Nanomed. J., 2(3): 167-174, Summer 2015
DOI: 10.7508/nmj. 2015.03.001

Nanotechnology; its significance in cancer and photodynamic therapy

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Received; 3 February 2015 Accepted; 21 March 2015

ABSTRACT:
In the last decade, developments in nanotechnology have provided a new field in medicine called "Nanomedicine". Nanomedicine has provided new tools for photodynamic therapy. Quantum dots are approximately spherical nanoparticles that have attracted broad attention and have been used in nanomedicine applications. Quantum dots have high molar extinction coefficients and photoluminescence quantum yield, narrow emission spectra, broad absorption, large effective stokes shifts. Quantum dots are more photostable and resistant to metabolic degradation. These photosensitizing properties can be used as photosensitizers for Photodynamic Therapy. Photodynamic Therapy has been recommended for its unique characteristic, such as low side effect and more efficiency. Therefore, nanomedicine leads a promising future for targeted therapy in cancer tumor. Furthermore, Quantum dots have recently been applied in Photodynamic Therapy, which will be addressed in this review letter. Also this review letter evaluates key aspects of nano-particulate design and engineering, including the advantage of the nanometer scale size range, biological behavior, and safety profile.

Keywords: *Cancer tumor, Nanomedicine, Photodynamic therapy (PDT), Quantum dots (QDs)*

INTRODUCTION

The development of a wide spectrum of nanoscale technologies is beginning to change the foundations of disease diagnosis, treatment, and prevention. Furthermore, there is a wide array of intriguing nanoscale particulate technologies capable of targeting different cells and extracellular elements in the body to deliver drugs, genetic materials and diagnostic agents specifically to these locations. Indeed, research into the rational delivery and targeting of pharmaceutical, therapeutic and diagnostic agents via intravenous and interstitial routes of administration with nano-sized particles is at the forefront of projects in Nano-medicine. Nanomedicine is the application of nanotechnology in the medical field for treatment, diagnosis, monitoring, and control of biological systems and includes nanoparticles that act as biological mimetics, nano-machines, nano-fibers, polymeric nanoconstructs as biomaterials and nanoscale microfabrication-based devices, sensors and laboratory diagnostics [1, 2]. Quantum dots (QDs) are nearly spherical semiconductor nanoparticles and have received considerable interests in biology and medicine applications. QDs have high photoluminescence quantum yield, high molar extinction coefficients, narrow emission spectra, broad absorption and large effective stokes shifts [3]. Initially QDs were produced in non-polar solution and were soluble in non-polar organic solvents. Nowadays, QDs can be generated in aqueous solution directly and are ready to be used in biological environment [4]. These special spectroscopy characteristics make QDs unique in fluorescent biological labels for imaging and tracking. Furthermore, QDs have recently been applied in photodynamic therapy (PDT) [5], which will be addressed in this review letter. Also this review letter evaluates key aspects of nano-particulate design and engineering, including the

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Note. This manuscript was submitted on February 3, 2015; approved on March 21, 2015

advantage of the nanometer scale size range, biological behavior, and safety profile.

QUANTUM DOTS

History

In the 1970s the first low dimensional structures QW (Quantum Wells) were developed. History of QDs begins with their first discovery in glass crystals in 1980 by Russian physicist Ekimov [6]. Systematic advancement in the science and technology of QDs was driven after 1984, when Luis Brus derived a relation between size and bandgap for semiconductor nanoparticles by applying a particle in a sphere model approximation to the wave function for bulk semiconductors [7 , 8].

Preparation of QDs and their derivatives

For traditional QDs, cadmium is the main element for their composition. However, it is well known that leaked cadmium ions are culprits for the observed cytotoxicity of cadmium-based QDs, which hampers their further applications to cellular or in vivo study. However, it took nearly a decade for a new promotion in QD research until the successful synthesis of colloidal CdX (X = S, Se, Te) QDs with size-tunable band-edge absorption and emissions by Murray *et al*. [9] So far, CdX is the most investigated QDs due to their excellent optical and electrochemical properties. However, with the further application in biological area, the toxicity of cadmium ion in CdX was paid more and more attention. In order to improve the biocompatibility as well as the PL quantum yield and stability of these core nanocrystals, a layer of a few atoms with a higher bandgap semiconductor was introduced to encapsulate the core nanocrystals to form core–shell nano-crystals. The luminescence efficiency is significantly improved when the nanocrystals are passivated on their surface by a shell of a larger band gap semiconductor and the leaching of metal ions from the core is blocked well by this structure [10].

