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# Application of photodynamic therapy in cancer: challenges and advancements

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**Abstract:** Although great achievements have been made in the past decades in medicine, cancer remains a worldwide public health issue. Surgery is usually accompanied by shortcomings such as residual lesions and poor treatment effects, and the successive appearance of other treatment methods, such as radiotherapy and chemotherapy, has not changed the postoperative recurrence rate, toxicity, and side effects. However, the advent of photodynamic therapy has greatly improved this situation. Photodynamic therapy is an emerging tumor diagnosis and treatment technology with good application prospects, photodynamic therapy uses a specific wavelength of light to excite a photosensitizer to generate reactive oxygen species, damage tumor blood vessels and promote tumor cell apoptosis, exerting an anti-tumor effect. Photodynamic therapy has become a new clinical anti-tumor therapy due to its clear efficacy, few side effects, and easy use in combination with other therapies. In this review, we summarized the main mechanism, current challenges, and advancements of photodynamic therapy.

## Introduction

According to the World Health Organization (WHO), in 2018, cancer has claimed 9.6 million lives, and the global cancer burden will rise to 18.1 million new cases (Siegel *et al.*, 2018). Over the years, researchers have studied the mechanism of cancer cell proliferation, infiltration, and migration to provide new ideas for treatment. Presently, cancer treatments mainly include surgery, radiotherapy, chemotherapy, and immunotherapy. For most patients with solid tumors, surgery is considered the most common and effective way to cure tumors. However, surgery may cause local metastases and positive margins, and radiation therapy and chemotherapy can lead to side effects such as fatigue, nausea and vomiting, hair loss, and blood cell reduction (Balcer-Kubiczek and Eley, 2018; Schirrmacher, 2019).

Photodynamic therapy (PDT) originated in 1900 by Oscar Raab (Raab, 1900), who stumbled on the finding that paramecia exposed to acridine orange and light can be quickly killed, thus, the theory of combining chemical and light energy to induce cell death was proposed. PDT uses a combination of a photosensitizer (PS), light, and oxygen molecules to selectively kill diseased tissues. When the PS absorbs sufficient energy from a specific light wavelength, they activate oxygen molecules in the surrounding environment of the tumor tissue, exerting cytotoxic effects to treat malignant lesions (Yanovsky *et al.*, 2019). In 1975, Kelly *et al.* (1975) successfully used hematoporphyrin derivative (HpD) as a PS to treat bladder cancer, setting a precedent for PDT in cancer treatment. Although PDT is still a new and non-invasive method of tumor treatment, it has been approved by the U.S. Food and Drug Administration (FDA) and Europe, the Middle East, and Africa (EMEA) to treat tumors and non-malignant diseases (Baskaran *et al.*, 2018; Gong *et al.*, 2016; Song *et al.*, 2018) (Fig. 1).

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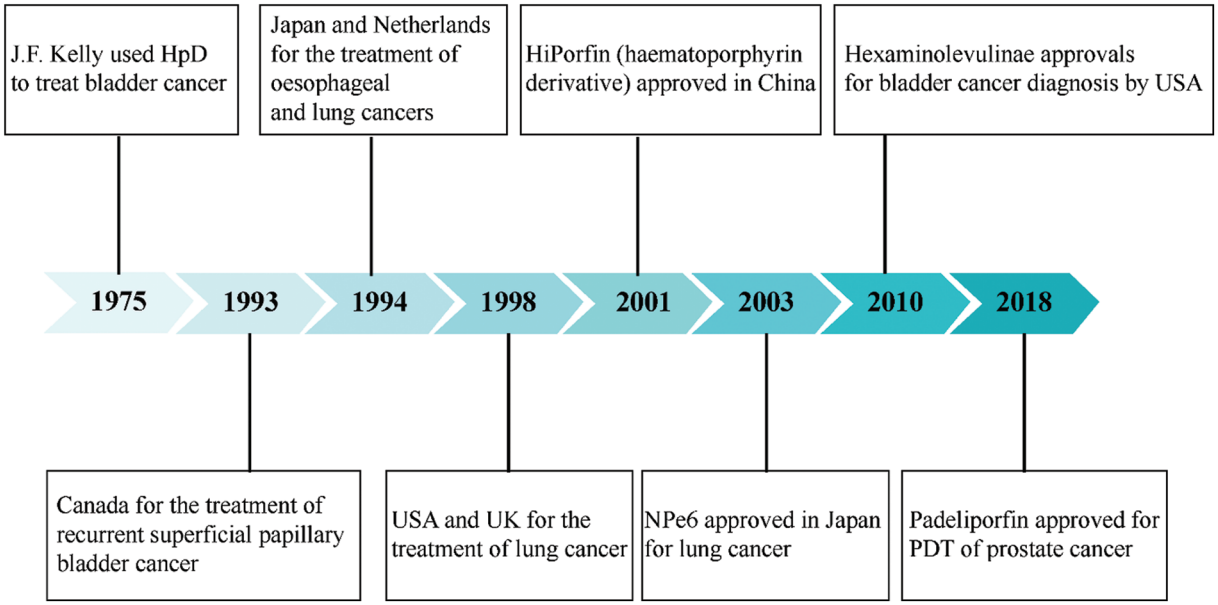


**FIGURE 1.** Timeline of select approvals of photodynamic therapy photosensitizers for cancer indications. Different countries or institutions have approved the use of various photosensitizers.

