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Research progress of photodynamic therapy in antitumor therapies

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Abstract. As one of the leading causes of disease death globally, conventional treatments for cancers have been developed, including surgery, chemotherapy, radiotherapy etc. However, some drawbacks restrain their therapeutic effects. Consequently, researchers have been struggling to develop novel strategies to cure tumors. Photodynamic therapy (PDT) is a significant means that utilizes light as well as photosensitizers to kill tumor cells. In PDT, a photosensitizer absorbs a photon and transfer to states with higher energy, then energy is released and generates free radicals and ground-state molecular oxygen by two distinct types of reaction to exert therapeutic functions. This review concentrates on the antitumor principles and mechanisms of PDT, common photosensitizers, combination of PDT and other cancer therapies and its effects on several typical cancers.

Keywords: Photodynamic therapy, Photosensitizer, Antitumor effect

1. Introduction

Traditional therapies targeting tumor consist surgery, chemotherapy, radiotherapy. Photodynamic therapy act as an adjuvant strategy for diseases, especially for cancers. The principle of photodynamic therapy can be concluded as the photochemical reaction between oxygen, photosensitizer (PS) and light. The process begins when a photon is absorbed by a photosensitizer and the PS is excited to several singlet states with higher energy (S_1, S_2, S_3) [1]. Then by the emission of energy as fluorescence or heat, the PS can go back to the ground state. Additionally, intersystem crossing after a spin inversion could produce photosensitizer in an excited triplet state T_1 which has a longer living period. The T_1 state is a significant feature for two kinds of photochemical reactions that possess therapeutic effects, producing free radicals (Type I reaction) and ground-state molecular oxygen (Type II reaction) respectively [2]. The photodynamic therapy tolerance for patients is optimistic due to its selectivity, provided by illumination volume control of certain tissues and localization of photosensitizers and chromophores to targeted tissues [3].

2. Antitumor Mechanisms of PDT

2.1. ROS damage

Most of the application of PDT take advantage of type II reaction, generating singlet oxygen $^1O_2$ which exerts primary cytotoxicity on malignant tumors. Its reaction with lipids on the membrane leads to lipid

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peroxidation and damage of cellular membranes. Besides, its reaction with amino acid affects functions of proteins [4]. However, the excessive proliferation and lack of blood supply form a hypoxic tumor microenvironment restricts the generation of ROS. Therefore, attempting to change the low-oxygen condition is of vital importance and many methods have been organized to alleviate hypoxia and promote the generation and tumor lethality of ROS [5].

One of the common strategies is to decompose H_2O_2 to generate O_2. Chen et al. developed a novel pH/H_2O_2 responsive HSA-MnO_2-Ce6&Pt (HMCP) nanoparticle was generated by a biomineralization process based on albumin. MnO_2 nanoclusters involved in the system would react with endogenous H_2O_2 inside tumor microenvironment (TME) when it was injected into the tumor issue, producing oxygen, relieving hypoxia and enhancing PDT cancer treatment [6].

Another method is to deliver exogenous oxygen directly. It is well known that red blood cells (RBC) take the responsibility to deliver oxygen in body. Zhang et al. constructed a "NanoRBCs" by assembling nanoliposomes based on PFOB (perfluorooctyl bromide), PFC-based blood substitution. A heptamethine dye IR780 was also added into the structure to enhance PDT efficacy. The PFOB@LIP-IR780 "Nano-RBCs" represented a high oxygen-delivery feature with enlarged PDT and mitochondria-targeting characteristic which could basically eliminate tumors. [7].

Other treatments to reduce hypoxia include normalization of tumor blood vessels, perfluorocarbon (PFC)-based and O_2 carriers based on metal-organic framework (MOF), reducing tumor oxygen consumption, destructing the extracellular matrix of tumor and inhibiting HIF-1 signal pathway [8].

