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Case Study

QUANTUM DOTS: A DIAGNOSTIC AND THERAPEUTIC BOON IN ORAL CANCER

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ABSTRACT
Oral squamous cell carcinoma is the sixth most common cancer worldwide and second most in India. The high mortality rate in cancer is commonly attributed to the difficulties in detecting the disease at an early and treatable stage. New methods of Nano-engineered materials such as Quantum Dots are being developed which might be effective in detecting the disease at an early treatable stage and treating illnesses and diseases such as oral cancer. Functional nanoparticles are considered to have the potential as novel molecular probes for both carcinoma imaging and targeting delivery, which plays a critical role in cancer diagnosis and therapy. Targeting ligands or anticancer drug/gene are the types of quantum dots (QDs) conjugated with it helps to treat cancer through selective binding to the receptors which are over-expressed on cancerous cells and tissue surface. Quantum dots, nanometer-sized semiconductors, are the new class of novel biosensors, now being exclusively employed as alternative fluorescent probes due to their unique properties, such as intense and stable fluorescence for a longer time, resistance to photo bleaching, large molar extinction coefficients, and highly sensitive detection, due to their ability to absorb and emit light very efficiently. Their size approximates that of individual biomolecules, which offers unique possibilities for the ultrasensitive detection of cancer in persons' serum, tissues, and other body fluids, when tagged with specific antibodies against specific tumor markers. In this review paper, we have account briefly the applications of semiconductor QDs employed for the early screening and diagnosis of cancer biomarkers between the years 2007-2017 and believe that this will enable workers in the field to develop new applications of these materials for the early detection of oral cancer, and ultimate reduction in incidence of the disease.

KEY WORDS: Quantum Dots, Oral Cancer, nanoparticle, advanced diagnostic aids

INTRODUCTION

Cancers have become the most common cause of death in today's time and oral cancer is among the top three types of cancers in India [1, 2]. Severe alcoholism, use of tobacco like cigarettes, smokeless tobacco, betel nut chewing and human papilloma virus (HPV) are the most common risk factors for oral cancer[3,4]. Oral cancer may also occur due to poor dental care and poor diet[5].The incidence of oral cancer is highest in India, South and Southeast Asian countries. In India, 90-95% of the oral cancers is squamous cell carcinoma[6]. By 2035researcers from the international agency has predicted an increase in the incidence of cancer in India to about 1.7 million. This indicates that the death rate because of cancer will also increase from 680000 to 1- 2 million in the same period[7, 8]. Early diagnosis and complete treatment of oral cancer is the challenging point of the cancer prevention and control strategy. Due to the various new and advanced techniques developed for the early diagnosis of cancer, the American Cancer Society (ACS) assessed an increase in the average 5-year survival rate for all cancers for the years 1996–2004 to 66%, compared to 50% for the years 1975–1977. The commonly employed methods for diagnosis of cancer include chemotherapy, immunotherapy, surgery medical imaging, enzyme linked immunosorbent assay (ELISA) and tissue biopsy, etc., but these are less sensitive, and are reliable only for early-stage cancer detection [9].

Quantum dots (QDs) are semiconductor inorganic non-materials ranging from 1-10 nm. QDs, containing elements found in groups II-IV (*e.g.*, CdSe, CdTe, CdS, and ZnSe) or III-V (*e.g.*, InP and InAs) of the periodic table, have shown great potential interest to medical scientists because of their unique advantages over traditional fluorescent dyes, such as broad excitation spectra, narrow and symmetric photoluminescence bands, large two-photon absorption cross-section, size-tunable absorption & photoluminescence spectra, exceptional photostability, high quantum yield, and versatility in surface modification[10]. QDs have initially been used for carcinoma cell imaging. Additionally, QDs has been designed to perform both imaging and drug delivery because it provides a versatile nanoscale scaffold [11]. Herein, QDs, conjugated with types of targeting ligands or anticancer drug/gene to simultaneously cancerous image, cancer treatment through selective binding to the receptors over-expressed on cancerous cells and tissue surface, has the potential to considerably improve the efficiency of fluorescence imaging and target delivery [12,13]. This article provides a brief review on the recent developments of the fabrication of functional QDs and promising applications in the early diagnosis and treatment of oral cancer.