In recent decades, PDT has become an effective method for cancer treatments in scientific research and clinical practice due to its many advantages, including the following: (1) PDT can kill tumor cells locally by producing reactive oxygen species (ROS) in a short time, without causing tumor resistance; (2) PS produces apoptosis-inducing ROS only after light exposure, and the time and location of the illumination are controllable, minimizing, the toxicity of the PS to the body; (3) PDT can avoid minor lesions that are invisible to the eyes during surgery, improve the prognosis and prevent recurrence; (4) PDT can be used multiple times for the same tumor site and can be combined with other therapies such as chemotherapy, radiation and gene therapy (Cheong *et al.*, 2015; Hwang *et al.*, 2018; Ozog *et al.*, 2016; Wachowska *et al.*, 2015a). Therefore, PDT is a new clinical method with huge potential advantages.

This review discussed the brief history and development of the first-generation to existing third-generation photosensitizers, and the principles and mechanisms of PDT, current challenges, and future perspectives.

## Principle of Photodynamic Therapy

Photodynamic therapy mainly comprises three elements: A light source that provides energy for the photodynamic response; PS that can absorb the corresponding light and perform the photodynamic response; and a large amount of ROS produced by electron or energy transfer through excited PS, particularly singlet oxygen ($^1O_2$) and superoxide (Ancona *et al.*, 2018; Shi *et al.*, 2019). Consequently, the role of PDT is based on the synergistic effect of excitation light of a precise wavelength, PS, and ROS (Dabrowski and Arnaut, 2015; Zhang and Li, 2018).

### *The light source*

In the process of optical imaging *in vivo*, the penetration depth of photons mainly depends on the absorption and scattering of tissue. Because the wavelength of the light source of traditional is mostly in the visible light region, the tissue penetration of photon is weak and easily interfered by endogenous substances; thus, they cannot be used in the photodynamic therapy of deep tumors (Mansoori *et al.*, 2019; Xiao *et al.*, 2018). Correspondingly, the near-infrared (NIR) light has low absorption and strong scattering in biological tissues, indicating that it has a large optical penetration depth. In the range of 650–950 nm, the NIR radiation absorption of tissue components is significantly lower than that of visible light, which is the "first optical window" (NIR-I). The NIR-II window for bioimaging applications is typically from 1000 to 1700 nm (Cao *et al.*, 2019). At the same time, the factors influencing clinical PDT include the intensity of the light source and light frequency. Hence, specific excitation wavelengths need to be selected according to the tumor type and PS for PDT.

### *Photosensitizers*

A PS is a photosensitive compound that can transit from the ground state to the excited state after being irradiated at a specific wavelength. As the core element of PDT, the characteristics of the PS determine the therapeutic effect. Currently, many PSs belonging to the first and second generations have been approved by the FDA for clinical treatment and trials (Tab. 1).

The first-generation PS, hematoporphyrin derivative (HpD), was isolated and identified in 1980 (Zhang *et al.*, 2018a). Compared with healthy cells, tumor cells can absorb more PS; thus, HpD was considered a suitable cancer diagnosis and PDT drug for a long period (Gray *et al.*, 1967). Peng and his group (Peng *et al.*, 2016) combined HpD with calcitriol to provide an effective and selective way to improve the treatment of breast cancer cells by PDT. However, HpD also has disadvantages such as a long half-life, poor tissue permeability, a low chemical purity, a weak effect on deep pathological tissues, and a long blood circulation time,

