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Biomedical and biological applications of quantum dots

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Abstract

Quantum dots (QDs) as colloidal nanocrystalline semiconductors have exceptional photophysical properties, due to their quantum confinement effects. Depending on their sizes and chemical compositions, QDs emit different wavelengths over a broad range of the light spectrum, from visible to infrared. QDs are typically extensively used for optical applications due to their high extinction coefficient. This article reviews biomedical applications of QDs, especially the application of QDs in cell targeting, delivery, diagnostics, cancer therapy, and imaging for cancer research.

Keywords: biomedical applications, cancer therapy, cell targeting, diagnostics, quantum dots

Introduction

Semiconductor nanocrystals composed of groups II–VI or III–V elements, known as quantum dots (QDs), are too small to exhibit quantum mechanical properties. QDs of elements in Groups III–V may supply a more stable alternative to QDs of elements in groups II–VI, due to the presence of a covalent bond, rather than an ionic bond, and have been reported to have lower cytotoxicity (Bharali et al. 2005). Alexei Ekimov discovered the QD in a glass matrix, and it was discovered in colloidal solutions by Louis E. Brus. The word "quantum dot" was coined by Mark Reed (Tokumasu et al. 2005). In contrast to quantum dots of type-I, which simultaneously entrap electrons and holes, blank dots of type-II exert a pull on the charge transfer of one type and repel the other (Jacak et al. 1998). QDs are mostly considered for optical applications, because of their high extinction coefficient (Leatherdale et al. 2002). The ability to tune the size of QDs is beneficial for numerous applications, such as larger quantum dots that have a larger spectrum-shift towards red compared to the smaller dots, and reveal less marked quantum properties. On the other hand, the smaller particles offer the benefit of extra subtle quantum effects. Until recently, diverse kinds of organic dyes were being used for biological analysis. To this end, QDs have quickly filled in the role, being found to be better than traditional organic dyes on a number of counts, one of the highest benefits immediately evident being their brightness as well as their stability (Michalet et al. 2005). The surface modification of QDs with aptamers, antibodies, peptides, or undersized molecules that combine with antigens present on the target cells or tissues has resulted in the improvement of sensitive and specific targeted imaging and diagnostic modalities for in vitro and in vivo applications (Medintz et al. 2003, Chu et al. 2006, Young and Rozengurt 2006). Current research studies have shown that these nanomaterials have magnitudes that are two-photon action cross sections larger than those of the usual fluorescent probes currently in use, plus more for deep tissue imaging (Larson et al. 2003).

Emission, high levels of brightness, and photo stability. QDs can be used in vitro and in vivo for multiple color imaging and targeted drug delivery. Biomedical applications necessitate high-quality water-soluble QDs; although they could be made directly in water, they mostly have thin accessible size ranges and wide size distribution (Wang et al. 2004, Zhuang et al. 2003, Kho et al. 2000, Winter et al. 2001). Therefore, the challenge lies in creating high-quality hydrophobic QDs that are soluble in water, and furthermore, QDs that are active in bioconjugate reactions. To solve this problem, the QDs synthesized in organic solvents usually have hydrophobic surface ligands, for instance, trioctylphosphine oxide, trioctylphosphine (Murray et al. 1993, Peng et al. 1998, Yu et al. 2003), and tetradecylphosphonic acid (Yu et al. 2003, Peng et al. 2000, Peng and Peng 2001). These hydrophobic ligands could be replaced by some water-soluble bifunctional molecules in which one side connects to the surface atoms of the QDs, and the other side is hydrophilic and may also be reactive to biomolecules (Figure 2) (Aldana et al. 2001, Chan and Nie 1998, Wuister et al. 2003).

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The photophysical properties of QDs, such as brightness, spectral range, long lifetimes, and their tendency to function as single-molecule probes may give good reason for the development of novel detectors that would have the temporal resolution and sensitivity of avalanche photodiodes and the 2D spatial resolution of cameras, for wide-field in vivo studies of protein dynamics and trafficking (Mokari et al. 2004) (Figure 1).

