cells with weakly acidic environments and high-expressed glutathione [67].

Adipic dihydrazide and heparin attached to ZnO QDs surface, and the ZnO-adipic dihydrazide-heparin nanocomplex was used as a drug delivery system to deliver paclitaxel for chemotherapy [68]. Polyacrylamide, which is nontoxic to animals was used as a protecting shell for the ZnO QDs and DOX attached to it could show better and effective results on human glioblastoma cells (U251), the most common cells in malignancies of the human brain [54]. The ZnO@polymer QDs are very stable in aqueous solution at pH 7.0, but rapidly decompose at pH 6.0, thus ensuring the safety of healthy tissues. Both ZnO and Polyacrylamide shell are biodegradable and thus safe for cells. ZnO@polymer is in general nontoxic to U251 cells at low concentrations, but it showed high cytotoxicity when DOX was loaded to it. Hence, ZnO@ Polyacrylamide –DOX in an appropriate concentration and composition can be used to realize healing efficiency and avoid systemic toxicity simultaneously. [69].

Core–shell structured multifunctional nanocarriers of ZnO QDs-conjugated gold nanoparticles as core and amphiphilic hyperbranched block copolymer as shell indicated a great potential as tumor-targeted drug delivery system and also assisted in the treatment of cancer [70].

Conclusion

The urgent and global need for cancer treatment has led to the extensive exploration of its early diagnosis. The development of QD-based assays for cancer detection has received a lot of attention. The semiconducting QDs with superior optical features can serve the purpose efficiently. The issues like cytotoxicity can also be overcome by suitable choice of the QDs. The most sought after choice is ZnO. However, water solubility, stability of luminous intensity in physiological environment etc. are still major challenges. Despite these challenges, ZnO QDs are able to demonstrate substantial efficacy in bioimaging, biosensing, and targeted drug delivery. Numerous developments such as doping, encapsulation, core–shell formation, surface functionalization and conjugation with polymer or other compounds are taking place day by day to overcome the challenges of effective and sustainable treatment of cancer.

However, selectivity and sensitivity enhancements are wholly new capabilities that could only show a minor increase. Furthermore, by enabling early detection, advanced initiatives in this area will increase the survival rate of cancer patients. There are still issues that need to be resolved more successfully in near future, such as the reliability of quantitative cancer detection, the large-scale production of nanoprobes under highly optimized conditions, the development of ZnO QD-based devices with high sensitivity that are user-friendly and economical, and potential toxicity of QDs brought on by their systemic administration. More efforts toward improving the drug loading and detaching strategies are necessarily required.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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