Applications and characteristics

Ligand exchange and covering QDs with amphiphilic polymers are two general strategies to render hydrophobic QDs soluble in aqueous solution. For example, when TOPO-coated QDs are mixed with a solution containing heterobifunctional ligands which have one functional group binding to QDs surface, and another functional group hydrophilic, these hydrophobic TOPO ligands can be displaced by these new bifunctional ligands and make QDs hydrophilic [11]. But these protocols process in high-temperature coordinating solvents which would decrease the level of QDs fluorescent efficiency, stability and monodispersity. Recently it has been shown that these issues can be alleviated if amphiphilic polymers can cover the hydro-phobic QDs, retaining native coordinating ligands on their surface [12]. This protective hydrophobic bilayer around QDs makes QDs disperse and stable in aqueous solution even after a long periods of time, although this encapsulation method brings about larger physical dimension of QDs and may affect their biological and physical properties [13]. Water-soluble QDs may be utilized in biological targets when cross-linked to biomolecules such as small molecule ligands, antibodies or oligonucleotides. The reactivities of these biomolecules have been found to remain after conjugated to nanoparticle surfaces, though the binding strength of biomolecules may be decreased to a certain extent [14]. QDs conjugation with cationic peptides, such as the HIV Tat peptide, can fasten the association with cells and become internalized quickly via endocytosis [15]. The surface of QDs can also be modified with hydrophilic and bio-inert molecules to eliminate possible non-specific binding or decrease the clearance rate from the bloodstream when intravenous injected. QDs can be modified to contain polyethylene glycol (PEG) which can increase colloidal stability and prevent QDs from capture of reticulo-endothelial system (RES)[16]. With surface modification and bio-conjugation, QDs can be more widely used compared to original QDs. Cellular labeling is where QDs application has attracted the greatest interest and made the most progress [13]. Numerous reports have described the ability of bio-functionalized QDs to label cells. Some of these reporters show that QDs labeling can allow extended visualization of cells under sustaining illumination and multicolor imaging which highlight advantages offered by fluorophores. Conventional organic fluoro-phores have some drawbacks, such as poor photostability, broad emission spectra and

narrow absorption spectra, which have limited their application in long-term imaging and multiplexing [17]. However, QDs have several advantages that could overcome these drawbacks. Unlike organic fluorophores, QDs have high molar extinct-tion coefficients and photoluminescence quantum yield, narrow emission spectra, broad absorption, large effective Stokes shifts. The wavelength between the excitation and emission maxima is widely separated, which can reduce cellular auto-fluorescence and increase sensitivity. Moreover, QDs are more photostable and resistant to metabolic degradation. The core compo-sition of QD imaging probe can be designed according to the desired emission wavelength [18]. For example, CdTe QDs may emit in the 500-750 nm range, while CdSe can emit in the 450-650 nm range [3]. Because QDs have a large fraction of exposed constituent atoms, their atomic or molecular orbitals are not bonded completely. These orbitals can quench QD fluorescence, and therefore it is necessary to grow a shell of another semiconductor which has a wider band-gap on the core surface insulating electronic after synthesis. The ZnS shell on the surface of CdSe cores can enhance photolumin-escence efficiency of CdSe QDs, increasing their chemical stability and decreasing oxidative photo-bleaching rate [19]. It is also reported that QDs can emerge as a new class of sensor, mediating energy transfer to organic dyes (fluorescence resonance energy transfer, FRET). In addition, QDs conjugation with enzymes, which are able to catalyze bio-luminescent reactions, can emit fluore-scence without an external excitation, due to bioluminescence resonance energy transfer(BRET) [20]. For instance, QDs conjugated to the luciferase enzyme can accept energy from luciferins and be excited via enzymatic bioluminescent oxidation, without the need for external illumination [21].