2.2. Necrosis and Apoptosis

Cell apoptosis and necrosis can be induced by Ca^{2+} release from the endoplasmic reticulum (ER), regarded as Ca^{2+}-regulated mitochondrial cell death. To further investigate the variations of the level of Ca^{2+} in tumor after the PDT, Zhao et al. utilized Ca^{2+} fluorescent indicator Rhod-3 AM to determine Ca^{2+} concentrations intracellularly. Together with elevating drug concentration, the A549 cells showed an increase of Ca^{2+} level after PDT treatments. The ER stress caused by photosensitizer EB-ER-Pc (EB: erlotinib; ER: ER-targetable moiety methyl sulfonamide; Pc: photosensitizing core) could rise calcium ion standard by causing ER stress. Therefore, induction of apoptosis and necrosis were achieved by the generation of ROS and excessive Ca^{2+} [9].

There are two major pathways considering apoptosis, extrinsic/death receptor-mediated apoptosis and intrinsic/mitochondria-mediated apoptosis. The death receptor-mediated pathway occurs when death ligands, such as FasL, TNF-α, TRAIL, attach to death receptors (DR) on cell surface, including Fas, TNF-RI, TRAIL receptor, forming the death-inducing signaling complex (DISC). It serves as a platform to recruit the initiator procaspases-8 as well as initiator procaspases-10 and lead to their activation, cleaving and activating procaspases-3 and initiator procaspases-7 to achieve apoptosis [10]. As for mitochondria-mediated pathway, an example is a pH-activatable nanoparticle M-TPPa designed by Qi et al. which could accurately target both early endosome and mitochondria and amplify theranostic signal for effective therapeutic results. M-TPPa could be rapidly absorbed by tumor cells by endocytosis in the acidic environment, accumulated into the mitochondria and activated the fluorescence signals and photoactivity of photosensitizer, inducing dysfunction of mitochondria and intrinsic tumor cell apoptosis [11].

2.3. Autophagy

Autophagy can be regarded as a double-edged sword which contains both pro-survival mechanism via the clearance of destroyed cellular components and a death mechanism, which particularly enhance organelle destructions. A vesicle with bilayer film called autophagosomes engulfs impaired materials and isolates them from the cytoplasm. After they are fused with lysosomes, autolysosome, a single-membraned vesicles, is formed to degrade autophagic cargos by lysosomal hydrolases [12]. The degradation contributes to the deletion of unfolded proteins, destructed organelles, microorganisms and recycling of cellular components and nutrition to tumor issues [13].

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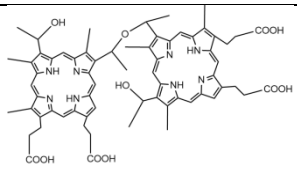
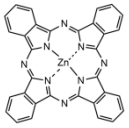
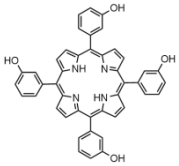
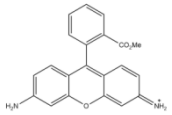
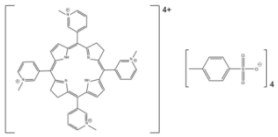
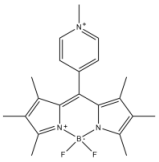
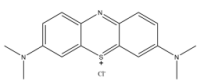
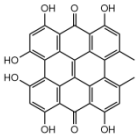
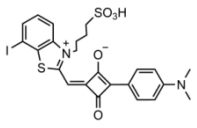
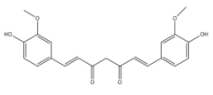
Function of autophagy relies on the damage standard of PDT. Once autophagy is activated, cell death can directly happen as a result of autophagy-dependent cell death. Considering the AKT-mTOR regulation system, 450-nm blue laser (BL) with PDT mediated by sinoporphyrin sodium (DVDMS) to treat human gastric cancer (GC) is researched by Li et al. The results showed apparent inhibition of cell growth and induction of apoptosis in GC in vitro by the generation of excessive ROS when treated with 450-nm laser-mediated DVDMS-based PDT. Additionally, autophagy flux was induced by BL-PDT in GC cells and the induction of autophagy was illustrated to offer positive contribution to apoptosis induced by BL-PDT on GC cells. Taking advantage of analyzing methods such as transcriptomic analysis, ROS/PI3K/AKT/mTOR pathway was proved to take part in the control of autophagy [15].

