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Review

A Review of Photodynamic Therapy in Different Types of Tumors

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HIGHLIGHTS

- The photosensitizer is a non-toxic agent activated by light leading to ROS production and increased oxidative stress to diminish cancer cells.
- Photodynamic therapy can be a gifted cancer management strategy.
- We present an overview of photodynamic therapy.

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ABSTRACT

Photodynamic therapy is a novel approach to cancer treatment. It is based on reactive oxygen species production by light illumination on the photosensitizer in the presence of molecular oxygen. The photosensitizer is a non-toxic agent activated by light with a specific wavelength and leads to ROS production and increased oxidative stress in cancer cells to kill them. For treating the patient, after administration of photosensitizer, it distributes to different organs and the tumor environment. The photodynamic actions happen with illuminating light on the tumor's location, and the tumor will be destructed. In this review, we introduce the mechanisms of photodynamic therapy and its components.

Keywords: Photodynamic Therapy; Cancer Treatment; Photosensitizer

Introduction

Photodynamic therapy (PDT) is a new cancer therapy process for some kinds of diseases like cancers. It is constituted by light, photosensitizer, and oxygen. The photosensitizer is excited and activated with the illumination of light at a specific wavelength, and it moves its exciting energy to the molecular oxygen in malignant tissues. This leads to the generation of singlet molecular oxygen ($1O_2$) and other reactive oxygen species, which induce apoptotic or necrotic tumor cell death (1, 2). The tumor environment is different from normal cells, so it is hypoxic with acidic PH, so its metabolites are different from normal cells (3, 4).

PDT effect was first discovered by Oscar Raab around the 1900s. He observed that exposure to light could kill micro-organisms such as paramecia incubated with certain dyes. In the 1970s, Dr. Thomas Dougherty's efforts in the U.S.A led to a new chapter using light. His co-workers introduced Haematoporphyrin Derivative' (HpD) as the first PS. In 1995, a more purified preparation of

HpD called Photofrin received FDA approval as a clinical application of PDT. The first applications of PDT were for superficial tissues using visible light. However, utilizing PDT to treat different deep tumors became feasible over time with some advancements. For example, optical fibers make it possible to transfer the light to the deep tumor and illuminate the target site (5, 6). The past 30 years have witnessed the clinical introduction of PDT as an approved or experimental treatment option for several solid neoplasms.

PDT has treated different cancers as an approved or empirical treatment option during the past three decades. Some examples of these cancers and the outcome of the treatments are:

Actinic keratosis: ALA-PDT for individual lesions is preferred from cryotherapy and has better cosmetic results.

Gastrointestinal system tumors: Esophageal carcinoma: Morbidity and mortality in PDT are less than in surgery. Palliating symptomatic advanced superficial esophageal cancers have been reported in PDT.

Non-small-cell lung cancer tumors: Surgical resection is more effective than PDT and stays the standard of care. However, PDT can ameliorate surgical outcomes, lessen symptoms, and extend survival.

Brain tumors (Glioma): PDT and fluorescence-guided surgical resection have been shown to have prolonged survival than surgery and radiotherapy.

Head and neck tumors: Oral squamous cell carcinoma: Surgery remains the gold standard for tumors larger than 2-3 mm. However, PDT is promising in early cancers, and it preserves oral tissue.

Genitourinary system tumors: Prostate cancer: Early-stage prostate cancer management with PDT is preferred from surgery or ionizing radiation therapy because of the selective targeting of the prostate gland. Vascular-targeted PDT by Padeliporfin as photosensitizer with a short drug-to-light interval has proven to be an effective treatment for low-risk localized PC.

Bladder cancer (BC): Urinary bladder cancer is a potential target for photodynamic diagnosis and therapy. PDT for superficial BC can be tolerated well with haematuria, and skin photosensitivity being the most common acute side effects. Although there are promising results for using Photodynamic therapy for BC, it remains experimental with limited use (7, 11).

This review will discuss the basics of PDT, mechanisms of its action, photosensitizers, cellular and molecular impressions of PDT, its limitations, and combinations with other treatment modalities.