PHOTODYNAMIC THERAPY

History

Photo-chemo therapy of cancer is often called ''photodynamic therapy (PDT).'' The term ''photodynamic action'' is used to distinguish photosensitized reactions in biology from the physicochemical proce-sses occurring in the emulsions of photographic films. This event was first reported by Raab *et al* [22] in 1900. H Tappeiner [23], in 1907, first described the term photodynamic effect when they reported their experiment in which an oxygen-consuming reaction process in protozoa occurred after aniline dyes were applied with fluorescence. In 1960 Lipson et al reported hematoporphyrin derivative (HpD) by treating hematoporphyrin chlor-ide with hydrochloric acid and sulfuric acid. They observed that injection of crude preparations of hematoporphyrin led to fluorescence of neoplastic lesions visuali-zed during surgery. The development of HpD established the basis of today's photodynamic therapy (PDT).

The physical mechanism

To achieve PDT, you need light, photosensitizer (PS) and oxygen. PS can be activated by light, from electronic ground state (S_0) to fluorescent excited state (S_1). After intersystem crossing, the singlet excited state PS converts to the triplet excited state, when PS interacts with tissue components producing cytotoxic species such as singlet oxygen. This interaction may precede via type I or II mechanisms or a combination. The type I mechanism is about production of free radicals or electron transfer from sensiti-zers. Type II mechanism is about resonant energy transfer from the triplet state to molecular oxygen that forms singlet oxygen, the main process in PDT. In a sense, activated PS can generate reactive oxygen species (ROS) and damage target cells, ROS is the main functional molecule during PDT [24].

The biological damage mechanisms

The great effort has been devoted to finding better PS which has specific light absorption and tissue distribution properties. Photofrin, hematoporphyrin derivative, is the first-generation PS and has been accepted for clinical use. The most impressing second-generation photosensitizers are phthalocyanines (Pc's). Pc's derivatives have favorable properties in photonics and chemistry. Pc's have strong absorbance at long wave-lengths, and can been changed through adding substituent on the periphery of the macro-cycle or on the axial ligands. However, Pc's have poor solubility in water and aggregate easily in aqueous solution. Thus, Pc's would lose their photochemical activity and cell-penetrating properties. To solve this issue, the third-generation PS is born, nano-particles are explored

as potential delivery systems for PDT photosensitizers. Silica-based nanoparticles can entrap water-insoluble PS and show efficiency as PDT drug carriers in aqueous media [25].An ideal cancer therapy should have strong selectivity to tumor cells, less or no injury to normal cells. Conventional therapies such as radiotherapy and chemo-therapy, they bring plenty of untoward outcomes, patients have to not only endure pain from tumor, but also the discomfort from these side effects. In PDT, only tissues that are simultaneously exposed to light, photosensitizer and in presence of oxygen can be damaged during PDT. PDT is more selective than conventional therapies, under appropriate circumstances; it can only treat diseased tissues leaving the surrounding normal cells undamaged. Although the exact mechanism of PDT has not been clarified yet, the genes and signal pathway involved in PDT still need exploration; PDT has been a hot area of research in tum or using their own advantages [5, 25].

Optical sensitizers

Research into the development of alternative photosensitizers to Photofrin for use in PDT, for a number of well-defined reasons, continues. A number of sensitizers absorbing at different wave-lengths studied in this section, which may have selective applications in the field of photomedicine. Tetraazoporphyrins were first described in 1952, with the synthesis of tetraazaporphyrin [26] A-1. (Table 1, Fig 1). Although these simple alkylated derivatives have absorption properties similar to those of porphyrins (i.e. absorption maximum at 620 nm), with metal coordination causing a blue shift (e.g. A-2, max 592 nm) [27], more recent studies have shown that incorporation of electron-donating substituent results in a red-shift in the visible spectrum. While these shifts can be modest in the case of t amylthio substituent (e.g. B, max 649 nm), the use of amino

Table 1. Examples of photosensitizers

AZINE	R_1	R_2	M
A-1	H	H	2H
A-2	H	H	Mg
B	H	t-amylS-	Mg
C	H	t- butylNH-	Mg
D-1	butylNH-	CN	Mg
D-2	butylNH-	CN	2H

