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Review Article

Quantum Dots as Nanoreporters in Biomedicines: A View Point

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Abstract

Quantum dots (QDs) represent a group of semiconductor nanomaterials with fascinating optical and fluorescence properties. Their unique optical and electronic properties have resulted in innumerable modes of synthesis, and subsequently, wide-ranging applications. However, disadvantage of QDs is its aqueous insolubility that limits its application when it comes to their use in biomedicines, like in vivo and in vitro imaging and sensing. Therefore, ligand exchange reactions and surface coatings are employed to circumvent this problem. Additionally, these protocols minimize the risk of toxicity normally associated with QDs. Furthermore, the use of QDs in bioimaging holds significant advantages over the conventionally used fluorescent dyes with regard to photostability, fluorescence lifetime and tunable emission behavior. Additionally, there has been significant advancement in the use of biorecognition of molecules that are conjugated to QDs for enhancing specificity. In this review, we have analyzed and discussed the advancements and the current state-of-art of QDs in biology and medicine.

INTRODUCTION

Wide ranging development in nanotechnology has resulted in growth of their applications in the area of biomedical science, specifically in imaging, disease diagnosis, and therapeutics and drug delivery. The use of gold nanoparticles (GNP) and quantum dots (QDs) has provided new insights into the mechanism of drug delivery pathways, and understanding the progression of diseases. QDs have been used in bioimaging, tumor detection and monitoring drug release and their distribution mechanisms. These nanocrystals were first discovered by Ekimov and Onushchenko in 1982 [1], and these represent a class of nanomaterials with an average size in the range of 2 -10 nm, where the size of particles is related to their energy levels, such that with increase in band gap energy there is decrease in particle size [2]. In QDs the motions of electrons, holes and excitons are limited which allows generation of a quasi-zero system. There is an increase in band gap energy of QDs compared to their bulk counterparts which is because of the phenomenon of quantization. Semiconductor QDs possess interesting fluorescence properties, associated with tunable emission, high photostability and long fluorescence lifetime [2-4]. QDs have fund wide-range of uses, however the use of QDs in bioimaging dates back to 1998 [5], and since then, are being used as highly fluorescent probes in diagnosis, cell and tissue imaging, and so on. QDs have been reported as excellent probes in bioimaging of lymph nodes [5-9], tumor detection [10], and as specific reporters [11,12].

QDs present superior advantages over the traditionally used fluorescent dyes [13-15], that has made them emerge as interesting probes for a wide variety of biomedical applications. Fluorescent dyes have the drawbacks of instability, narrow emission band, susceptibility to environmental conditions as pH. Additionally, auto-fluorescence from cells interferes with the fluorescence of dye molecules. These limitations are overcome by QDs as they present the advantages of high quantum yield, stability, tunable optical properties with broad excitation and ease of functionalization. These properties of QDs provide advantages in their use as bioimaging probes. The high quantum yield allows intensity-based imaging while multiple color imaging is possible due to their narrow emission spectra.

In this report, we have analyzed and presented a brief review on the application of QDs as probes in biological imaging and sensing studies. We have discussed the current state-of-art of use of QDs in biology and have presented the future prospects in the area. There are several recent studies that have investigated the use of QDs in biology and medicines by focusing on the synthesis of Cd-free nontoxic QDs with improved surface properties and aqueous solubility. Therefore, a comprehensive, but compact overview is called for.

DISCUSSION

The stability and subsequent application of QDs depends on a number of factors such as size, charge, surface coating material

and the functional groups [16]. These are also the determining factors that affect the cytotoxicity of nanomaterials. The use of QDs in bioimaging has two major requirements non toxicity and aqueous solubility. To circumvent this, two major approaches are performed namely, synthesis of core-shell QDs [17], and ligand exchange reaction [18]. Additionally, QDs with an emission wavelength in the range of 700 - 900 nm are basically preferred in bioimaging studies as they have a maximum penetration depth in tissues and the interference caused by autofluorescence (400-600 nm) is mostly eliminated [19,20]. There have been a lot of studies on the use of QDs in *in vivo* and *in vitro* imaging analysis.