**TABLE 1**

**First and second-generation photosensitizers approved for clinical use or undergoing clinical trials**

| | Photosensitizer | Indications | λmax/nm | References |
|---|---|---|---|---|
| First-generation Photosensitizer | Hematoporphyrin derivative (HpD) | Bronchial non-small cell lung cancer; esophageal cancer; bladder cancer; gastric cancer; cervical cancer | 630 | (Kessel, 1986) |
| Second-generation Photosensitizer | 5-Aminolevulinic acid (5-ALA) | Skin cancer; alimentary tract tumor; oral cancer; bladder cancer | 635 | (Mahmoudi *et al.*, 2019) |
| | 5-ALA-hexylester/H-ALA | Diagnosis of bladder tumors | 375–400 | (Felsher, 2003) |
| | 5-ALA-methlester/M-ALA | Bowen's disease; basal cell carcinoma and actinic keratosis | 635 | (Felsher, 2003) |
| | meta-tetrahydroxyphenylchlorin (mTHPC) | Head and neck cancer; breast cancer | 652 | (Bonnett *et al.*, 1999) |
| | p-bromo-phenylhydrazone-methyl pyropheophorbide-a (BPMppa) | Deep cancer | 683 | (Zhang *et al.*, 2017a) |
| | HPPH (2-[1hexyloxyethyl])-2-devinylpyropheophorbide-a) | Lung cancer; esophageal cancer; head and neck cancer; bladder cancer; gastric cancer | 665 | (Shafirstein *et al.*, 2016) |
| | N-aspartyl chlorin e6 (NPe6) | Lung cancer; liver cancer; skin cancer and spreading tumors | 664 | (Usuda *et al.*, 2010) |

leading to a poor therapeutic effect and limiting its wide clinical application (Li *et al.*, 2018b; Zhang *et al.*, 2018a).

The second-generation PS is an optimized monomer compound developed based on the first-generation PS, and most of them are heterocyclic porphyrins (Morgan, 1989; Morgan *et al.*, 1985), including bacteriochlorins (Ethirajan *et al.*, 2011), bacterial chlorophyll (Zhang *et al.*, 2017a), chlorin (Zhou *et al.*, 2016), protoporphyrins (Singh *et al.*, 2015), phthalocyanines (Kinsella *et al.*, 2001), and their derivatives. Some compounds also have a non-porphyrin structure, such as 5-aminolevulinic acid, curcumin, quinone, phenothiazine, and psoralen (Harris and Pierpoint, 2012). Most of the porphyrin PS have been developed from the structure of hematoporphyrin, mainly including chlorine and chlorophyll derivatives. For PDT to act on deeper tumor tissues during treatment, modifying groups on porphyrin rings will shift the maximum absorption wavelength of PS toward the NIR region (James *et al.*, 2013). Chlorin e6 (Ce6) is a type of natural chlorophyll extracted from algae and silkworm sand that, is obtained via a series of separation, purification, and modification steps (James *et al.*, 2018). As an excellent new PS, Ce6 has a maximum absorption wavelength of approximately 660 nm and has fewer side effects on healthy tissues, making it a good choice for PDT. Feng *et al.* (2019) developed a co-delivery albumin nano-system based on bovine serum albumin, cyclopamine and diselenide-containing amphiphilic hyaluronic acid-chlorin e6 polymers. This nano-system had the advantages of targeting tumor cells and releasing Ce6 through redox reaction in the cell and proved its anti-tumor efficacy in *in vitro* and *in vivo* experiments. 5-ALA is a non-fluorescent endogenous biochemical substance in PS with a non-porphyrin structure (Harris and Pierpoint, 2012; He *et al.*, 2017a; Mahmoudi *et al.*, 2019), serving as a precursor to the synthesis of protoporphyrin IX (PpIX), which is photosensitive *in vivo* and does not accumulate in large quantities under normal conditions. However, PpIX is generated in rapidly dividing cells *in vivo* in the presence of a large amount of exogenous 5-ALA, and PDT could be performed after light exposure (Arnaut *et al.*, 2014). The advantages of 5-ALA include its relatively fixed excitation wavelength, lower toxicity, higher enrichment in tumor tissues, and rapid removal from healthy tissues and plasma (Champeau *et al.*, 2019). Presently, ALA-mediated photodynamic therapy has been widely used in neoplastic and non-tumor skin diseases, such as psoriasis (Yi *et al.*, 2019), acne (Barbaric *et al.*, 2018), squamous cell carcinoma (Morton and Braathen, 2018), basal cell carcinoma (Trafalski *et al.*, 2019), and mycosis fungoides (Han *et al.*, 2016). However, the second-generation of PS cannot be injected intravenously due to their poor water solubility (Lucky *et al.*, 2015).

