

Mechanisms of photodynamic therapy with applications in tumor cells

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Abstract:

Photodynamic therapy (PDT), as an innovative cancer treatment, has attracted widespread attention in recent years. The aim of this study was to explore the efficacy of PDT in the treatment of specific types of cancer and its mechanism of action, especially how to destroy tumor cells by selectively using photosensitizers and specific wavelengths of light while minimizing the damage to the surrounding normal tissues. By comparing and analyzing the effects of multiple photosensitizers, this study focuses on evaluating the efficacy and safety of PDT in clinical applications. This paper analyzed a variety of cancer models, including skin cancer, head and neck cancer, and certain deep-seated tumors, to evaluate the therapeutic effects under different photosensitizers and light conditions. The results show that by optimizing the choice of photosensitizer and light parameters, PDT can significantly inhibit tumor growth with high selectivity and reduce the damage to healthy tissues. In addition, PDT activates the immune response, which includes immune activation, antigen presentation, immune memory, and regulation of the immune microenvironment (TME), providing an additional mechanism of action for tumor therapy.

Keywords: Photodynamic therapy; tumor cells; photosensitizer; efficacy; immunotherapy.

1. Introduction

In today's medical field, the development of cancer treatment methods is moving towards greater precision and personalization. Photodynamic therapy, as a method that uses photosensitizers and light irradiation at specific wavelengths to generate reactive oxygen species, directly kills cancer cells and destroys tumor blood vessels. This process not only leads to local physical damage to the tumor, but also triggers an inflammatory response that promotes heat shock protein expression and immune cell infiltration, thereby activating the host's immune system. PDT-induced cell death releases tumor-associated antigens, which are captured by the immune system and undergo antigenic presentation, triggering a specific immune response against the tumor, including the establishment of a long-term immune memory and the regulation of TME. This mechanism provides a theoretical basis for combining PDT with other immunotherapies aimed at enhancing therapeutic efficacy, particularly through immune checkpoint inhibitors (ICIs) to overcome tumor immune evasion.

PDT offers unique advantages over traditional surgery, radiotherapy and chemotherapy, including lower side effects, high selectivity and protection of surrounding healthy tissues. In addition, PDT is associated with less discomfort and faster recovery time, which greatly im-

proves patients' quality of life. However, despite the fact that PDT shows great potential in clinical treatment, there is variability in its efficacy in different cancer types, at different stages, and among individual patients. This variability requires more in-depth research and optimization of the mechanism of action of PDT, the selection of photosensitizers, light parameters, and treatment strategies. Currently, scientists and clinicians are working to expand the application of PDT and improve its therapeutic efficacy through the development of innovative photosensitizers, the improvement of light source technology, and the exploration of combined therapeutic strategies.

The aim of this paper is to review the recent advances of PDT in cancer therapy, to discuss its challenges and future directions, as well as to provide new perspectives and strategies for cancer treatment. Through an in-depth analysis of the existing literature, this paper will provide a comprehensive understanding of the therapeutic principles of PDT, the current state of clinical application, and potential avenues for improvement for further research and clinical practice.

2. PDT

2.1 Introduction of PDT:

PDT is a method of treating cancer using a photochemical reaction produced by the interaction of a photosensitizer,

light and oxygen.

In the early 1900s, German scientists Oscar Raab and Hermann von Tappeiner conducted research that is considered to be the beginning of the field of PDT. They discovered that microbial cells could be killed in the presence of certain dyes (e.g., goitrogens) and light. This phenomenon is known as „photodynamic action“. Based on this, American scientist Thomas Dougherty and others conducted a series of studies, and Dougherty’s team discovered that the use of hematoporphyrin derivatives as photosensitizers successfully inhibited tumor growth in animal models. With the development of the first generation of photosensitizers and clinical trials, PDT began to be used in the treatment of skin cancer, head and neck cancer and many other types of cancer. And the development of second-generation photosensitizers has led to a dramatic expansion of the application of PDT. These new photosensitizers have higher selectivity and lower side effects, allowing PDT to be used more effectively in the treatment of deep-seated tumors. Today, with advances in nanotechnology, targeted delivery systems, and improvements in light source devices, the therapeutic efficacy and application areas of PDT continue to expand.

