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Quantum Dots in Photodynamic Therapy for Cancer

Abstract

Photodynamic therapy (PDT) is a promising, non-invasive therapeutic approach. PDT involves Photosensitizer (PS) drugs and an external light source is the essential components of PDT and cytotoxic reactive oxygen species are generated that destroys cancer cells. Despite of a new potential anticancer therapeutic strategy, success of PDT is limited due to low water solubility of photosensitizers which limits the wide applicability of these molecules. Nano-platforms based on PS incorporated in nanomaterials can be applied for targeted PDT with reduced side effects and better efficiency. This article provides an insight on few recent advancements of quantum dots based PDT and future aspects.

Keywords: Photodynamic therapy; Nanotechnology; Quantum dots; Cancer; Photosensitizers; Nano-platforms

Opinion

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Abbreviations: PDT: Photodynamic Therapy; PS: Photosensitizer; NIR: Near Infra Red; ALA: Aminolevulinic Acid; MAOP: Methyl Aminolevulinate; BRET: Bioluminescence Resonance Energy Transfer

Introduction

From ancient Egypt civilization, light and chemicals in combination are being used for therapeutic purposes like treatment of psoriasis and vitiligo [1]. However, modern PDT was discovered by Raab, Tappeiner, Huang [2-4] in the beginning of 20th century. The principal of PDT involves light activation of some specific kind of chemicals called photosensitizers (PS) that generates reactive oxygen species; specifically singlet oxygen ($^1O_2$) that is deleterious to cells. Cancer is still the most fatal disease that claims many life world-wide every year and despite of tremendous medical advancements no cure has been found for this disease and chemotherapy; the most explored treatment option is also not effective in many cases. In this regard alternative therapy approaches are a must and PDT is the most suitable and effective alternative of conventional therapies. The prime components of any PDT are: a photosensitizer (PS), a light source, and oxygen. This approach is distinct from laser-activated photothermal approaches where high intensity pulsed lasers are used to generate thermal effects, while in PDT typically low irradiances in the mW/cm^2 ranges are required and instead of thermally induced tissue burning, PDT is a gentle approach where dose depends on the induced photochemistry with no alternation in biological activity after removal of light source [4].

Advantages and Limitations of PDT

PDT has several advantages over conventional cancer treatment approaches. Firstly, it has no long-term side effects when properly used although, with first generation PSs, minor self-limited photosensitivity to the eyes and skin was observed [5,6]. PDT procedures are most often performed on an outpatient basis and it is a less invasive technique as compare to surgical procedures with relatively short span of side effects as compare to chemotherapy or radiotherapy. Based on its mode of action, it also annihilates the vasculature associated with the tumor besides the tumor itself, which contributes significantly to tumor death [7]. Furthermore, PDT is a localized therapy and can be directed to a target tissue very precisely as only the irradiated area receives the PS and the light simultaneously. Another important feature of PDT is, it's cost effective and can be repeated several times at one location if necessary without leaving any scar, a major limiting factor with radiation [6]. Despite of several advantages and a better alternative of conventional chemotherapy approaches, PDT has its own set of draw backs like mostly photosensitizers are less water soluble that prevents their effective utilization, it's a light dependent technique and for deep tissue penetration like treatment of lung. liver, pancreatic cancers, a PS excitation wavelengths should fall in near infra red (NIR) and it's the need of hour to develop new PS with their optical properties as require as to date PDT has mostly applied for skin cancers only. Moreover, PDT can't be applied for metastatic cancers as it's a localized therapy. Oxygenation of tumor and tissues is required for the effective photodynamic therapy as tumors surrounded by necrotic tissue or intense tumor masses impede PDT efficacy. Many PS have been granted FDA approvals like sodium (Photofrin), 5-aminolevulinic acid or ALA (Levulan), and methyl aminolevulinate [MAOP] (Metvix) and research is going on for its wider applicability for other cancers also [6,8].

Nanotechnology Intervention and quantum dots: New paradigm for PDT

Nanotechnology is a truly revolutionary field of modern era that has influenced almost every research arena and medical sciences also witnessed the deep impact of nanotechnology in the area of drug delivery and diagnostics where a new branch-'nanotheranostics' has been evolved. PDT has also been greatly benefited by nanotechnology and nano based liposomal, lipid, metallic nanoparticles and quantum dots have seen vast

applications in recent years that have enriched the potential of this alternate therapy for cancer. In 2001, the first clinical approval of PDT was given to Visudyne®, a liposomal verteporfin formulation, and red light for the treatment of age-related macular degeneration [9]. In combination with nanotechnology, PDT provides brilliant opportunities for therapeutic agents delivery and newer approaches for photomedicine. The major advantages of nano-PDT include enhanced PS delivery to target site, modification of PS physiochemical properties, and development of novel light sources, personalized predictive dosimetry and advancement of combinatorial therapeutic approaches [4].