Photosensitizers have many innate advantages, but their inherent disadvantages greatly limit their development space in medicine. More specifically, most PSs have a lower solubility in water and higher polymerization capacity, resulting in a lower photodynamic activity. Additionally, these PSs lack selectivity toward diseased tissue or tumor cells, causing serious side effects in humans (Li *et al.*, 2017b; Zhang *et al.*, 2020). However, activatable PSs can be designed to be activated only in the context of specific tumor markers or the tumor microenvironment to effectively avoid light damage to normal tissue and skin, thus improving the precision of PDT (Liu and Li, 2020). Therefore, the development of third-generation PS mostly focuses on novel derivatives of second-generation PSs that enlarges the functional group or molecule, such as linking biospecific targeted molecules (Abrahamse and Hamblin, 2016), binding to molecules that increase biocompatibility (Li *et al.*, 2018b), introducing complexes formed from

compounds with specific physiological functions (Li *et al.*, 2017a), and loading on multifunctional carriers (Chilakamarthi and Giribabu, 2017; Shen *et al.*, 2016). They accumulate less in healthy tissues, reducing the effective concentration, and improving safety (Kataoka *et al.*, 2017). Ruiyun Zhang and others (Zhang *et al.*, 2016b) treated breast cancer with nanoparticles (NPs), which are formed by the self-assembly of Ce6 and DOX. Thus, a new type of carrier-free nano-drug was manufactured that plays a synergistic role in tumor treatment. Molina *et al.* (2016) adopted the method of nanoprecipitation to obtain abundant human serum albumin (HSA) NPs with a diameter of about 295 ± 5 nm, loaded with Ce6, which can reduce the extracellular residence time of the NPs, and play a key role in the drug metabolism and transportation. Core-shell NPs with liposome and polymer compounds, which were loaded with PS, chemotherapeutic drug oxaliplatin, and programmed death-1 (PD-1) antibody, were synthesized by He *et al.* (2016); in subsequent experiments, the synergistic effect of PDT, chemotherapy, and immunotherapy on colon cancer was confirmed. A novel nanocluster was synthesized by Cai *et al.* (2020) that can be hydrolyzed by the tumor-specific carboxylesterase (CE) and penetrate through the deep tumor. PDT can be promoted by enhancing the singlet oxygen generation capacity. Su's team (Su *et al.*, 2019b) presented a strategy using an amphiphilic diblock copolymer and a stimulus-responsive dye as components to distinguish between healthy and diseased cells. Zhai's team (Zhai *et al.*, 2019) successfully developed a new class of activated photosensitizers to achieve the transformation of photosensitivity performance from complete inhibition to stress initiation.

*Reactive oxygen species*

A PS has two ground state electrons that rotate in opposite directions (Zhang and Feng, 2018). When the light absorbed by a PS is excited by appropriate energy, an electron will be excited into a higher energy orbit, forming an excited state (Moan *et al.*, 1998; Ochsner, 1997). Excited PSs are extremely unstable. After reacting with surrounding oxygen molecules, they can react with non-oxygen substrates, transfer protons or electrons to generate free radicals, and further interact with ground oxygen to generate ROS (Type I reaction) (Hong *et al.*, 2016; Hu *et al.*, 2018). However, activated PSs can also directly react with the ground state oxygen and then return to the ground state, transfer energy to the ground state oxygen to generate ROS (Type II reaction) (Lucky *et al.*, 2015). Regardless of the Type I reaction or Type II reaction, a large amount of ROS will be produced, leading to apoptosis and necrosis after oxidative stress (Abrahamse and Hamblin, 2016; Gdovin *et al.*, 2017; Jiang *et al.*, 2019; Mansoori *et al.*, 2019; Xiao *et al.*, 2018) (Fig. 2). In the presence of oxygen, most PSs work primarily in Type II reactions. At the same time, it is generally believed that the photodynamic destruction of $^1O_2$ is dominant. Thus, Type II reaction is considered the main reaction in PDT (Lange and Bednarski, 2016; Xiao *et al.*, 2018; Zou *et al.*, 2020).

Reactive oxygen species are by-products of the body's metabolism in an aerobic environment. During the process of oxidative phosphorylation of mitochondria to produce ATP, oxygen molecules are generated through Complex I and Complex III of the inner mitochondrial membrane (IMM) respiratory chain (Battogtokh *et al.*, 2018; Zhang *et al.*, 2018b). When the body is in a pathological state, electrons escape from the mitochondrial respiratory chain, and oxygen molecules are catalyzed by peroxidase to form peroxide ions or superoxide ions. After continuous transformation in the cell, oxygen radicals with active chemical reactions are formed, including superoxide radicals ($\cdot O_2^-$), hydroxyl radicals ($\cdot$OH), hydrogen peroxide ($H_2O_2$), and singlet oxygen ($^1O_2$) (Battogtokh *et al.*, 2018;