3. Photosensitizer

From the mechanism of photodynamic therapy, it is apparent that photosensitizer is of vital importance in PDT. Generally, PSs can be categorized into three generations. Some typical photosensitizers are listed in the Table 1.

Table 1. Typical photosensitizers.

Category	Name	Structure	Category	Name	Structure
Porphyrin	Photofrin		Phthalocyanine	Liposomal ZnPC	
Chlorin	Foscan		Rhodamine	Rh123	
Bacterio-chlorin	Tetrahydroporphyrin-Tetratosylat (THPTS)		BODIPY	DIMPy-BODIPY	
Phenothiazinium salt	Methylene Blue		Perylene-quinone	Hypericin	
Squaraine	ASQI		Curcuminoid	Curcumin	

3.1. First-generation Photosensitizer

The first discovered PS agent was porphyrin excreted in urine, also known as uroporphyrin. However, it was not put into practice for PDT in the beginning [16]. From 1950s to 1960s, Schwartz and Lipson and their colleagues figured out a way to develop a sensitizer with a refined form that is more active called Hematoporphyrin Derivative (HpD), which was the first PS that was applied in clinical uses to treat bladder cancer and commercialized as Photofrin® by Dr. Thomas Dougherty, a mixture containing dimers and oligomers that are water soluble but lipophilic with 2 to 9 porphyrin units connected by ether bonds [17]. Wang et al. discovered that in Extramammary Paget's Disease (EMPD), HpD-PDT resulted

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in relatively high complete remission (CR) rate. However, in this study, pain during light irradiation was considered to be the major unwanted result and there are plenty of distinct side effects including partial irritation, photosensitivity, scar generation, infection of urinary tract, hepatic injury and uroschesis in the previous researches. Moreover, considering esophageal carcinoma, the primary disadvantage of HpD-PDT was the extended photosensitivity of the skin [18]. Therefore, photosensitizers that possess less adverse reactions still required to be developed.

3.2. Second-generation Photosensitizer

The second-generation photosensitizers include chlorin, benzoporphyrin derivatives, texaphyrins, bacteriochlorin analogues and phthalocyanines. Common properties of second-generation PSs include higher chemical purity, higher singlet oxygen production and better penetration capability. Additionally, they illustrate fewer side effects as they own better selectivity for tumor sites and faster eradication speed. However, the major drawback of the second-generation PS is their poor water solubility, limiting intravenous administration [19].

Meso-tetrahydroxyphenylchlorin (mTHPC), also known as Foscan®, is a clinically approved chlorin photosensitizer. Haimov-Talmoud et al. designed a Ce-doped-γ-Fe_2O_3 maghemite nanoparticles (MNPs) combined with mTHPC, which showed high uptake and death rate in cancer cells after PDT in MDA-MB231 (human breast cancer) cells. What's more, PDT results in a decreased tumor size and significant tumor regression [20]. A novel bacteriochlorin-based photosensitizer FBC was developed by Wu et al., which could not only generate oxygen-dependent $^1O_2$, but also produce oxygen-independent ROS $O_2^{\cdot-}$ and $OH^{\cdot}$. relieving tumor hypoxic microenvironment and enhancing therapeutic effects [21].

3.3. Third-generation Photosensitizer

The third generation aims at optimizing delivery process and targeting tumor cells. To promote the selectivity, several measurements have been taken by scientists, including combined second-generation PSs and molecules that targets certain receptor, assemblies of PSs with low density lipoprotein, conjugation of PSs with antibody that targets certain antigen, the utilization of markers for tumor surface including growth factor receptors, transferrin receptors or hormones [19].

4. PDT Combined with Other Cancer Therapies

4.1. PDT Combined with Immunotherapy

Traditional strategies against cancer include surgery, radiotherapy, chemotherapy, endocrine therapy and biological therapy, which have limitations such as high aggressiveness, undesired therapeutic effect, toxicity, tumor specificity deficiency and the possibility of recurrence of tumor. Therefore, novel treatments have been applied in cancers and immunotherapy is one of them developed to promote natural defenses to eliminate malignant cells [22].