Principles of PDT

For interstitial tumors, the photosensitizer (PS) can be administered Intravenous (i.v) or topically. The light can be illuminated by tumor tissue via optical fibers to activate the PS accumulated in the target tissue (12). The duration time between administration of the PS and the illumination of light called the drug-to-light interval, can be different according to the PS's pharmacokinetics and other properties. The PS administrational route is chosen according to the tumor site and PS pharmacokinetic properties. For example, topical application is utilized for cutaneous lesions, while Intravenous administration is used for deep-seated tumors. After administration of the PS, it distributes in many tissues, and by illumination of light to the specific site, the photochemical reactions start, which leads to oxidative stress in tumor cells and destruction (13) (Figure 1).

Photochemical Mechanisms

The photosensitizer molecule absorbs the light's energy and transfers from its ground state with two electrons in opposite spins (singlet state) to a singlet excited state with one electron into a higher-energy orbital. This exciting photosensitizer has a very short lifetime and can return to the ground state without losing the excess energy as fluorescence emission or heat production. However, it can form a more stable excited triplet state with parallel spins with a process known as 'intersystem crossing.' So, this can transfer its energy to molecular oxygen (O_2), which

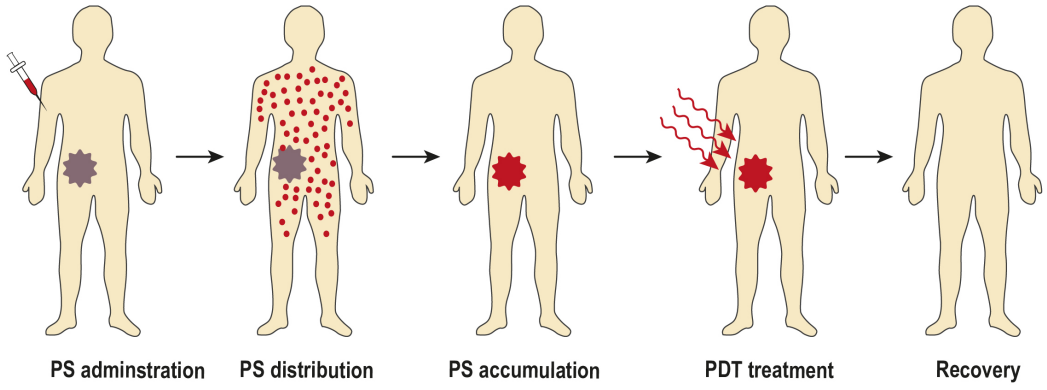

Figure1. Photodynamic therapy for cancer treatment.

is in a triplet state in its ground state and forms singlet oxygen ($^1O_2$) and returns to its ground state (Type II photochemical process). On the other hand, the excited-state photosensitizer can form reactive oxygen species (ROS) hydroxyl radicals ($HO^{\bullet}$), hydrogen peroxide (H_2O_2), and superoxide ($O2^{-\bullet}$) through electron transfer reactions (Type I photochemical process). The process of Type II is more desirable in anti-cancer PDT because it is more straightforward than Type I, and the PS is reproduced at the end of the reaction so it can be used many times (14) (Figure 2).

Mechanisms of Action

The reactive singlet oxygen can lead to different consequences, either inducing tumor cell death (apoptosis or necrosis), occluding tumor vasculature, or modulation of immune responses (15). Each mechanism will be discussed below.

1. Direct photo killing of cancer cells

PDT can cause irreversible photodamage to different cell organelles such as the mitochondria's plasma membrane and intracellular membranes, endoplasmic reticulum (ER), Golgi apparatus, and lysosomes. The location of the photodamage depends on the subcellular accumulation of the photosensitizer. As most PSs' localizations are out of the cell nucleus, DNA damage, mutations, and carcinogenesis is not common in PDT. In general, apoptosis is a consequence of the activation of PS in mitochondria or the ER with a sufficient amount of oxidative stress, while necrosis results from the plasma membrane or lysosome's destruction upon PDT (16).

2. PDT and Apoptosis

Programmed cell death, also known as apoptosis, is encoded in various cell types and can be activated by different pathways. For instance, the release of cytochrome c from mitochondria to the cytoplasm or the activation of death receptors leads to the initiation of caspase cascades such as caspase-3, 6, and 7 called "executioner caspases" (17).