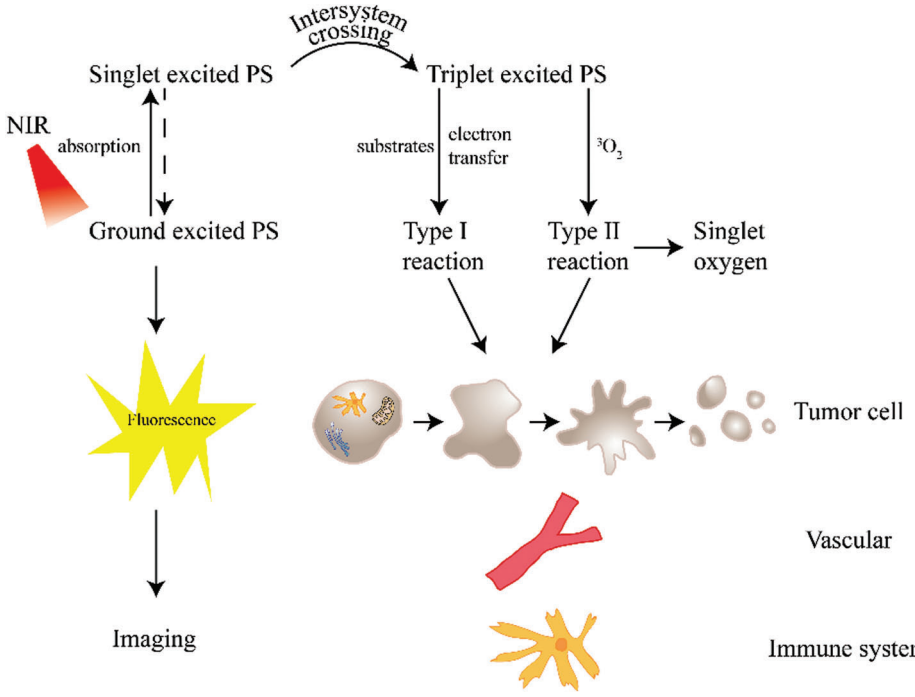


**FIGURE 2.** Mechanism of action of PDT.
The PS absorb photons, it is activated from the ground state to the excited singlet state and emits fluorescence for imaging. Type I or Type II reactions occur after the formation of triplet-excited PSs after intersystem crossing.

Dryden, 2018). Moreover, cytochromeP450 (CYP450), lipoxidase (LOX), cyclooxygenase (COX), and xanthine oxidase (XO) are the pathways of endogenous ROS production (Bouzid *et al.*, 2015; Costa *et al.*, 2016). Some external environments (such as drugs, chemical pollutants, and radiation therapy) can also induce the production of exogenous ROS.

Under normal circumstances, the oxidation and anti-oxidation systems in the cell are in equilibrium (Fig. 3). On the one hand, ROS are continuously generated during the metabolism of healthy cells and participates in many physical functions, such as defense functions and the synthesis of specific physiologically active substances. On the other hand, even if a large amount of ROS is synthesized, it will be adjusted to balance by the body's enzyme and non-enzyme systems. ROS enzymatic scavengers mainly comprise antioxidant enzymes, superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GSH-Px), and glutathione S-transferase (GST). They will continuously clear the ROS produced in the cells (He *et al.*, 2017b). Non-enzymatic ROS scavengers can provide an electron to oxygen free radicals to change their unpaired state to neutralize it, such as glutathione (GSH), thioredoxin (TrxA), vitamin C, and vitamin E (Pizzino *et al.*, 2017).

However, when the body is in a state of disease or stimulated by foreign substances, this dynamic balance may be affected. Excessive ROS accumulation and weakening of the antioxidant capacity will lead to mitochondria dysfunction, which will lead to oxidative stress (Diaz-Vivancos *et al.*, 2015) and excessive oxidation of DNA (Milisav *et al.*, 2018; Singh *et al.*, 2019; Taverne *et al.*, 2018), proteins (Sies, 2018) and lipids (Su *et al.*, 2019a) in cells, inducing cancer (Klaunig, 2018; Moloney and Cotter, 2018). Kasai and Nishimura (Kasai, 1984) first reported the formation of 8-OHdG by oxygen radicals in 1984. ROS attack the 8th carbon atom of the guanine nucleobase in the DNA molecule to produce 8-hydroxy-2 deoxyguanosine (8-OHdG), leading to the translocation of G:C→T:A, which mediates the activation of proto-oncogenes or inactivation of tumor suppressor genes and is involved in tumorigenesis. Chernigina's team (Chernigina *et al.*, 2017) used the DNA comet assay to measure the DNA levels of leukocytes in tumor-carrying rats treated with PDT to indirectly assess and predict the rate of malignant tumor growth. ROS will change the tertiary structure of proteins, facilitate the formation of protein-protein cross-linking, and degrade proteins and inactivate enzymes. Polyunsaturated fatty acids (PUFAs) in the phospholipid of biofilm are very sensitive to ROS attack due to the multiple double bonds with active chemical properties. The oxidation and decomposition of lipids easily occur, causing damage to cells and leading to cell death and body damage (Hauck *et al.*, 2019).