Metabolism and toxicity

QDs are versatile new nanoparticles for in vivo biomedical application. It is important to characterize their activities in vivo, rather than rely on ex vivo measurements and theoretical considerations alone (Choi et al. 2009). One obstacle to the in vivo study of QDs is the nonspecific uptake by the reticuloendothelial system (RES) including the liver, spleen, and lymph system. Particle size, surface coating and PEGgylation influence the biodistribution of QDs. The in vivo distribution and metabolism of QDs have been studied in some research studies, which have shown that QDs are generally localized in liver, kidney, spleen, and lung (Choi et al. 2007, Inoue et al. 2007, Karabanovas et al. 2008, Liu et al. 2007, Hardman 2006). However, has been no universal conclusion about the pathway of QD clearance and its influencing factors. All engineered QDs cannot be considered to be of the same group of materials. The absorption, metabolism, distribution, excretion, and toxicity of QDs depend on manifold factors ensuing from both inherent physicochemical properties and environmental conditions; the size, charge, concentration, bioactivity of the outer coating, oxidative, photolytic, and mechanical constancy of QDs have each been identified as determining parameters in QD toxicity. Even though they propose potentially significant societal profits, for example in drug targeting and in vivo biomedical imaging, QDs may also pose risks to human health and the environment under certain situations (Mishra et al. 2012).

Epitaxy

The controlled growth of a single crystalline material on top of a substrate is called epitaxy, which is a very essential process in semiconductor technology (Ben-Ari 2003). QDs are really formed when very slim semiconductor films buckle due to the stress of having a lattice structure slightly different in size from those on which the films are grown. Self-assembled dots are then used to make quantum dot lasers (Derfus et al. 2004).

Application

When QDs were first created in the early 1980s, researchers forecasted their use in optics, electronics, and computing. Although the primary sensible applications of these small bits of semiconductor may really occur in biology and medicine (Qi and Gao 2008), the potential applications of QDs in biology and medicine were limited due to the toxic effects of semiconductor QDs, which have received enormous attention over the past few years (Zhang et al. 2011).

Intended for biological applications, QDs must be linked to biomolecules without changing the biological activity of the conjugated structure. A type of successful conjugation technique has been developed, including covalent and noncovalent attachment methodologies. Particular conjugation methodologies include direct adsorption on the surface of the QD, the use of inert polymer coatings, or biotin-streptavidin linkages. Present biomedical applications of QDs are paying attention to molecular imaging and sensing due to the above-mentioned optical properties. The structural properties of QDs are maybe as important as the optical properties, as it has been realized in research on drug delivery (Zhang et al. 2011, Gregor 2010). In addition, with the development of new techniques and detection methods, QDs are shown to have applications in wider fields. Zhang et al. successfully introduced Kelvin force microscopy (KFM) as a method to examine the binding of QDs with DNA, both in vitro and in vivo (Gregor 2010) (Figure 3).

Biological imaging

The purpose of molecular imaging is to create image contrast due to the molecular difference in diverse tissues and organs. It shows the fluorescence images from Vero cells with the inclusion of silicon quantum dots transfected into the cytosol. The fluorescence illuminating the cells comes from direct band gap emission from the silicon quantum dots in Vero cells, illustrating the use of hydrophilic silicon QDs as biological fluorescence imaging agents (Weng et al. 2008). QDs are extensively used as in vivo imaging agents (Smith et al. 2008, Choi et al. 2010, Papagiannaros et al. 2010, Han et al. 2001). In the treatment of cancer, a particular antibody coupled to near-IR QDs with a polymer coating is a very popular QD agent for tumor-targeted imaging (Smith et al. 2008). Quantum dots have also been extensively used as in vitro imaging agents. By reducing the quantity of Cd released in the region of cells, scientists have been trying to create in vitro and in vivo testing methods for imaging nanoscale and microscale structures. The high resolution within the nanometer scale demonstrates behavior that is not beneficial for imaging DNA behavior for both biological engineering feedback and biological and chemical observation and analysis. The ability to control the emission spectra by changing the size of the QDs allows researchers to code many diverse targets by color (Gerion et al. 2001, Li et al. 2009, Hyun et al. 2007).