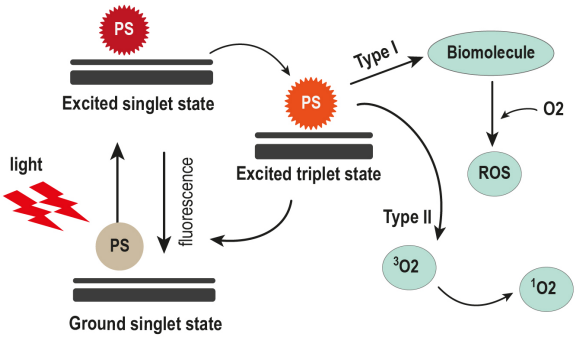

Figure 2. Photochemical mechanism of activation of photosensitizer by light. Following light absorption, the PS reaches an excited singlet state. After an intersystem crossing, the PS can react with a hydrogen atom transfer to shape radicals. It can react with molecular oxygen (type I reaction) or singlet oxygen (Type II reaction).

2.1. Bcl-2 Family and PDT Response

A) The Pro-Survival Family

Studies have shown that Bcl-2 and related ant apoptotic proteins are degraded through photo damaging by the PDT, and PDT activates the pro-apoptotic family members. It has been stated that PDT leads to Bcl-2 family protein expression changes.

It is proposed that overexpression of both Bcl-2 and Bax, caused by transfection of Bcl-2, increased the Bax: Bcl-2 ratio and induced initiation of apoptosis because Bcl-2 is vulnerable to photodamage, unlike Bax (18-22).

B) The Pro-Apoptotic Family

Comparing normal cells and cells treated with PDT showed that PDT increases Bax protein and Bax/Bcl-2 ratio. There are also damage sensors in cells known as the BH3-only proteins, which antagonize the pro-survival proteins (17).

2.2. Cytochrome Release after PDT

The significant role of mitochondria in initiating the apoptotic cascade is widely accepted. It does this job by reserving the critical factors for initiating apoptotic cascade mainly, such as cytochrome c. releasing the cytochrome c into cytosol activates the caspases. Proteins of the Bcl-2 family regulate this process (23).

2.3. Death Receptors and PDT Response

Death receptors are members of the tumor necrosis factor receptor superfamily (TNFR), and most of them are transmembrane signal transducers. At least one specific ligand for each death receptor, but some ligands can bind to several receptors. PDT can cause upregulation of Fas protein in a time-dependent manner. The increase of Fas-associated death domain level (FADD) in immunoblot analysis confirmed that PDT induces apoptosis through Fas activation. Evidence suggests that APO2/TRAIL also results in apoptosis following PDT (17,24).

3. PDT and Necrosis

Physical or chemical damage to a cell can result in accidental or unprogrammed cell death, known as necrosis. PDT also can induce necrosis. However, the cell death type is determined by factors such as the cell type, the presence of an intact set of apoptosis machinery, the subcellular localization of the PS, the light dose applied to activate it locally, and the oxygen partial pressure. For example, it is widely accepted that high dose PDT leads to necrosis while low dose PDT tends to induce apoptosis (16, 25).

4. PDT and Autophagy

ROS production of PDT increases oxidative stress and leads to cellular organelle damage. So, autophagy is initiated by Beclin one protein and degrades these damaged organelles. This process can have a cytoprotective effect or lead to autophagic cell death. Whether one of these consequences happens depends on the type of ROS and degree of oxidative injury. In addition, following PDT, autophagy has a pro-survival effect in a cell with an efficient apoptotic pathway, while it has a pro-death effect in apoptosis-deficient cells. Inactivation of negative regulators of autophagy by PDT has a more critical role in the induction of autophagy than activating autophagic proteins by PDT (17).

5. Vascular Effects of Photodynamic Therapy

Application of PDT with many photosensitizers on solid tumors would lead to vascular damage and blood flow stasis. Generally, this phenomenon initiates endothelial cell changes and the formation of thrombogenic sites. Cascade of responses starts in these sites such as; the release of vasoactive molecules, platelet aggregation, and vessel constriction, leading to blood flow stasis. Vasculature network of tumor disruption can cause tissue hypoxia, death of tumor cells, and nutrient deprivation. On the other hand, blood flow stasis and hypoxia during PDT would limit ROS generation and decrease the efficiency of the PDT. Studies showed that endothelial cells' response to PDT occurs in lower than cytotoxic doses.