## Mechanism of Action of Photodynamic Therapy

Studies have shown that the anti-tumor effect of PDT stems from three interrelated mechanisms: (1) Direct cytotoxic effect of ROS on tumor cells; (2) Targeting the tumor vasculature, leading to vascular damage; and (3) Activating the immune system, inducing and regulating immune responses (Lan *et al.*, 2019; Van Straten *et al.*, 2017). Cell death and apoptosis mediated by ROS are the fundamental mechanisms for the effect of PDT (Dobson *et al.*, 2018; Olsen *et al.*, 2017; Zou *et al.*, 2017).

### *Cytotoxic effects of reactive oxygen species*

Gapeyev *et al.* (2001) proposed that calcium channels of the plasma membrane could be chosen as the target by external periodic signals under the influence of some external factors. A high concentration of ROS can lead to the opening of the mitochondrial membrane permeability transition pore (mPTP), causing a reduced the mitochondrial membrane potential ($\Delta\psi m$), the release of cytochrome C, the triggering

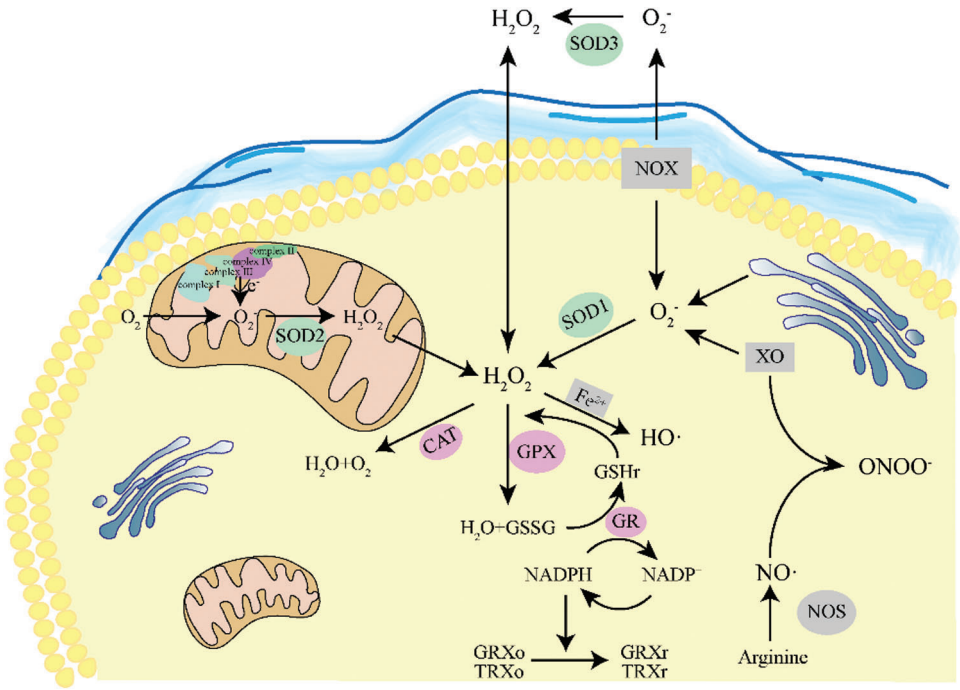


**FIGURE 3.** Schematic diagram of intracellular redox.
The main sites of ROS production include the mitochondrial respiratory chain, endoplasmic reticulum, and NADPH oxidase (NOX) complex.

of the caspase cascade, the destruction of DNA, and accelerate of cell apoptosis. A close relationship exists between the increased ROS content and increased $Ca^{2+}$ concentration in the process of apoptosis (Bertero and Maack, 2018; Zhang *et al.*, 2016a; Zhang *et al.*, 2016c). Cao's study (Cao *et al.*, 2011) showed that, in the apoptosis pathway of breast cancer cells, the $Ca^{2+}$ released in the endoplasmic reticulum and mitochondria was caused by ROS generation, increased $Ca^{2+}$ resulting in the opening of mPTP and decreased of $\Delta\psi m$. The opening of mPTP and decreased $\Delta\psi m$ increased the content of $Ca^{2+}$ in the mitochondria, further intensifying the opening of the pores in the form of positive feedback and amplifying the apoptosis signal in turn, thus forming a cycle favorable to the mitochondrial apoptosis pathway.