Physiology of Quantum Dots (QDs)

Most recently, QD probes have been used for *in vivo* tumor targeting in passive and active modes[14]. In passive targeting, QD probes are delivered and aggregated at tumor sites because of the enhanced permeability and retention effects. In the active mode, QD probes were conjugated with a prostate-specific membrane antigen (PSMA) monoclonal antibody to target PSMA preferentially, which is known as an attractive marker for prostate cancer. After *in vivo* imaging, histologic and immunocytochemical examinations confirmed that the QD signals came from an underlying tumor[14,15]. Similarly, QD probes could be conjugated to monoclonal antibodies to oral cancer-specific antigens, such as epidermal growth factor receptor, to detect oral cancer cells specifically [16].

Semiconductor quantum dots are extremely small particles of cadmium selenide (CdSe) or zinc sulfide whose sizes are in the range of 1 to 10 nm[17]. For biomedical applications, QD surfaces are modified further to target specific cells or molecules. QD–peptide conjugates have been used to target tumor vasculatures and homed to tumor vessels[18]. Antibody conjugated QDs have been used for real-time imaging and tracking of molecules in living cells and have demonstrated high sensitivity and resolution [19].

Quantum dots such as size-tunable light emission, when used in conjunction with magnetic resonance imaging, can produce exceptional images of tumor sites. These nanoparticles are much brighter than organic dyes and only need one light source for excitation. This means that the use of fluorescent quantum dots could produce a higher contrast image and at a lower cost than today’s organic dyes used as contrast media. However, the downside is that quantum dots are usually made of quite toxic elements [20,21].

QDs enable highly sensitive optical imaging of cancer at cellular and animal level. Many researchers Worldwide have suggested a novel way to kill tumor cells using nanoparticles and light. The technique, devised by Wensha Yang, an instructor in radiation oncology employs QDs. QDs are semiconductor nanostructures, 25 billionths of a meter in diameter, which can confine electrons in three dimensions and emit light when exposed to ultraviolet radiation[22]. QDs are fluorescent nanoparticles with sizes of 2-10 nm that contain a core of 100s-1000s of atoms of group II and VI elements (*e.g*., cadmium, technetium, zinc and selenide) or group III (e.g., tantalum) and V elements (*e.g*., indium) [23,24]. These can be used as photosensitizers and carriers. They can give rise to reactive oxygen species and thus will be lethal to the target cells. QDs contain a core of cadmium selenide and a zinc sulfide shell, surrounded by coordinating ligand and an amphiphilic polymer coating. They are most commonly used for biological application[25,26].This structure enables QDs to emit powerful fluorescence that differs in nature from organic dyes. QDs can be tuned to emit at between 450 nm and 850 nm (*i.e*., from ultraviolet to near-infrared) by changing the size or chemical composition of the nanoparticle. This produces many QDs colors, which can be visualized simultaneously with one light source. QDs emit narrow symmetrical emission peaks with minimum overlap between spectra, allowing unique resolution of their spectra and measurement of fluorescent intensity from several multicolor fluorophores by real-time quantitative spectroscopy. QDs also have a greater surface area and more functionalities that can be used for linking to multiple diagnostic (*e.g*. radio-isotopic or magnetic) and therapeutic (*e.g*. anticancer) agents. Disadvantages include toxic effect of metal core [27-30].

QDs in the Treatment of Oral Cancer

QD probes can target and accumulate in tumors both by their enhanced permeability and retention (EPR) effect and by recognition of cancer cell surface biomarkers. Chemotherapeutic agents bound to QD probes that will recognize and bind to cancer cells may offer a new strategy for molecular cancer therapy by avoiding systemic toxicity [31,32]. One of the major advances in minimally invasive therapies for cancer is photodynamic therapy (PDT). First discovered in the early 1900s, it is now an approved cancer treatment for various superficial malignancies, including basal cell carcinoma, oral, esophageal and lung cancers [33]. Samia *et al*. in the year 2003 were the first to report the application of QDs-PS complexes as therapeutic PDT agents [34]. Quantum dots can be used in PDT as photosensitizers (PS), which can mediate targeted cellular destruction. They can bind to antibody present on surface target cell and when stimulated by ultraviolet light, will release reactive oxygen species (ROS); this is lethal to target cells [31, 35, 36].