In a study conducted by Liu et al., QDs conjugated with antibodies were used for detection of Hodgkin's and Reed-Sternberg (HRS) cells from T and B lymphocytes [21]. Fluorescent super paramagnetic QDs obtained by conjugating amine-terminated QDs with Fe_3O_4 were analyzed for their in vivo and in vitro imaging potential [22]. Silicon QDs were investigated as probes for bioimaging analysis because of their wide emission range and resistivity to photobleaching [23]. Additionally, their nontoxicity and eco-friendly nature makes them good candidates for use in biomedical applications. Reports have suggested that compared to Cd based QDs, Si-QDs are around 10-times non-toxic [24]. Even the dergradation product of Si QDs which is silicic acid is removed from the body through urine [25], however their aqueous solubility limits their applications when it comes to biomedicines. CdTe functionalized with mercaptopropionic acid (3-MPA) were used as reporters for labeling S. typhimurium cells [26], similarly, HeLa cell lines were labeled with CdSe/ZnS QDs and the studies suggested the storage of QDs in cellular vesicles [27]. In yet another study, QDs functionalized with polyethylene glycol (PEG) and grafted with polyethylenimine were reported to effectively penetrate cell membrane leading to subsequent disruption of cell organelles [28]. QDs conjugated with transferrin protein were observed to enter cancer cells via endocytosis and showed fluorescence suggesting their potential use as labels for intracellular detection [29,30].

In vivo imaging using QDs was first performed using phospholipid micelle coated QDs [31], which led to the successful development of several functionalized QDs for imaging studies. Multi-colored QD based imaging analysis was performed in mice model. In the study, QDs were initially encapsulated with an ABC triblock copolymer and conjugated with tumor targeting ligand molecule. The QDs have very high sensitivity which was comparable to green fluorescent proteins, and this allowed both passive and active tumor imaging. This modified QD had the advantages of permeability, retention in the tumor sites with cancer recognizing antibody [32]. In order to allow deep penetration into the tissues, cadmium free QDs (InAs/InP/ZnSe) functionalized with MPA were synthesized. These QDs showed an emission at 800 nm and gave interesting results both in *in vivo* and *in vitro* imaging analysis [33]. In yet another study, Ag_2Se QDs with fluorescence in NIR region were used for *in vivo* studies by allowing them to penetrate to the abdominal cavity of model mouse organisms [34].

In addition to imaging, QDs have also found significant use in detection of biomarkers like peptides and oligonucleotides. QDs have been used for successful detection of several cancer biomarkers. For example, multi-coloured QDs were used as sensors for detection of α-fetoprotein and carcinoembryonic antigens (human tumor) biomarkers [35]. Similarly, DNA sequences were detected by embedding multi-colored QDs into polymeric microbeads. The detection was based on DNA based hybridization between the oligonucleotide probe and the QD-embedded microbead [36]. In another DNA detection approach, Ag nanoclusters and graphene oxide were used as reporter, and quencher respectively. The method was based on the observation of high fluorescence intensity when a double helix was formed while ssDNA-Ag nanocluster complex generated very low background fluorescence intensity [37].

The high surface to volume ratio of QDs in addition with the ease of surface modulation provides excellent advantages for surface engineering by functionalizing QD surface with a variety of ligand, antibodies and biomolecules. As discussed above, there have been significant advancements in the use of QDs for bioimaging assay. The results suggest the ease of penetration and labeling efficiency of QDs, hence approaches should focus towards site-specific drug delivery by loading the QDs with drug molecules and observing their release and degradation in cells. One such approach involved linking QDs with prostate specific membrane antigen (PSMA) targeted aptamers and the aptamers were loaded with doxorubicin (Dox) in the ratio of 1:1[38]. They observed the drug loading capability by keeping a track of QDs fluorescence emission and absorption of Dox. They observed a slow release of Dox in PSMA expressing prostate cancer cell lines and concluded that number of aptamer molecules bound to QDs was a major determining factor in release of drug within the cell. Compared to conventional drug delivery methods, QDs as drug carrier has the advantage of being miniature in size that allows easy endocytosis of QDs into the cell, and their eventual accumulation. However, the small size limits the amount of drug that can be loaded, and therefore future work should focus on the delivery of more potent drugs with higher efficiency. The use of non-toxic coating with improved biodistribution and use of ligands with enhanced specificity is called for.

CONCLUSION

A thorough investigation has suggested that QDs have found significant use as in vivo and in vitro imaging probes. However, cytotoxicity associated with QDs, more specifically cadmium containing QDs because of their release of free metal ions into the solution, has limited their applicability. Therefore, the future prospects should focus on minimizing the toxicity of these particles as well as to understand the biodistribution, and the effect of heavy metal ions on human metabolism. Though several studies have made use of functionalization and surface coating of QDs to limit their toxicity, still the release of heavy metal ions into the body remains a major concern. The focus should therefore be on ensuring the safety of QDs prior to their use in biological applications with the simultaneous synthesis of non-toxic cadmium-free nanocrystals. We thus anticipate that the development of non-toxic semiconductor QDs with improved properties, and functionality, would be the promising candidates for biological applications with wide versatility.

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