Early studies of in vitro imaging used QDs to label cells. For instance, PbS and PbSe, capped with carboxylic groups, had been achieved in aqueous solution by replacing the ligands of label cells (Gac et al. 2006). It has been discovered that the cells can amass QDs in vesicles through endo-

Size (nm)	Emission peak (nm)	Color
2.2	495	Blue
2.9	550	Green
3.1	576	Yellow
4.1	595	Orange
4.4	611	Orange
4.8	644	Red
7.3	655	Dark Red

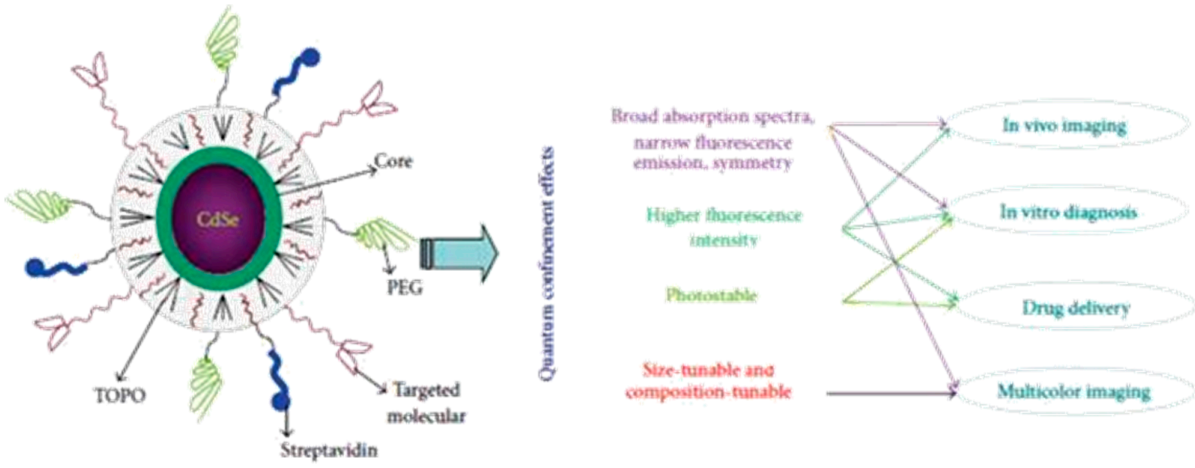

Figure 1. *Properties of QDs*. QDs are characterized by broad absorption spectra, are composition-tunable, size- tunable, and show slight fluorescence.

cytosis after washing away the overload QDs. Additionally, scientists have also verified the potential application of QDs in cell tracking by using avidin-conjugated QDs to tag cells (Tilley 2008). Silicon nanoparticles can be synthesized with a controlled size, in micelles and with surfaces that are defined from reactions with C = C compounds. The particles emit light in the blue region of the visible spectrum and are suitable as fluorescent markers in cell imaging. Additional research in the field of nanosized silicon is required, for both the design of synthetic protocols and to gain an improved understanding of the fundamental physics involved (Contag and Bachmann 2002). Self-illuminating quantum dots (QDBRET conjugates) are a group of new QDs that do not require external excitation light to fluoresce. Instead, energy comes from a bioluminescent protein through non-radiative energy transfer from the nearest bioluminescent proteins. Bioluminescence resonance energy transfer (BRET) is similar to FRET (Fluorescence Resonance Energy Transfer), except that the energy comes from a chemical reaction catalyzed by the donor enzyme rather than from absorption of excitation photons. Compared to fluorescence imaging, bioluminescence has tremendously high sensitivity for in vivo imaging purposes (Xing et al. 2008) (Figure 4).