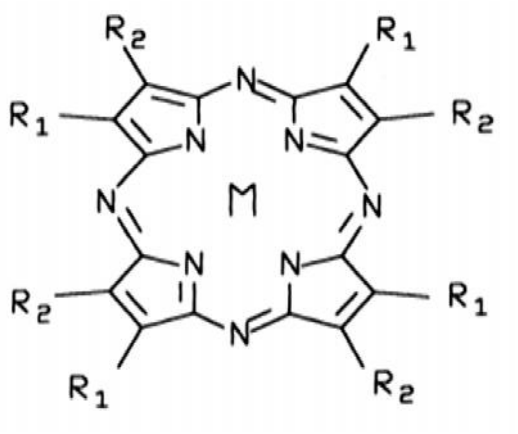

Fig. 1. Diagram of photosensitizers

groups results in a greater shift (e.g. C, max 7l0 nm) [28]. Additional substitution with electron withdrawing groups, performed to increase the stability of the tetraazaporphyrin to oxidation, is reported to result in a further red shift of the Q band (e.g. D-1, 756 nm) [29].Removal of the metal from D-1 (to generate D-2) results in a further red-shift of some 20 nm, an observation similar to that observed in the porphyrin series. Given the red-shifted absorption spectra which can be generated by selected tetra-azaporphyrins, it seemed appropriate to study the photodynamic properties of these molecules.

QDs as photosensitizers in PDT

QDs range from 1 to 6 nm; they are neither bulk crystals nor quite small molecules. The size of QDs gives them unique properties that they can tune from UV to the infrared region when their size and composition have changed. More import-antly, the surface coating of QDs can be modified to make them hydro soluble and biocompatible, which facilitates systemic delivery. Most of the studies on QDs are done on fluorescence imaging applica-tions. However, QDs are also potential for PDT [30].QDs are energy donors, and there exists possibility for energy transfer between cell molecules and QDs. When energy transferred from QDs to cell molecules and induced ROS, apoptosis may be provoked in cells that as a result the apoptosis is the only mechanism for controlling of cancer cells in PDT. Lovric *et al*. [31] demonstrated that QDs could generate ROS via electron or energy transfer to

nearby oxygen molecules. Furthermore, they reported that antioxidant scavengers such as N-acetylcysteine could decrease QD-induced cell death significantly, proving that ROS are important factors during QD-induced cell death.Although the generation of ROS following illumination could potentially be exploited for PDT, the efficiency of ROS generation is insufficient for reliable PDT. Samia *et al*. find that Cadmium Selenide (CdSe) QDs can generate singlet oxygen in toluene [32]. The quantum yield of CdSe-generated singlet oxygen is very slow, less than 5% compared to 40-60% for classic photosensitizers. However, the photo-bleaching of classical photosensi-tizers is more rapid than that of QDs. After prolonged and repetitive exposing under light irradiation, QDs-treated cells may mediate a comparatively high level of singlet oxygen, inducing apoptosis or necrosis in the target tissue. Therefore, great interest has been stimulated in using QDs as FRET donors to induce photosensitization [33]. FRET is a process of nonradiative energy transfer from photo excited donor molecules to a nearby acceptor molecule after absorption of a higher energy photon. Bawendi *et al*. [34] reported that two different sized close-packed CdSe QDs have resonance energy transfer with each other based on FRET. CdSe QDs can also be linked to a silicon Pc photosensitizer (Pc4), which is known as PDT agent undergoing clinical trials [35]. The Pc4's excitation wavelengths range from 550 to 630 nm, but the conjugation of QDs activate Pc4 indirectly at 488 nm by fluorescence resonance energy transfer (FRET) mechanism. As QDs exhibit a board absorption spectrum, they can simply adjust their size to match any PDT photosensitizers. The combin-ation of QDs with PDT photosensitizers enables the use of excitation wavelengths where photosensitizers alone do not absorb [36].

Toxicity of QDs

QDs are cytotoxic in mammalian cells, because of their surface molecules and core themselves. QDs are known composed of group II–VI or group III–V elements, which are toxic to cells. For instance, CdSe QDs can release Cd^{2+} ions and affect mitochondria proteins function, leading to cell poisoning. When QDs are exposed under light, they can produce hydroxyl radicals to damage cell organelles, enzymes, and nucleic acids as well [37]. The mechanisms are still poorly understood; some studies indicated that ROS generation may be the reason leading cellular damages. Lovric ì *et al*. [31] found that ROS was generated when solubilized CdTe QDs were incubated with live cells. The cellular damage is in a dose- and time-dependent manner. After 12 to 24 h of QDs exposure, the damage of plasma membrane, mitochondria and nucleus were observed. When QDs concentrations come to 1 ìm, cytochrome c released from mitochondria and induced cell apoptosis. Thus, QDs cytotoxicity is also relevant with exposure concentrations.