The responses include releasing clotting factors, such as the von Willebrand factor, and Calcium influx into the endothelial cells. The latter is responsible for cytoskeletal changes and changes in cell shape. It leads to interruption of cell-cell communication and the extracellular matrix exposure to circulating platelets and activating them. There is also a release of vasoactive factors like eicosanoids, cytokines, and histamine. The release of these factors leads to arteriole constriction and enhances vessel permeability. The latter can increase the interstitial pressure in tissue, leading to the compression of small vessels and assisting blood flow stasis in the treated compartment. PDT also can damage platelets directly and make them release proaggregatory substances, thus leading to platelet activation. Photosensitizers that work through the vascular mechanism have shorter drug to light intervals than PSs that work interstitially. Some instances of this group of photosensitizers include Photofrin, hematoporphyrin, , phthalocyanines, protoporphyrin IX, benzoporphyrin derivatives, and purpurins (26).

6. Immunological mechanism of PDT

Inflammatory response and release of cytokines, activation of the innate immune system, and adaptive immune induction can result from photodynamic therapy. The systemic antitumor immune response can control distant metastases and prevent tumor relapse, an Ideal anticancer therapy. However, PDT alone is often insufficient to activate an immune response that could result in tumor rejection (27).

6.1. Induction of inflammatory response

Post PDT inflammatory response would be employed to clear dead and damaged cells, restore injured tissue, and recover its function and homeostasis. Inflammatory mediators and vascular events induce this response. Arachidonic acid metabolites are potent mediators released by photo-oxidative damage of cell membranes due to the peroxidation of lipids. In addition, PDT-mediated oxidative stress can upregulate the expression of stress-induced proteins and cytokines (28).

6.2. Innate arm of immune response

Although the release of inflammatory mediators and cytokines directly results from damage to the tumor and stroma cells, further elevations are caused by signaling pathways and transcription factors such as activator protein 1 (AP-1) or nuclear factor κB (NF-κB). Animal and human studies demonstrated the increase of tumor necrosis factor α (TNF-α) and several cytokines, like interleukins (IL)-1B, 2, 6 after PDT that the IL-1β was thought to be the most important one. These signals result in the infiltration of various immune cells in the targeted tissue. Immune cells infiltrated mainly consist of neutrophils, mast cells, monocytes/ macrophages, and NK cells.

Different natural and oxidatively changed tumor antigens and cell stress factors known as damage-associated molecular patterns (DAMPs) are released from PDT-induced damaged cells. These factors, plus other pro-inflammatory signals, could activate both innate and adaptive immune responses (21, 28, 29).

6.3. Adaptive arm of immune response

The mentioned effects of PDT on inflammatory response and tumor antigens release can stimulate T cell effector functions by maturation and activation of DCs. Activated T lymphocytes could become effector T cells within an effective immune response and kill the malignant cells after migrating to tumor tissue (27).

6.4.Immunosuppressive effect of photodynamic therapy

Immunosuppressive mechanisms prohibit destructive over-active immune responses after every solid immune activation. So, several studies have revealed post-PDT immunosuppression. It was also demonstrated that macrophages could transfer adoptive immunosuppression and cause systemic immunosuppression after PDT. Transporting tumor antigens by PDT-activated DCs to

the lymph nodes inhibits immune response and stimulates it. T cells' function could be limited by regulatory T cells (Tregs) or immunosuppressive cytokines such as IL-10 or transforming growth factor β (TGF-β), which are increased after PDT treatment. Tregs levels are increased in spleens and lymph nodes (LNs) in a tumor-bearing mouse in response to PDT treatment. Immunogenic molecules, such as DAMPs, released post-PDT may become inactivated by ROS generated during PDT (30).

Properties of ideal Photosensitizers

An ideal PS should produce a high yield of singlet oxygen efficiently. It should have a high absorption coefficient in the long-wavelength region (700 nm to 800 nm) because of better penetration of this range and sufficient energy to excite the PS. It should have no dark toxicity and not influence the tissues without applying light to them. It should selectively accumulate in tumor tissue (fast tumor accumulation, rapid clearance from other organs , and preferential tumor retention). Tumor uptake of the photosensitizer is affected by its distribution, so it should be amphiphilic water-soluble and have a hydrophobic matrix. It should be stable and easy to dissolve in injectable solvents (31, 32).

