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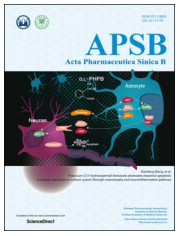

REVIEW

An updated overview on the development of new photosensitizers for anticancer photodynamic therapy

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Abstract Photodynamic therapy (PDT), based on the photoactivation of photosensitizers (PSs), has become a well-studied therapy for cancer. Photofrin®, belonging to the first generation of PS, is still widely used for the treatment of different kinds of cancers; however, it has several drawbacks that significantly limit its general clinical use. Consequently, there has been extensive research on the design of PS molecules with optimized pharmaceutical properties, with aiming of overcoming the disadvantages of traditional PS, such as poor chemical purity, long half-life, excessive accumulation into the skin, and low attenuation coefficients. The rational design of novel PS with desirable properties has attracted considerable research in the pharmaceutical field. This review presents an overview on the classical photosensitizers and the most significant recent advances in the development of PS with regard to their potential application in oncology.

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1. Introduction

Cancer is among the leading causes of morbidity and mortality worldwide. In 2012, approximately 14 million cancer cases were newly diagnosed, and the number of cancer-related deaths was 8.2 million, which is projected to rise by about 70% over the next two decades.[1] Currently, clinical treatments for cancer include surgery, radiation therapy, chemotherapy and, more recently, immunotherapy and other small-molecule targeted therapies, along with a combination of these strategies.[2] However, these treatments present some important drawbacks. For instance, traditional chemotherapy, as it interferes in cell division, is often associated with severe systemic adverse effects, such as myelosuppression, mucositis, alopecia, and others.[3] Also, surgical resection of certain tumors cannot avoid a high recurrence rate,[4] while the cumulative radiation dose extremely limits the radiotherapy.[5] Thus, although refinement of the conventional anticancer therapy is important, development of new treatment approaches that are safe, potent, and cost-effective seems especially urgent.

2. Photodynamic therapy

2.1. An accidental finding for cancer treatment

In the 1890s, Raab[6] accidentally found that the irradiation with visible light was lethal to paramecia previously exposed to acridine, and postulated that the transfer of light energy to the acridine red was the crucial event behind the cytotoxicity observed in paramecia and that this effect was related to the fluorescence of the dye.[7] Then the first clinical observation of PDT with oral eosin to treat epilepsy was reported by the neurologist Jean Prime in 1900.[8] Later, von Tappeiner and Jesionek[9] proposed the use of topical eosin with light exposure to treat skin tumors. This was the first published report on the use of PDT to treat tumors in human patients. Subsequently, von Tappeiner[10] observed that O_2 was an important component of the events found by Raab, and coined the term "photodynamic action".

The study of the anticancer potential of PDT was conducted by few researchers up to the 1950s when the interest in this field began to increase. The publication of some seminal reports on the use of porphyrins as both PSs and fluorescence diagnostic tools[11] in the 1950s and 1960s was followed by a series of works on the anticancer activity of PDT against different tumors.[12] Mainly over the last three decades, several types of PSs have been developed and applied in preclinical and clinical trials; some of these molecules reached the market and have shown to be effective against different kinds of cancers.[13–15] The main advantage of PDT over conventional anticancer therapies is the ability to limit toxic effects to the biological tissues exposed to both the PS and light, thus protecting normal tissues.

In addition, PDT has also been used successfully against non-malignant disorders in diverse fields, such as urology,[16] immunology,[17] ophthalmology,[18] dentistry,[19] dermatology,[20] and others.

2.2. Photodynamic therapy mechanisms

PDT is based on the excitation of PS with light at specific wavelengths, culminating in type I and type II photochemical reactions.[21] As shown in Fig. 1, a PS can be activated from its ground state to a short-lived excited singlet state (PS_{Es}) by light. Then, either the excited PS may decay back to the ground state by emitting fluorescence, or it can undergo intersystem crossing whereby the spin of its excited electron inverts to form a relatively long-lived triplet state (PS_{Et}). The triplet excited PS can also decay back to the ground state by emitting phosphorescence, but most importantly it can directly interact with surrounding substrates (*e.g.*, cell membrane or other biomolecules) to form radicals, which then react with O_2 to produce reactive oxygen species (ROS), such as superoxide anion radicals ($O_2^{\cdot-}$), hydroxyl radicals (.OH), and hydrogen peroxides (H_2O_2, type I reaction). Alternatively, the energy of the excited PS can be directly transferred to $^3O_2$ (itself a triplet in the ground state) to form $^1O_2$ (type II reaction). It is worth noting that both type I and type II reactions can occur simultaneously, and the ratio between these processes is affected by the nature of the PS, as well as by the concentrations of $^3O_2$ and other substrates. However, most of the experimental studies indicate that the photoactivated production of $^1O_2$, namely type II reaction, plays a dominant role in *in vivo* PDT.

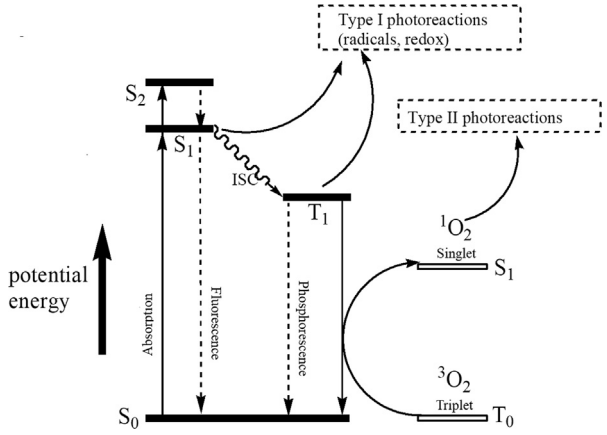

Figure 1 Jablonski diagram showing the main events leading to type I and type II photochemical reactions, which eventually may result in oxidative cell damage. S_0, ground state of the photosensitizer (PS); S_1, first excited singlet state of PS; S_2, second excited singlet state of PS; T_1, first excited triplet state of PS; ISC, intersystem crossing; $^3O_2$, triplet oxygen; $^1O_2$, singlet oxygen.

In a biological medium the reactive species generated by the photodynamic process can react with a large number of biomolecules, mainly proteins, nucleic acids, and lipids. The damage to biomolecules may (i) irreversibly damage tumor cells resulting in necrosis, apoptosis, or autophagy, (ii) cause tumor ischemia following PDT-induced vascular injury, and (iii) activate the immune response against tumor antigens.[22–25] Therefore, the main downstream targets of PDT include tumor cells, as well as tumor-associated microvasculature, and, indirectly, the host immune system.[26] Moreover, the combination of PDT with other chemotherapeutic drugs may help to achieve a long-term tumor control, due to their possible synergistic effects resulting from the combination of downstream responses in PDT and the mechanisms of chemotherapeutic drugs.[27]

3. The photosensitizers for anticancer PDT

3.1. First generation PSs

Hematoporphyrin (Hp), a complex mixture of porphyrinic compounds,[28] was the first porphyrin used as PS. The purification and chemical modification of Hp led to the discovery of a

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