2.2 The Application of PDT in Clinical Care

PTD has evolved from an exploratory treatment to an important complementary cancer therapy, and with its unique therapeutic mechanism - combining photosensitizers, specific wavelengths of light, and oxygen to produce a photochemical effect that directly kills cancer cells, destroys the tumor vasculature, and triggers an immune response - it has demonstrated significant benefits in the treatment of certain cancers and non-cancer diseases. certain cancerous and non-cancerous diseases.

2.3 Principle of Operation of PDT

PDT is mainly composed of three elements: PS, excitation light of specific wavelengths and oxygen (O₂). PDT can be categorized into two types, type I and type II, based on photophysics and photochemistry [1]. Type I PDT is a photodynamic reaction based on electron transfer that generates free radicals (e.g., O₂^{-•}, HO[•] and H O₂₂), but it is not the main mechanism of most PDTs; Type II PDT is the interaction of triplet-state photosensitizers with triplet-state molecular oxygen, which results in the formation of singlet-line oxygen (¹O₂), which then induces apoptosis and kills the tumor cells, and the process requires the participation of O₂ [2].

2.4 Mechanism of Action of Type I PDT and its Effects

Type I PDT is a photodynamic reaction based on electron transfer that generates free radicals (e.g., O₂^{-•}, HO[•] and H O₂₂), but is not the primary mechanism of most PDTs [2], During type I PDT, activated photosensitizers interact directly with cellular components (e.g., membrane lipids or proteins) to generate free radicals by electron transfer. These free radicals are extremely reactive and are capable of directly damaging the cell membrane, leading to cell death. In addition, this direct action triggers oxidative stress within the cell, accelerating the apoptotic program [3], as shown in Figure 1.

In terms of effects on the immune system, type I PDT is able to induce a localized inflammatory response, a process that attracts immune cells such as macrophages and T-cells to congregate in the treated area through the release of cytokines and chemotactic factors. This activation and aggregation of immune cells contributes to the removal of dead tumor cells while increasing the body’s immune surveillance of the tumor.

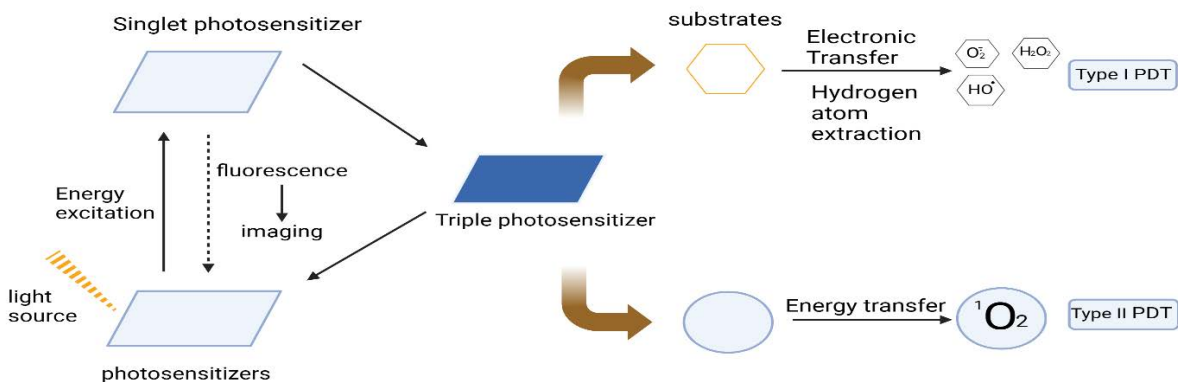


Fig. 1 Schematic diagram of the mechanism of PDT

2.4.1 Mechanism of action of type II PDT and its effects

Type II PDT involves the interaction of a triplet photosensitizer with triplet molecular oxygen to form ¹O₂, which