Gene technology

Gene therapy is a marvelous method to complement a deficient gene function. Even if there has been some success with the delivery of particular genes using diverse methods, such as the use of liposomes and viral vectors, most of these methods have a limited yield and also carry a risk of oncogenesis (Chen et al. 2006). The development of a safe and effective nonviral gene vector is a considerable challenge in the field of gene therapy. QDs have emerged as efficient FRET donors due to their wide absorption, narrow emission spectra, and high quantum yield, thereby minimizing cross-talk between the donor and acceptor (Pathak et al. 2001). QD-conjugated oligonucleotide sequences (attached via surface carboxylic acid groups) may be targeted to bind with DNA or mRNA (Gerion et al. 2002, Chan et al. 2005). QDs have been found to be considerably better than present methods in the cessation of gene activity. Observations show that a cell's production of a test protein dropped to 2 percent when siRNA was delivered with QDs. By contrast, the test protein was produced at 13 percent to 51 percent of standard levels when the siRNA was delivered with one of

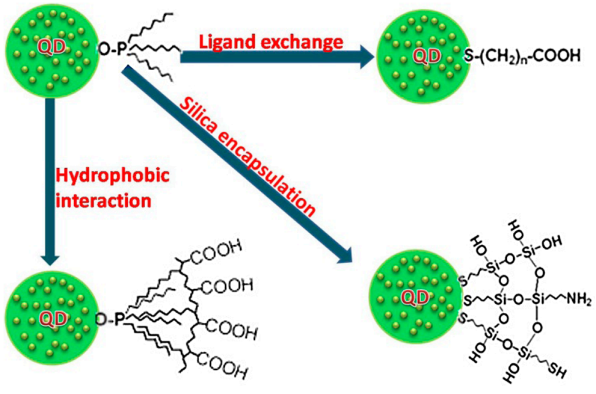

Figure 2. One more approach includes wrapping the hydrophobic surface groups with block copolymers or phospholipid micelles.

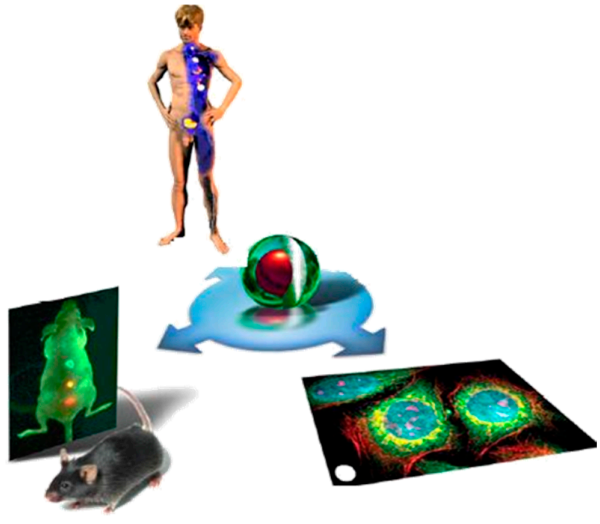

Figure 3. Schematic examples for some bio-applications of QDs (Tilley et al. 2005, Warner et al. 2005).

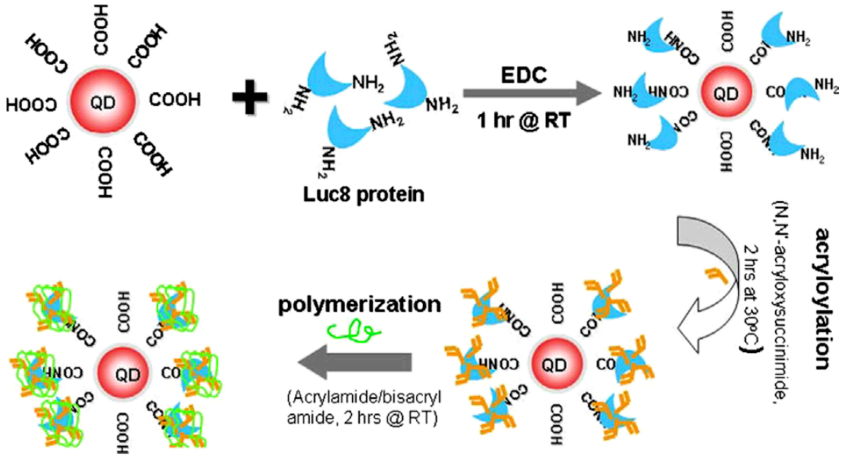

Figure 4. Schematic representation of the encapsulation procedure of QD-BRET probes (Hoshino et al. 2008).

three prevalent reagents, or reaction-causing substances, which are now typically used in laboratories. In addition to their role in DNA technology, QDs perhaps find use in RNA technologies, in the detection of mRNA molecules using in situ hybridization (ISH), and in combining with siRNA in RNA intervention applications. QDs have been successfully used in the ISH method to study the expression of definite mRNA transcripts in mouse midbrain sections (Choi et al. 2007).