However, complicated tumor immunosuppressive microenvironment restrains the therapeutic effect of immunotherapy, which can be greatly improved with the aid of phototherapy. Wang et al. focused on the membrane-targeted photosensitizer TBD-3C that was able to induce immunotherapy efficacy containing aggregation-induced emission (AIE) property via photodynamic therapy. Not only did pyroptotic cell serves as a tumor-associated antigens (TAAs), secreting cell contents (e.g. cytokines and proinflammatory factors), but also it emitted signals of danger-associated molecular patterns (DAMPs), indispensable for the recruitment and maturation of antigen-presenting cells (APCs). Induced by TBD-3C, it stimulated M1-polarization of macrophages, the ripeness of dendritic cells (DCs), and upregulation of CD8+ cytotoxic T-lymphocytes (CTLs), transforming immunosuppressive "cold" TME to immunogenic "hot" TME and inhibiting the growth of pancreatic cancer [23].

4.2. PDT Combined with Chemotherapy

Chemotherapy is a conventional cancer therapy that utilize cytotoxic drugs to attack rapid proliferating cells, widely regarded as the first option of tumor metastases. However, shortcoming of it is that it also

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influences normal cells that split rapidly including cells in digestive tract and the bone marrow [24]. Consequently, combination strategies arouse more and more attention aiming at achieving synergistic effect and reducing side effects at the same time and nanotechnology is widely applied in recent studies.

In the research of Su et al., a polymer PEG(-b-PCLCe6)-b-PBEMA with star shape was designed to improve ROS production of photodynamic therapy and the reduction of GSH in situ in tumor cells. The conjugation of polycaprolactone (PCL) and photosensitizer Ce6 composed lipophilic part to assist the formation of micelle and fulfilled photodynamic therapy under illumination. The H_2O_2-labile group of arylboronic esters played a character of producing H_2O_2-indeced quinone methide (QM) to deplete GSH. Besides, this artificial micelle could load Doxorubicin (DOX) and carry DOX into tumor tissue in high efficiency as well, resulting in the fusion of photodynamic therapy and chemotherapy [25].

4.3. PDT Combined with Photothermal Therapy (PTT)

PTT is a treating method based on photothermal conversion, which means PTT agents generate heat when they are exposed to light [26]. Electrons of ground state transfer to excited state when light is absorbed by the agents, generating electronic excitation energy that could cause overheating of topical environment. The produced heat has the effect of aggregation and denaturation of proteins, evaporation of cytosols and lysis of cells. However, PTT also has many drawbacks such as limitation of penetration depth for NIR light, photobleaching leads to a reduction in therapeutic effect, high risks of cancer relapse and metastasis. Additionally, incorrect dosage may result in tissue burning, swelling, and inflammation [27].

To combine PDT and PTT, Li et al. selected BD3, 1,10-phenanthroline-2,9-dimethyl-linked berberine dimer, from all of four compounds BD1, BD2, BD3 and BD4 (BD1 and BD2: pyridine-2,6-dimethyl-/ 2,2'-bipyridine-3,3'-dimethyl-tethered berberine dimers, BD4: tetrakis(4-benzyl)ethylene linked berberine tetramer), which possessed the lowest singlet-triplet energy level difference (ΔE_{ST}) and most generation of $^1O_2$, to build AuNSs–BD3@HA (abbreviation ABH, AuNSs: gold nanostars; HA: hyaluronic acid). Combined PDT and PTT anti-breast cancer therapeutic effects were achieved by BD3 and AuNSs respectively, together with the targeting-CD44 (a variety of receptor overexpressed in cancer cells) property of HA [28].

5. The Antitumor Effects of PDT

5.1. Breast Cancer

As the most familiar malignancy in female, breast cancer (BC) usually generates in the breast lobules, tubes, or connective tissue [29]. In spite of improvements of mammographic breast screening, surgery, chemotherapy and the use of adjuvant hormonal therapies have been increasing the survival rate of breast cancer patients, novel technologies are still in need to for patients who are not eligible or responsive to standard managements [30]. Therefore, a rising number of scientists have been investigating new PDT-assisted immunotherapy nanomedicines for breast cancer [31].