Cancer detection using quantum dots

Earlier studies open new avenues for application of QDs as bio-imaging tools and their applicability in multiplexed imaging by various researchers. Their photo stability makes them ideal candidates for multicolor imaging and for studying various events in living cells. For the early and accurate cancer cells detection, use was made of dendrimer/ QD nanocrystals (NCs) as an ECL signal probe for cancer cells [37]. This study is advantageous, since large numbers of CdSe/ ZnS QDs were assembled onto the dendrimer NCs due to the many functional amine groups of NCs, which greatly amplifies QDs ECL signals. Targeting of blood vessels and cancer cells was done using QDs, wherein the surfaces were conjugated with specific peptides[38]. Earlier in 2004, QDs encapsulated with an ABC triblock copolymer proved the multiplexed fluorescence imaging of human prostate cancer biomarkers developing in mice due to the successful binding of the QD-antibody to tumor specific antigens[39].QDs spontaneously endocytosed by HeLa cancer cells retained their bright fluorescence when mercaptoacetic acid-coated CdSe/ZnS QDs were covalently conjugated to the transferrin protein, indicating that QDs could be used as intracellular labels[40].

Many researchers have applied Functional QDs both as *in vitro* and *in vivo* imaging of cancer cells. Ovarian carcinoma, melanoma, breast cancer, pancreatic cancer, glioblastoma, ovarian epidermoid carcinoma, lung carcinoma and hepatocellular carcinoma are some of the applications of functional QDs for *in vitro* fluorescence imaging [41-49]. The QD-EGF (Epidermal growth factor) conjugate has been utilized for cancer cells fluorescence imaging. The application of functional NIR (near infrared)

QDs have been applied in vivo by targeting and imaging using bio distribution and pharmacokinetics. They have the potential for tumor diagnostics like carcinoma cell labeling or tracking, tumors markers targeted imaging and tumor vessel imaging [50-56].

Applications of QDs in cancer therapy

Drug therapy

Targeting Drug by nanoparticles or nanocapsules reduces dosage and side-effects and ensures pharmaceutical effects and drug stability. QDs as nanoparticles have unique optical properties which are used as visualization probes, targeted delivery and therapy applications. Functional QDs are developed for performing imaging and drug delivery tasks without usage of any external dyes [57-59]. Conjugated QDs can be delivered to specific sites for targeting drug delivery *in vitro and in vivo*. According to past literatures, QDs conjugated therapeutic drug has been used in treatment of breast cancers [60,61].

Gene therapy

Past literatures and studies have proved that there is some genetic link with the development and progression of tumor and gene therapy plays a safe and efficient strategy in therapeutics at the desired target. QDs intricate genes like small interfering RNA (siRNA) giving physiological stability and target specificity. Nanocomposites which are loaded with QDs used to overcome the barriers in siRNA delivery like cellular penetration and gene silencing. In past literatures, functional QDs delivers siRNA into HeLa cells as well as silence the target gene[62].

Photodynamic therapy

It is a promising invasive antitumor strategy which involves administration of photosensitizing agent. It can be curative mostly in the early stage by causing direct tumor cell death. QDs are designed for specific purposes such as Fluorescence Resonance Energy Transfer (FRET) which can transfer energy to photosensitizers. One of the most important properties for Photodynamic therapy is giving photostability of QDs [63].

CONCLUSION

Quantum Dots has been evolved as an advanced diagnostic aid for Cancer from past few decades. Nanoparticles have made an incredible contribution towards detection as well as therapeutics in cancer Worldwide. Quantum Dots can be designed for effective therapeutics such as drug and gene therapy which can be boon for the Society making a revolutionary change in the early diagnosis and management of Cancer.

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