Quantum dots as tags for drug carriers

The research of various drug nanocarriers is an imperative part of the progress of nanomedicine. The mechanism of delivery of QD/drug formulations to tumor cells is determined by the structure and properties of the nanomaterials (Zhang et al. 2011). The structural properties of QDs, which are perhaps equally as important, have just been realized in research on drug delivery. First, the size of QDs can be continuously tuned, from 2–10 nm, and particles smaller than 5 nm are rapidly cleared by renal filtration, Second, polymer encapsulation in general raises the size to 5–20 nm in diameter (Azzazy et al. 2007). Recently, Xu et al. (2003) defined a novel process for high-throughput and multiplexed SNP (Single Nucleotide Polymorphisms) genotyping for using the Qbead system that uses quantum dots to encode microspheres employed as a platform for multiplexed assays. By mixing blends of QDs with separate emission wavelengths and intensities, exclusive spectral barcodes are formed that enable the high levels of multiplexing necessary for complex genetic analyses (Tabatabaei Mirakabad et al. 2014, Davaran et al. 2014, Kouhi et al. 2014, Mohs et al. 2009, Sze 1985, Ebrahimnezhad et al. 2013, Pourhassan-Moghaddam et al. 2013, Ahmadi et al. 2014). The second group of QD application in traceable drug delivery is more straightforward – tagging a conventional medicine carrier with QDs, which serve as photostable fluorescent reporters. A novel approach to the enhancement of biocompatible nanoformulations that can target and treat human diseases involves the utilization of functionalized nanoparticles engineered to deliver drugs to the preferred tissues or organs (Michalet et al. 2005, Modani et al. 2013). QDs have been tagged as both organic and inorganic drug carriers and potentially even bacteria and viruses have been used, with an explosion of activity in the field of ODN and siRNA delivery (Bentolila et al. 2009).

Anticancer applications

QDs, or fluorescent semiconductor nanocrystals, which are clusters of a few hundred to a few thousand atoms that emit

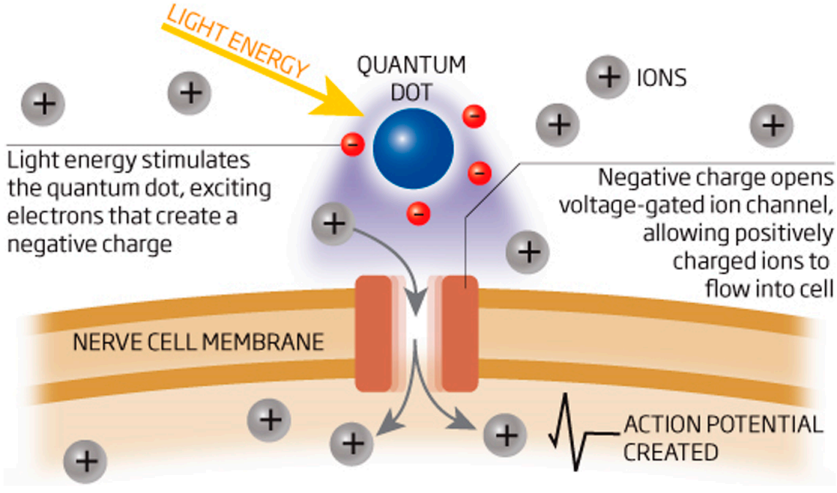

Figure 5. Quantum dots could be used to stimulate damaged cells in the brain and eye, for treating a range of conditions (Lakowicz 1999).

light in rainbow hues, are among the nanomaterials in the spotlight for cancer therapy. One of the real challenges in cancer is diagnosing the state of a tumor and the potential for therapeutic treatment of that tumor. Near infrared QDs are detected by good tissue penetration and lower background, which are appropriate for the analysis of lymph node metastasis (Yong et al. 2009, Ballou et al. 2007, Fang et al. 2012). It has been demonstrated that the QDs injected into two model tumors rapidly move around to sentinel lymph nodes. In one study, scientists observed that four rhesus monkeys injected with cadmium-selenide QDs remained in normal health for over 90 days. Blood and biochemical parameters remained within normal ranges, and the major organs developed no abnormalities. The animals didn't lose weight. Bruchez and others expect to use the sensitivity and multiplexing facility of QDs for in vitro revealing of multiple protein or nucleic acid tumor cell markers that are changed at various stages of cancer (Qi and Gao 2008).