To obtain clear images of magnetic resonance imaging (MRI) for cancer diagnosis using transition metal manganese ion (Mn^{2+}) and treating tumor by PDT, Zhou et al. created a dendrimer composite-based self-assembly nanoparticle by combining hypericin, MnO_2 particles and polyglycerol dendrimer with cysteine (G1-Cys). In this research, not only did Mn^{2+} show well T_1-weighted imaging (T_1WI) performance, it could also convert H_2O_2 into hydroxyl radicals, intensifying PDT therapeutic efficacy. Moreover, activation of the photosensitizer hypericin resulted in the production of ROS, thus amplifying the treatment effect [32].

5.2. Lung Cancer

Lung cancer is the uppermost reason of cancer death in the world, killing more people than colon, breast, and prostate cancers together and is the major cancer death cause in men and the second highest cancer death cause in women, just behind breast cancer [33]. It can be categorized into small-cell carcinoma (SCLC, takes up 13%) and non-small-cell carcinoma (NSCLC, takes up 83%) [34]. Even though PDT

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has limitations such as short half-life in plasma, insufficient tumor tissue infiltration and moderate specificity, it is extensively studied in lung cancers to reduce adverse effects caused by conventional therapeutic strategies due to its ability to reduce drug resistance and minimize toxicity.

Epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) is a drug targeting NSCLC which resistance has become a major hindrance to treat NSCLC and Yes-associated protein (YAP) regulates resistance to EGFR-TKI. Huang et al. created a stimuli-responsive and block dendritic polymer to load EGFR-TKI gefitinib (Gef), YAP-siRNA and photosensitizer polymer-pyropheophorbide a (Ppa) and irradiate light to eliminate EGFR-TKI resistant cancers. Apart from the inhibition effect of Gef targeting EGFR signaling, YAP-siRNA could also block the MAPK/ERK and PI3K/AKT pathway to inhibit tumor cell proliferation and Ppa-based PDT induced tumor apoptosis by generated ROS [35].

5.3. Glioma

Glioma is one of the most common central nervous system (CNS) primary malignant tumor, taking up about 30% of primary brain and CNS tumors and 80% of brain cancers [36]. With special features like hypoxia, the blood-brain barrier (BBB), ROS and angiogenesis, the treatment efficacies of conventional therapies are restrained. In most cases, anti-glioma drugs have troubles in crossing BBB to get to tumor sites. Furthermore, promotion of tumor initiation and progression are also achieved by oxidative stress and hypoxia-induced invasion of glioma, drug resistance, and angiogenesis contributes to the growth of cancer and leads to the tumor recurrence [37].

The internalizing RGD peptide (iRGD), a cyclic peptide with 9 amino acids, includes a tumor cell targeting motif CendR. Lu et al. produced a prodrug polymer that contained chemotherapeutics camptothecin (CPT), polyethylene glycol (PEG), modified iRGD peptide with disulfide bond conjugation, forming CPT-S-S-PEG-COOH nanosized polymeric micelles with photosensitizer IR780. The modification of iRGD allowed micelles to pass through the BBB and target glioma cells via ligand transportation mediated by αv β integrin and neuropilin-1 both in vitro and in vivo, possessing a more excellent tumor-eliminating efficacy [38].

6. Conclusions

The research progress of photodynamic therapy shows that it is an effective way to treat cancers mainly by ROS damage, necrosis, apoptosis and autophagy mechanisms. In addition, the combination of PDT with other treatments for cancers enhances the therapeutic efficiency and PDT is proved to be effective in various cancers. However, the major challenges of PDT are the hypoxia TME, limited depth of light penetration and the selectivity of PSs, which restrict the application of photodynamic therapy. As a result, numerous attempts have been made to solve these problems in the past few years. The rapid development of nanocarriers for PSs delivery makes it possible to elevate PDT efficiency and selectivity. With the further development of nanotechnology, photodynamic therapy possesses a fascinating opportunity to play an indispensable character in cancer treatments and widely applied in clinical practice.

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