First-Generation Photosensitizers

First-generation PSs are tetrapyrroles derived from hemin named hematoporphyrins. The first clinically approved photosensitizing agent and Photofrin were purified oligomeric mixtures of hematoporphyrin. It was administered intravenously, and the light was applied 48–72 h later. Subcellular accumulation of Photofrin is in the mitochondria and lysosomes, inducing cell death mainly via apoptosis. First-generation limitations can be summarized in low penetrance of their chemical instability, low in vivo yield of singlet oxygen, offsite accumulation, hydrophobicity-induced aggregation, and excitation wavelengths (31, 32) (Figure 3).

Second-Generation Photosensitizers

Second-generation PSs are improved agents in consideration of the limitations of the first-generation. Water solubility, tumor targeting, and peak absorption wavelength were increased. They are monomeric mixtures of porphyrin precursors, phthalocyanines, chlorins, and bacteriochlorins. They have more solubility because of different side chains, faster clearance times, and improved intratumoral distribution. Increasing the singlet oxygen generation and intracellular localization were the primary aims of designing the second-generation PSs. However, the results were not encouraging for using these agents in clinical models. The drawback of these agents is low specificity to tumor cells in passive targeting. Also, decreasing oxygen concentration by oxygen consumption of PDT and intratumoral light scattering are not assessed by in vitro studies (Figure 3). 5-Aminolevulinic acid (5-ALA) is an essential precursor of porphyrins. It is a natural metabolite found in all cells. While utilizing exogenous 5-ALA leads to the accumulation of PS protoporphyrin IX (PPIX) in neoplastic tissue, which can be used in PDT (31, 32) (Figure 4).

Third-Generation Photosensitizers

Designing the new agents as third-generation PSs for improving tumor targeting by conjugation targeting moieties and nanostructure, increasing the phototoxicity, and absorbing even longer wavelengths has been in progress (Figure 3). These photosensitizers are also designed for combinatorial therapies with photothermal therapy, Photodynamic therapy, and chemotherapy (33).