There are two methods by which QDs locate and mark tumor cells. In active targeting, QDs can be adjoining tumor-specific active binding sites so as to join themselves to tumor cells. Consequently, immunofluorescent probes are contrived with antibodies to identify these tumors (Dey and Rao 2011, Abbasi et al. 2014, Eatemadi et al. 2014, Alizadeh et al. 2014, Abbasi et al. 2014, Ebrahimi et al. 2014). A QD system can discover the existence of particles of the RSV (Respiratory Syncytial Virus) in a matter of hours. It is, in addition, extra sensitive, allowing detection of the virus earlier in the route of a disease (Abbasi et al. 2014, Daraee et al. 2014, Tabatabaei Mirakabad et al. 2014, Daraee et al. 2014, Nasrabadi et al. 2014, Chung et al. 2014, Fekri Aval et al. 2014, Valizadeh et al. 2014, Rahimzadeh et al. 2014, Ebrahimi et al. 2014, de Lang 2012).

Quantum dots and neuroscience

QDs are seen as a novel tool of remarkable possibilities in neuroscience investigations. These nano sized materials are useful for experiments that are controlled by the limited anatomy of neuronal and glial interactions, for instance the small size of the synaptic cleft, or between an astrocyte and a neuron. In one unique linkage of quantum physics and neuroscience, QDs have been used to control brain cells, for the first time. Taking control of the brain could one day provide a non-invasive treatment for situations like depression, Alzheimer's, and epilepsy. In the near term, QDs can be used to treat blindness by activating damaged retinal cells (Lakowicz 1999) (Figure 5).

Biosensing and energy transfer

Quantum dots as strong fluorophores are companionable with ordinary biosensing techniques that apply fluorescence to generate a large measurable signal. In one research study, Medintz and coworkers used a related approach to expand a prototype FRET-based Quantum dot biosensor capable of detecting the nutrient sugar maltose in solution. The maltose-binding protein (MBP), pre-bound to an analog sugar-dye complex, was attached to water-soluble QDs, resulting in numerous MBPs linked to every QD (Medintz et al. 2003, Al-Ahmadi 2012).

QD blends for biological coding

The barcodes and the related readers are the most major technologies used for object detection. Since the barcode requires space to arrange the ordered data either in a 1D bar sequence or a 2D image, and therefore the barcode reader has to scan the 1D bar-sequence or register the 2D image, the systems for information retrieval are bulky and complicated (Resch-Genger et al. 2008).

Biomedicine is a research field where most significant and innovative advances have been carried out through the last decades. One of the most important activities in this area, which should be studied, is the large number of proteins and nucleic acids. Hence, the expansion of a fast and efficient coding method for biological molecules, which could allow high throughput analysis, would be desirable (Bruchez et al. 1998). Compared with the traditional organic dyes, the fluorescence properties of QDs offer unique photochemical and photophysical properties. In addition, they show longer photostability and lower photobleaching (Davaran et al. 2013, Ghasemali et al. 2013).

Conclusion

The exceptional performance characteristics of Quantum dots (QDs), such as stability against photobleaching, high fluorescence yields, and the size-dependent luminescence features, give wide a variety of possibilities for their application in many fields. The ability to tune the size of QDs is favorable for numerous applications. Combined together, the large surface area of QDs is useful to covalently bond to biorecognition molecules, such as antibodies, peptides, nucleic acids, or small-molecule ligands, for further application as fluorescent probes.

Authors' contributions

AA conceived of the study and participated in its design and coordination. EA and MM participated in the sequence alignment and drafted the manuscript. All authors read and approved the final manuscript.

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Declaration of interest

The authors report no declaration of interest. The authors alone are responsible for the content and writing of the paper.

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