As a multi-potent cytokine, tumor necrosis factor-alpha (TNF-α) not only induces cell differentiation, survival, and apoptosis but also changes the intracellular redox state in the cell and increases ROS content (Blaser *et al.*, 2016; Pinegin *et al.*, 2018). TNF-α can change the structure of mitochondrial membrane receptors, inhibit the initial stage of the respiratory chain, and leak unpaired electrons to oxygen molecules so that the intracellular mitochondrial permeability and ROS increase, eventually leading to apoptosis (Zhang *et al.*, 2017b). NOX is one of the most important enzymes responsible for ROS formation. It generates superoxide through the assembly of a multisubunit protein complex utilizing nicotinamide adenine dinucleotide (NADH) or nicotinamide adenine dinucleotide phosphate (NADPH) as the electron donor (Musicki *et al.*, 2010). Studies have shown that FasL can activate Racl protein expression by regulating Ras signaling, and Racl protein can transfer electrons from NADPH to oxygen molecules to form $\cdot O_2^-$. The expression of inhibitor of apoptosis proteins was then down-regulated by the ROS generated through the ubiquitination pathway, causing the activation of downstream caspase-8 and cell apoptosis (Wang, 2008).

*Targeting of blood vessels*

Blood vessels carry nutrients and oxygen to tumor cells, which are essential for tumors to survive and metastasize to other parts of the body. The large blood vessel wall space, poor structure, and insufficient lymphatic circulation in tumor tissue are conducive to PS accumulation (Baluk *et al.*, 2005). However, the tumor area surrounding the normal vasculature may help remove PS. Many specific receptors have been identified in vascular endothelial cells, and the binding of PS to specific vectors such as albumin, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) will enhance the affinity of receptors and uptake of endothelial cells (Bin *et al.*, 2006). When the light source irradiates the PS, singlet oxygen acts on the blood vessel and produces a series of physiological responses such as leukocyte adhesion, platelet aggregation, increased vascular permeability, vasoactive molecule release, and vasoconstriction to prevent tumor vascular remodeling (Dolmans *et al.*, 2002; Hamblin and Abrahamse, 2020; Yanovsky *et al.*, 2019). Vascular endothelial growth factor (VEGF) is a key protein that is a major signaling molecule of hypoxic cells (Chatterjee *et al.*, 2013); PDT can down-regulate VEGF (Bucher *et al.*, 2014; Tong *et al.*, 2016), leading to blood stasis, vascular obstruction, and the lack of oxygen and nutrition in tumor tissue, to achieve the photodynamic treatment effect of the tumor. Aleksandra *et al.* (Kawczyk-Krupka *et al.*, 2018) confirmed that, under hypoxia conditions, ALA-PDT reduces the release of VEGF in SW620 colon cancer cell line, producing an anti-angiogenesis effect.

*The immune response*

Photodynamic therapy also triggers an immune response when it induces necrosis of the tumor and its vasculature. PDT activates the body's innate immunity by triggering inflammation-related signaling pathways, promoting cytokine release, inducing neutrophils and macrophages to accumulate at the tumor site, and activating complement (Maeding *et al.*, 2016; Nath *et al.*, 2019; Showalter *et al.*, 2017). At the same time, macrophages present tumor antigens to $CD4^+$ T lymphocytes by phagocytosis of the killed tumor cells and then activates $CD8^+$ T lymphocytes to induce necrosis and apoptosis of nearby tumor cells, further stimulating specific anti-tumor immunity (Dobson *et al.*, 2018; Wachowska *et al.*, 2015b; Yang *et al.*, 2016). The immune response may occur not only in the PDT site but also in local and distant lymphoid tissues. Kousis's team (Kousis *et al.*, 2007) reported that PDT induces neutrophilic infiltration into the tumor cells and enhances the strength of the tumor-specific primary immune response and establishment of memory antitumor immune responses. Canti *et al.* (2010) confirmed the mechanism by which tumor-bearing mice treated with PDT induce a specific immune response against reattack by tumor cells. Therefore, compared with the immunosuppressive effects of chemotherapy, radiotherapy, and other treatment methods, PDT shows superiority to activate the immune response and control tumor recurrence.

## Challenges and Future Perspectives

The anti-cancer effect of PDT has been discovered for more than a century. PDT, which is a non-invasive and harmless, involving tumor phototherapy tools, plays an increasingly important role in cancer treatment. However, due to complex biological systems and individual differences in patients, different measures should be taken in different clinical situations, such as, changing the light source, designing new photosensitizers to relieve tumor hypoxia microenvironment and combining chemotherapy, photothermal therapy (PTT), and immunotherapy (Liang *et al.*, 2020). It will be a long time and challenge before PDT becomes a first-line treatment strategy for cancer. Researchers hope that synergistically enhanced interactions will have an effect greater than the sum of the treatments, improving the overall outcome and even achieving the optimal outcome of eradicating malignant solid tumors.

