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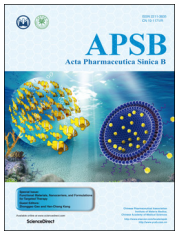

REVIEW

Targeted and effective photodynamic therapy for cancer using functionalized nanomaterials

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Abstract Photodynamic therapy (PDT) is an emerging, non-invasive therapeutic strategy that involves photosensitizer (PS) drugs and external light for the treatment of diseases. Despite the great progress in PS-mediated PDT, their clinical applications are still hampered by poor water solubility and tissue/cell specificity of conventional PS drugs. Therefore, great efforts have been made towards the development of nanomaterials that can tackle fundamental challenges in conventional PS drug–mediated PDT for cancer treatment. This review highlights recent advances in the development of nano-platforms, in which various functionalized organic and inorganic nanomaterials are integrated with PS drugs, for significantly enhanced efficacy and tumor-selectivity of PDT.

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1. Introduction

Photodynamic therapy (PDT) is a treatment option in which activation of photosensitizer (PS) drugs with specific wavelengths of light leads to energy transfer to oxygen molecules or other substrates in the surrounding areas, generating cytotoxic reactive oxygen species (ROS) which can trigger apoptotic and necrotic cell death[1,2]. In the absence of external photo-activating light, the PS drugs are minimally toxic. Therefore, PDT provides a safe and effective way to selectively eradicate target cells/tissues such as cancerous cells while avoiding systemic toxicity and side effects on healthy tissues[3]. Compared to traditional chemotherapy and radiotherapy, PDT-based cancer treatment significantly reduces side effects and improves target specificity because only the lesion under light irradiation is treated[1,4]. Moreover, PDT-based cancer therapy is more beneficial to patients in which location or size of lesions limits the acceptability of conventional therapy[5].

Despite the many positive features of PDT on cancer therapy, PDT is still not fully adapted in the clinical settings because of some inherent properties of PS drugs. Most existing PS drugs are hydrophobic with poor solubility in water[6]. Therefore, they are easily aggregated under physiological conditions, drastically lowering the quantum yields of ROS production[7]. Even in the case of some modified PS drugs for increased water solubility, their accumulation selectivity at target tissues/cells remains insufficient for successful clinical use. In this regard, development of effective delivery systems that incorporate PS drugs and transfer them into target tissues/cells, addressing critical biological barriers for the conventional PS delivery, is indispensable.

Recently, nanomaterials in combination with PS drugs find considerable attention in PDT because they can overcome critical limitations of conventional PS drugs[8,9]. Nanomaterials can significantly enhance the solubility of PS drugs in water through hydrophilic properties and thus increase their cellular uptake. When formulated as nanoparticles with nanomaterials, PS drugs can achieve passive targeting to tumor by the enhanced permeability and retention (EPR) effect[10], which is attributed to the leaky tumor vasculature and poor lymphatic drainage of tumor tissues. Moreover, cell-specificity of PS drugs can be significantly increased by surface modification of the nanoparticles to bind active targeting moieties, such as antibodies, peptides, and aptamers[11,12]. This also improves bioavailability of PS drugs and reduces undesirable side effects of PS drugs to surrounding health tissues.

To date, numerous nano-platforms using a variety of organic and inorganic nanomaterials have been investigated for efficient and targeted PS delivery[6,13]. Organic nanomaterials for PDT, such as liposomes and polymeric nanoparticles, have achieved safe and controlled delivery of PS drugs by using biodegradable/biocompatible materials and tailoring chemical compositions of the materials[14,15]. Flexibility for versatile formulations is another benefit of using organic nanomaterials. Inorganic nanomaterials hold high potential for PDT due to tunable optoelectronic properties by tailoring their shape and size[16,17]. Therefore, they can offer additional functionalities to PS drugs such as diagnosis and imaging. In addition to the benefits of each material, they both provide an effective solution to overcome the drawbacks of current PS drugs associated with stability in physiological conditions and selective delivery to the target sites by further surface functionalization. PS drugs have been generally combined with organic/inorganic nanocarriers *via* both physical methods using hydrophobic or electrostatic interactions between PS and the nanocarriers and chemical methods using various conjugation reactions. Here, we introduce various combinations of nanomaterials and PS drugs that have demonstrated effective PDT both *in vitro* and pre-clinical animal studies. We mainly concentrate on innovative formulations, molecular designs, and modifications that have been utilized for targeted and effective PDT while categorizing them into organic and inorganic nanomaterials.

2. Mechanism of PDT using PS

Mechanism of PDT using PS has been elucidated in several studies[1,18,19]. Briefly, PS in the ground state absorbs a photon and is activated to an excited singlet state upon irradiation with suitable light. The excited singlet state can convert into the triplet state *via* intersystem crossing caused by a change in the spin of electrons. The PS in the triplet state interacts with surrounding molecules and thus produces ROS through Type I and Type II reactions. The Type I reaction involves the transfer of either hydrogen atom or an electron between the excited PS and the substrates, leading to the generation of free radicals. These radicals then react with oxygen, resulting in the production of ROS such as superoxide and hydroxyl radicals. The Type II reaction involves the energy transfer between the excited PS and the molecular oxygen in the ground state ($^3O_2$), resulting in the formation of highly reactive state of oxygen known as singlet oxygen ($^1O_2$). The resulting ROS can cause irreversible damage to target tissues/cells.

3. Functionalized nanomaterials for effective and targeted PDT

For effective and targeted PDT, functionalized nanomaterials are required to efficiently incorporate and deliver hydrophobic PS drugs only into target tissues/cells and to activate them to produce ROS. In addition, functionalized nanomaterials need to be biocompatible and to have sufficient PS-loading capacity. They may need active targeting moieties to enhance the accumulation selectivity of PS drugs in the target tissue/cells. To achieve these requirements, various functionalized organic/inorganic nanomaterials have been developed, which will be reviewed in the following sections.

3.1. *Organic nanomaterials for PDT*

To improve the water solubility of PS drugs and their specific accumulation at the target site, a general strategy is encapsulation of the PS drugs to polymeric or lipid-based nanocarriers. In this respect, liposomes, polymeric micelles, and polymeric nanoparticles have been extensively explored for serving as PS carriers in PDT.

3.1.1. *Liposomes*

Liposomes are one of the first nano-platforms to be applied in drug delivery systems[20]. Their unique ability to contain hydrophilic drugs in their aqueous core and hydrophobic agents within their lipid bilayers renders them excellent delivery vehicles. 5-Aminolevulinic acid (ALA) prodrugs for PDT were encapsulated in dipalmitoyl-phosphatidyl choline–based liposomes[21]. ALA was used as a precursor of phototoxic protoporphyrin IX (PpIX) for PDT[22]. The chemical structure and molar extinction coefficient of PpIX are represented in Table 1[23] *In vitro* experiments