Targeting

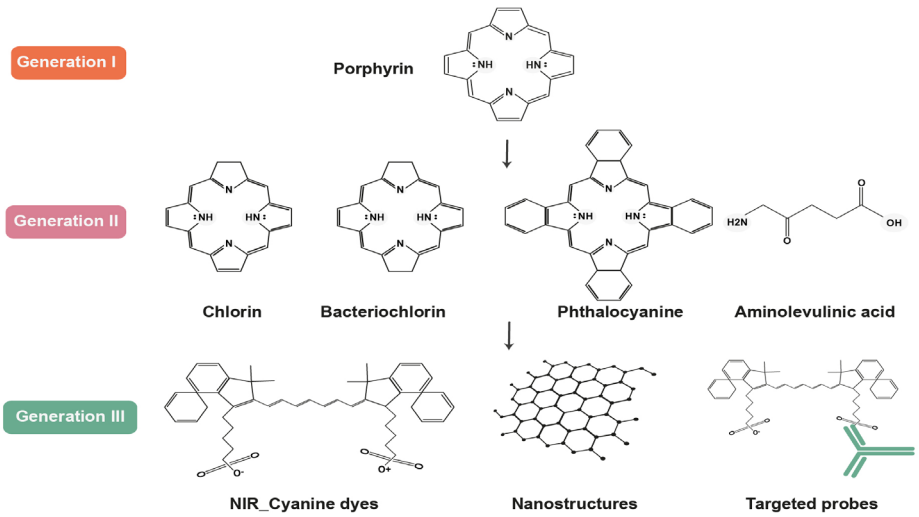

Figure 3. Three generations of photosensitizers

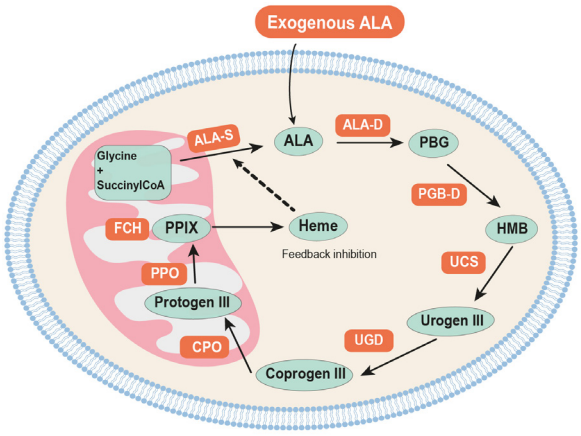

Figure 4. Protoporphyrin IX (PPIX) and Heme production from 5-ALA. Schematic expression of the formation of protoporphyrin IX (PpIX) through the Heme formation pathway after external dosing of 5-aminolevulinic acid (ALA).

1. Passive Targeting

The property of the tumor tissue, such as high permeable vasculature and low lymphatic drainage, known as the enhanced permeability and retention (EPR) effect, leads to more accumulation of PS in these sites than in normal tissues. This passive targeting has been used in traditional PDT and Nanomedicine to deliver chemotherapeutics to the tumor sites and reduce the side effect in other organs. The EPR effect is not similar in various kinds of cancers, patients, and even tumors within the same individual (33, 34).

2. Active Targeting

Tumor-targeting agents have been used to improve the tumor specificity of PS and overcome the limitations of passive targeting. Small molecules and antibodies are the tumor-specific agents that can conjugate with PSs. Small molecules are not expensive and do not inhibit the cellular uptake of PSs. For instance, Simple sugars like glucose are used in tumor targeting because of overexpression of glucose transporter 1 (GLUT-1) in tumor cells. Tumor cell specificity of antibodies is much more than small molecules. However, significant antibodies conjugated to PSs have low distribution in tumors and more vascular circulation. Smaller antibody fragments can be used to improve penetration and reduce circulation. On the other hand, they need higher-affinity binding to inhibit dispersing from cancer tissue and clearance. Expensive manufacturing, inducing an immune response, and lack of targetable receptors in several tumors are some limitations in antibody targeting (33, 34).

Gene expression alterations after PDT

Transcriptomic analysis after treating tumor cells with PDT demonstrated that several physiological and biochemical interactions are altered in these cells. Many studies reported that sub-lethal PDT leads to activation of survival signaling through HIF-1, NF- κB, AP-1, and HSF, while supralethal PDT does not. The clinical outcome of the PDT would be threatened by survival signaling. In addition, it reported that the cells treated with sub and supralethal PDT downregulated proteins associated with (Epidermal growth factor receptor) EGFR signaling. Proteins involved in EGFR signaling are overexpressed in several cancer types. Thus, it may be an important therapeutic target. Inhibiting this pathway would result in deterring tumor growth and inducing apoptosis. Reports of the metabolomics analysis of cells exposed to PDT revealed downregulation of several components of energy metabolism (glycolysis, TCA cycle), changed cellular redox homeostasis, and upregulation of components of nucleotide metabolism and the pentose phosphate pathway. Disrupted energy metabolism is detrimental to cell viability and proliferation. However, altered redox status would be because ROS production and the pro-oxidative state after PDT can lead to upregulation of the pentose phosphate pathway, which plays a vital role in antioxidant response. Downregulations of proteins involved in adherence junctions (EpCAM), tight junctions (phosphorylated ZO1 and ZO3), and focal adhesion (CAV1) have been reported for Photodynamic therapy at LC90. PDT might damage proteins involved in cell-cell adhesion, cytoskeletal structure, and focal adhesion depending on cell type, photosensitizer concentration, and light dose. Loss of adhesion proteins would be associated with invasion and higher metastatic potential after PDT (35).

Using MB as a photosensitizer in a study on the HNSCC cell line demonstrated that PDT reported significant down-regulation of BCL2 and up-regulation of CASP3 and BAX genes at the mRNA level. In another study, untreated cells were compared with cells surviving PDT and revealed lower expression of hsa-miR-16 in treated cells. These results suggest that the survived population has increased their viability via reducing hsa-miR-16. The mechanism seems to be related to damage protection, the cell cycle, proliferation, and apoptosis (36).