*Deep tumor therapy*

The depth of light penetration is one of the prevalent limitations of the applications PDT. Thus, in recent years, the efficacy of PDT has been improved by using

electromagnetic radiation X-rays or fluorescence rays (Mallidi *et al.*, 2016). A series of photodynamic reactions occurs after a PS absorbs light of a specific wavelength, but different irradiation schemes will also produce different results under the same light source. Photons at high fluence rates of light transmission can penetrate the skin to about 3 mm of subcutaneous tissue, but the oxygen content of tumor tissue can also be consumed too quickly. Therefore, the light dosage regimen may also affect the anti-tumor effect, and the optimal dosage regimen may depend on the situation (Keereweer *et al.*, 2014).

*Location of photosensitizer*

Although the enhanced permeability and retention effect (EPR) can increase the concentration of PSs in tumors, the size distribution, morphology, and surface modification can affect the location. HSA consists of three homologous domains, two of which are the major drug binding sites. In clinical application, PS can be administered intravenously or locally, and different PSs will bind to HSA at different sites, so their distribution and pharmacokinetics will change accordingly. From the moment the drug is administered until the PS reaches the target location, various physical, chemical, and biological events occur that together affect the final location of PS.

*Hypoxic tumor therapy*

The Type I reaction in the PDT process and limited range of singlet oxygen causes a hypoxia microenvironment of the tumor, which enhances the resistance of the tumor to PDT. The combination of PS and a catalyst can alleviate hypoxia. Li *et al.* (2018a) assembled a new type of nanostructured phthalocyanine that can efficiently promote ROS production through a Type I reaction. Luo's team (Luo *et al.*, 2020) designed a nano-scale metal-organic framework based on bacterial chlorine, which can perform efficient PDT through Type I and Type II reactions. Deng *et al.* (2020) synthesized IR780 and catalase-co-loaded liposomes and promoted tumor oxygenation by utilizing the high catalytic efficiency of CAT when it encountered $H_2O_2$.

*Combination therapy*

Simple PDT treatment cannot eradicate solid tumors accurately and completely due to its limitations. Chemotherapy drugs inhibit cell division and cause cancer cell death. However, the serious side effects of the drug on the whole body limit its clinical application. Chen *et al.* (2017) described the covalent coupling of HSA to Ce6 after the self-assembly and encapsulation of catalase and the chemotherapy drug paclitaxel (PTX). This effect significantly regulates TME and enhances the anti-tumor effect.

Photothermal therapy is a technique that converts energy from near-infrared radiation absorbed by certain molecules into heat that destroys cancer cells. Different from PDT using external ROS and other oxygen free radicals to kill cancer cells, PTT uses the combination of light and a special light absorption system to induce local overheat, leading to cell death. Li Wei's team (Li *et al.*, 2019) generated a nanosystem comprising indocyanine green conjugated to hollow gold nanospheres and oxygen-transporting hemoglobin liposomes that modify targeted peptides to achieve PDT and PTT.

The immune response induced by PDT involves almost all aspects of the immune system, which may become the target of treatment. Gollnick *et al.* (2002) proposed that, unlike other traditional vaccines, the PDT-generated tumor cell lysates do not require a combination of adjuvants. Ishida *et al.* (2016) used a monoclonal antibody that binds to epidermal growth factor receptors (EGFRs) with PS to allow deeper penetration into tissue and specifically target and eliminate tumors.

## Conclusion

The importance of this review is to briefly introduce the development process, treatment mechanism, current challenges, and prospects for the future of photodynamic therapy. PDT has made great progress with its unique advantages; however, its full potential has yet to be shown. Additionally, the photodynamic reaction is a complex process involving molecular, subcellular, and vascular changes that cause tumor necrosis or apoptosis. There are still many problems in its mechanism of action and clinical application, and clinicians still use a double-edged sword to target and treat tumors. However, as nano-medicine, biology and cutting-edge optical technology development and integration, researchers are working on mechanisms to improve the anti-tumor effect, while reducing the side effects and improving the safety of patients. The combination of knowledge from these fields will ultimately lead to the development of a powerful and immediate treatment for cancer.

We hope this work will raise awareness of the cellular biomechanical aspects of PDT in health and disease, as a direction for the future development of PDT in combination with other therapies, individualized treatment planning, and real-time monitoring, let it play an increasingly important role in the treatment of various malignant tumors and becoming one of the important means of clinical treatment.

**Author Contribution:** Zixuan Wang, Hongmei Peng and Shi Wei wrote the paper and prepared figures and table. Lu Gan, Linlin Xie and Pan Wu conceived the review. Liping Zhong, Jian He and Yongxiang Zhao reviewed drafts of the paper. Zhiming Deng, Hongliang Tang and Yong Huang analyzed and corrected the paper. All authors read and approved the final paper.

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