Recent studies have shown that limited QDs concentration and appropriate modifying can reduce the possibility of cytotoxicity [38]. However, there remain amount of questions before QDs applied in clinical trials; first of all is metabolism of QDs in vivo. The cell uptake of QDs is through endocytosis or receptor-mediated endocytosis if QDs are modified with antigen or ligands. But the excretion of QDs is complicated, as QDs are too small to excrete from kidney. In fact, QDs prioritize reticuloendothelial system for excreting such as liver, spleen, and lymph nodes. As a result, QDs may bring inevitable damage to these organs. Ling *et al*. [39] gave intravenous injection to rhesus macaques with phospholipid micelle-encapsulated CdSe/CdS/ZnS QDs, no toxicity evidence was exhibited. After 90 days, the histology of major organs shown no abnormalities, however, the chemical analysis revealed that most of cadmium remained in the liver, spleen and kidneys. These indicated that acute toxicity of QDs in vivo can be minimal, and the clearance of QDs is quite slow, requiring long-term studies to figure out the ultimate fate of these heavy metals and any arising ill effects due to QDs. The longer QDs exist in vivo, the more unpredictable influence it may be. The safety of QDs is tough issue; we need more comprehensive and deeper research to figure it out.

Nanomedical safety

Nanomedicine is the application of nanotechnology in the medical field. As physiological processes at cellular and sub-cellular levels occur on a nanoscale, nanomedicine holds great promise for improving medical diagnosis and therap-eutics [40].

Nanomedicine in oncology has received enormous attention in recent years. Special efforts have been made to utilize nanotechnology in cancer diagnosis and treatment to improve the efficiency and safety of conventional anticancer regiments, such as radiotherapy, chemotherapy and surgery. For instance, the nanomedical photodynamic therapy (PDT) has been used to treat tumors [41].The application of nanotechnology in carcinoma is a double-eged sword. Nanotechnology makes a fascinating development of new devices and modalities. Also, it gives rise to potential toxicity in humans. Some studies focused on the evaluation of nanotechnology toxicity have been done [42]. However, in vivo nanotoxicity is harder to quantify and monitor than in vitro, most of these studies are based on cells.The potential nanotoxicity can be mainly divided into two parts. One is about the nanomaterial itself. As we all known, nanomaterial is complicated, the physical and chemical composition of it can be toxic. Nanomaterial also has large surface to volume ratio, which may lead to uncontrollable bioactivity and finally cause cytotoxicity. The other is about the metabolism of nanomaterial in vivo. Nanomaterial is too small compared with bio-molecule, once got into cells; it is harder to excrete out of cells. The longer nanomaterial stay in vivo, the more unpredictable untoward effect may occur. All these uncertain factors may impede the application of nanotechnology in tumor [43].

CONCLUSION

QDs have photosensitizing properties and can be used as photosensitizers for PDT. Although the ROS generation of QDs themselves is rarely low that cannot induce enough damage to cells, they can be utilized as energy donor to enhance conventional photosensitizers damaging effectiveness.The obstacle of QDs clinical application may be the underlying cytotoxicity. Few researches have been done on the toxicity of QDs in vivo because of the long period observation and requirement for huge convincible samples. QDs may have some advantages and shown potential capacities in PDT, there are still amounts of work to accomplish before final utilization in clinical practice. Nanomedicine has shown great potential in tumor target therapy. Targeted therapy has been recommended for its unique characteristic, such as low side effect and more efficiency. However, there is nanotoxicity still remained. Nanomedicine leads a promising future for targeted therapy in tumor.

ACKNOWLEDGMENTS

We gratefully acknowledge Tehran University of Medical Sciences (TUMS) for the financial support of this work. We also would like to thank Dr. Amir Khalili for his help during various stages of this research.

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How to cite this article:
Gaeeni MR, Sasani Ghamsari M, Tohidian M, Majles Ara MH**.** Nanotechnology; its significance in cancer and photodynamic therapy. Nanomed. J., 2015; 2(3): 167-174.