Proteomic analysis of PDT on prostatic cancer cells showed a reduction of translationally-controlled tumor protein (TCTP) in both PC-3 and LNCaP, up-regulation in Human RAB GDP dissociation inhibitor (GDI) in LNCaP cells, and RAS-related homologs (Rho) GDI in PC-3 cells. TCTP is related to such vital processes in human prostate cancer cells, such as apoptosis, cellular differentiation, and the control of sperm functions. GDIs inhibit the detachment of GDP from RAS superfamily members and keep them inactive that leading to cell growth inhibition. In addition, the mass spectrometry analysis revealed the expression of the peroxiredoxin-2, 3, and 6 after PDT related to the antioxidant defense system (21, 37-39).

Resistance to PDT

1. Survival pathways activated in tumor cells post-PDT

Survival mechanisms of tumor cells exposed to sub-lethal oxidative stress can be activated and lead to resistance of the tumor to PDT.

Activation of the PS in cells by PDT generates ROS with a very short lifetime, and this ROS leads to changes in other substances like (per) oxidized proteins, protein residues, and lipids. These secondary metabolites can disrupt cellular redox homeostasis in tumor tissues. The incapability of these cells to restore cell function and homeostasis results in the second wave of cell death (40, 41).

2. The NRF2 pathway

NRF2 activation can result in antioxidant response after PDT and restore intracellular redox homeostasis. In addition, NRF2 increases the expression of HO-1 and MDR proteins (at least ABCG2) which are cytoprotective against PDT (42).

3. The NF-κB pathway

Nuclear factor-kappa B (NF-kB) is a family of dimeric transcription factors kept in the cytoplasm by IkBs (specific inhibitors of kappa B), and they can be translocated to the nucleus following specific stimulations. Then, they target four categories of genes: immune regulatory and inflammatory genes; anti apoptotic genes; genes that positively regulate cell proliferation; genes that encode negative regulators of NF-kB. NF-kB act as a programmed cell death inhibitor. Oxidative stress caused by PDT leads to activation and translocation of NF-kB to the nucleus, resulting in an anti-apoptotic signal for cells exposed to PDT. PDT induces the NF-κB pathway that leads to the increase of at least two downstream targets, including COX-2 and surviving. Preventing apoptosis and promoting angiogenesis can result from the activation of this pathway. However, it was reported that PDT downregulated NF-κB in nasopharyngeal carcinoma (hypericin as photosensitizer) and breast cancer cell lines (C-phycocyanin as photosensitizer). On the other hand, NF-κB upregulates many pro-inflammatory cytokines that induce an antitumor immune response. As inhibition of this pathway can reduce cytokines and chemokines released from PDT-treated tumor cells, antitumor immune response and long-term therapeutic efficacy can be disrupted. Thus, further studies should be done to clarify the benefits of the pharmacological inhibition of the NF-κB pathway (42).

4. The HIF-1 pathway

Hypoxic conditions in tumor tissues activate HIF-1, which leads to upregulation of transcription of genes involved in anaerobic metabolism and antioxidant responses. Hyperactivation of HIF-1 in severe hypoxia or anoxia regulates downstream responses to increase cell survival. Activation of HIF-1 following PDT results in the release of proangiogenic factors. Hypoxic preconditioning caused by poor vasculature of the tumor can both upregulate HIF-1, and low accumulation of photosensitizer molecules administered systematically. Overexpression of HIF-1 in tumor cells decreases PDT efficacy, and the co-administration of HIF1 inhibitors can prevent this phenomenon which was reported in several studies (42).

5. The proteotoxic stress response

As mentioned before, ROS generation leads to the oxidation of lipids and proteins. Protein oxidation results in misfolding protein or protein aggregation formation, known as proteotoxic stress. UPR is a group of transcriptional responses triggered by proteotoxic stress. ATF6, protein kinase RNA-like ER kinase (PERK), and Inositol requiring protein 1 (IRE1) are the main transcription factors that mediate UPR (43). Whatever cell type and PDT strategy is, proteotoxic stress is the primary response to PDT. However, photosensitizers localize in ER, such as hypericin, induce UPR more effectively than other photosensitizers. The net effect of this response can be both protective and destructive in tumor cells. For developing tumor cell death, inhibiting pharmacologically the protective effects can be helpful. Inhibitions of HSP70, HSP90, and proteasome have been studied, and it was demonstrated that they could increase the efficacy of PDT (42).