Although various nanoparticles have been applied but quantum dots (QDs) - tiny nanoparticles of semiconductors or graphene/carbon size ≤ 20 nm are rather special due to their excellent size tunable optical properties, needed for effective PDT in deep tissue cancers. QDs have their typical photoluminance property and can be tuned for excitation at NIR wavelengths also that makes them excellent entities for their application in PDT. QDs are superior to conventional PS in terms of photostability and water dispersiblity [10,11]. Despite of these advantages, cytotoxicity and less ROS generation has impaired the clinical utility of these agents. Therefore, alternate approaches like surface modified QDs conjugated with a traditional PDT agent (porphyrin derivative, Ce6) have been designed to mitigate the cytotoxicity with enhanced ROS generation. Moreover, another strategy of QDs driven PDT based on Forster resonance energy transfer (FRET) has also been proposed. Owing to their distinctive optical and spectroscopic properties of tunable emission spectra, high molar extinction coefficient and high PL quantum yield, QDs are ideal donors/ acceptors for FRET and can be explored for either via FRET or direct electron transfer to oxygen molecules for generation of ROS in PDT [12]. Similar findings were reported by Burda et al. also in their study, evaluating interaction of CdSe QDs with a silicon phthalocyanine PS (Pc4) [13]. Bioluminescence resonance energy transfer (BRET); an analogue of FRET, is another concept that has explored initially for in vivo bioimaging by Rao et al. [14,15] with CdSe/ZnS Qds and later for PDT, by Lai et al. [14,15]. In BRET, QDs accept energy from luciferase catalyzed reaction through non-radiation energy transfer and as per the findings of Yun et al. and Lai et al. is a promising strategy with numerous clinical benefits, such as overcoming light penetration issues and treating deeper lesions that are intractable by PDT alone [16,17].

Apart from semiconductor quantum dots, since the discovery of graphene quantum dots (GQDs), with their comparable optical properties with existing QDs and excellent biocompatibility, lots of attention has been paid on GQDs for their numerous applications as theranostic agents from drug delivery to bioimaging. For PDT also few reports are there that signify the wide applicability of GQDs as better alternatives of their semiconductor counter parts [10,18].

Limiting factors for QDs in PDT Applications

QDs are good nanomaterials for PDT owing to their size tunable opto-electrical properties and have seen multiple applications in recent years, toxicity of these compounds is an important issue that needs to be addressed and nowadays ecofriendly synthesis of nanomaterials is gaining considerable interest. With semiconductor quantum dots in PDT (i.e. CdSe, CdTe etc), the prime hurdle is release of Cd^{+2} due to colloidal instability in body fluids that is extremely toxic for in vivo application due to subsequent generation of radicals and malfunction of cellular organelles like disruption of plasma membrane, nuclei and mitochondria [19,20]. To prevent the toxicity of semiconductor quantum dots, approaches like QD core and polymer shell types structures have been adopted. But the systematic evaluation of circulation time and deterioration of shell that would release the QD hasn't been evaluated fully which limits the wide acceptability of these materials in PDT. However QDs of graphene and other carbon materials are more biocompatible and exhibit similar properties like their semi conductor counterparts. Due to their less toxicity and ease of surface modification, these are better substitute than the former semiconductor QDs.

PDT is a potential alternate of traditional chemotherapy but few drawbacks like low water solubility of photosensitizer drugs, lack of targeted delivery at tumor site and desired fluorescence properties of PS in NIR regions for better penetration for deep tissue cancers, limits its wide applicability. The rise of QDs has opened new avenues in PDT and with the flexibility of surface modifications to enhance biocompatibility and optoelectrical modulation; these new materials have significantly enrich the field of PDT.

In recent years, many QDs based nanoconjugates for PDT have been reported and the encouraging results indicate bright future of such alternate approaches to overcome the limitations of existing photodynamic therapy. QDs due to their excellent opto-electrical properties, easy surface modification techniques are a preferred choice for PDT applications and with involvement of FRET /BRET mechanism are good alternatives of other nanomaterials. In a nut shell it can be concluded that although in nascent stage, these small nano entities holds lots of potential and we can expect their wide applications towards an efficient PDT in future.

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