6. Other Resistance Mechanisms

Autophagy, as discussed above, has a prosurvival effect under specific conditions. The efficacy of PDT targeting mitochondria would be influenced by autophagy. Autophagy-inhibiting agents have been used to sensitize cells to PDT. A combination of lysosome- and mitochondria-targeting PSs would help prevent autophagy-mediated resistance, but more preclinical studies are required to evaluate the efficacy of this strategy. The function of the PDT primarily depends on ROS generation and the formation of oxidative damages to membranes and organelles. However, some agents in tumor cells promote resistance to cell death following PDT. These include high superoxide dismutases (SODs), glutathione peroxidase, and thioredoxins. Applying PDT on MDA-MB-231 breast cancer cell xenografts demonstrated a rapid rise in inducible nitric oxide synthase (iNOS) and nitric oxide, preventing ROS-induced apoptosis and promoting tumor growth. Drug efflux pumps like ABCG2 have essential roles in drug resistance. This also happens in PDT. ABCG2 was found to be expressed in multidrug-resistant tumors and decrease the concentration of some PSs that are its substrate in the targeted cells. Low-dose PDT upregulates its expression and leads to a decrease the PDT efficiency. Several studies showed that utilizing inhibitors of these pumps improves the outcome of the PDT (33).

Recent Limitations of PDT Utilization in Cancer

1. Light

As discussed earlier, activating a photosensitizer requires light illumination with a specific wavelength. This necessity has both advantages and disadvantages. The site where PS should be excited can be selected by applying the light. On the other hand, light penetration in tissues does not go beyond

millimeters (7, 44).

2. Oxygen

Oxygen is a critical component of PDT that can limit the effect of PDT. Tumor tissues have a hypoxic condition due to their fast development and inadequate vasculature. This hypoxic condition can induce resistance to certain chemotherapies, radiotherapies, and PDT (7, 44).

3. Photosensitizer (PS)

The properties of an ideal photosensitizer were mentioned above. In addition to those properties that affect PDT efficiency, pharmacokinetic properties and subcellular compartment targeting are also important. Fluorescence emission can be helpful for theranostic purposes besides PDT (7, 44).

Combinations with PDT and Novel approaches

A combination of different cancer treatment modalities such as chemotherapy, immunotherapy, photothermal therapy (PTT), and son dynamic therapy (SDT) can enhance the efficacy of PDT. The use of chemotherapeutic agents like Methotrexate for cell cycle arrest has been shown to increase the efficiency of PDT. PDT can induce an immune response against tumor cells, and synergistic therapy approaches combined with cancer immunotherapy lead to tumor regression and achievement of immune memory. PTT is oxygen-independent and generates high temperatures that damage the surrounding cell membranes or cause protein denaturation. In combination with PDT, increasing blood flow improves drug delivery efficiency, alleviates hypoxia in tumor tissue, and improves PDT efficiency. Similar to photosensitizers, some agents called sonosensitizer can be active by ultrasound. The penetration of ultrasound is much higher than light. However, the sonosensitizerF variety is much lower than the photosensitizer. Thus, combining these two therapies can have a synergistic effect and have higher efficiency than monotherapy (7, 44).

Conclusion

Photodynamic therapy can be an appropriate approach in many cancers and substantial tumors. It is used as a focal treatment, so it has not many serious side effects. PDT has some limitations, and research is conducted to overcome these limitations by designing new photosensitizers and agents based on nanotechnology and combining PDT with other treatment modalities.

Authors' contributions

All authors contributed equally.

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Conflict of interest

All authors declare that there is no conflict of interest.

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Ethical statement

Not applicable.

Data availability

Data will be provided by the corresponding author on request.

Abbreviations

DAMP	Damage-associated molecular patterns
EGFR	Epidermal growth factor receptor
EPR	Enhanced permeability and retention
FADD	Fas-associated death domain level
HpD	Haematoporphyrin derivative
IL	Interleukin
PC	Photosensitizer
PDT	Photodynamic therapy
PTT	Photothermal therapy
ROS	Reactive oxygen species
SDT	Son dynamic therapy
SOD	Superoxide dismutases
TCTP	Translationally-controlled tumor protein

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