in turn induces apoptosis to kill tumor cells, a process that requires the participation of O₂ Type II PDT, on the other hand, relies mainly on energy transfer, whereby light energy absorbed by the photosensitizer is transferred to the oxygen molecules, generating single-linear state oxygen [2]. Single-linear state oxygen is very chemically active and can rapidly react with a variety of biomolecules in the cell, including lipids, proteins and nucleic acids, leading to cell damage and death [3], as shown in Figure 1.

In terms of the immune system, type II PDT is able to stimulate a more intense immune response. Monoliner oxygen can not only kill tumor cells directly, but also activate the specific immune response by promoting the release of inflammatory mediators and enhancing the presentation of tumor antigens. This specific immune response not only targets tumor cells in the treated area, but also fights against distal untreated tumors in the body, showing a certain „immune memory“ effect.

2.4.2 Combined effects

Type I and type II PDT affect tumor cells and the immune system through different mechanisms, which together constitute the compounding effect of PDT therapy. These two responses do not exist in isolation, but interact and complement each other during PDT to improve the therapeutic effect. In this way, PDT not only directly removes tumor cells, but also activates the body's immune response and enhances long-term defense against tumors, providing a multifaceted strategy for cancer treatment.

3. The Role of Photodynamic Forces

3.1 Immune Effects of PDT

PDT-induced immune effects are mainly realized through two pathways, one is the activation of the body's intrinsic immunity, PDT treatment will trigger an acute inflammatory response, promote neutrophil infiltration, and activate the body's intrinsic immunity [1]; the other is that the therapy can activate the body's specific immunity, inducing the expression and release of damage-associated molecular patterns (DAMPs) and triggering immunogenic

cell death (ICD), which in turn activates the body's specific immunity. It can activate the specific immunity of the body [1]. The PDT-mediated immune effect can enhance its anti-tumor efficacy to a certain extent; however, the level of the induced immune effect is affected by the intracellular localization and dose of photosensitizer, tumor oxygen content and light parameters [1].

3.2 Application of PDT in Immune Cells

It was found that PDT could act on immune cells, including macrophages, neutrophils, NK cells, dendritic cells, and CD8⁺ cytotoxic T lymphocytes in the process of immune effects. It was found that significant neutrophil elevation was observed 24 h after photosensitizer induction, this result suggests that PDT can induce neutrophil activation and chemotaxis [4] PDT can help neutrophils to exert antimicrobial effects and activate CD8⁺, which improves anti-tumor and cancer efficacy. In addition, macrophages are able to phagocytose photodamaged diseased tissues, and PDT induces tumor cells to release Hsp70, which can bind with macrophage receptor TLR2/4, activate macrophages and release TNF- α , which is indirectly cytotoxic to tumor cells [5]. Some related studies have pointed out that after tumor treatment with PDT, CD8⁺ T cells in the presence of NK cells have an effect on the proliferation of distant tumors [4]. Therefore, in vitro mouse splenic NK cells treated with PDT were not cytotoxic to EMT6 cells (mouse breast cancer cells), suggesting that NK cells play an indirect role in PDT-induced anti-tumor immunity [7]. Depletion of CD8⁺ cytotoxic T lymphocytes in mice using anti-CD8⁺ antibody showed that the anti-tumor effect of PDT was reduced, suggesting that the CD8⁺ T cell population is essential for an effective immune response secondary to PDT [7], therefore, it is considered that CD8⁺ cells are the main immune effector cells of PDT-mediated anti-tumor. MDSC are myeloid-derived suppressor cells, which are able to play an immune suppressing function, further indirectly suppressing the immune response and playing a negative regulatory role in diseases such as cancer, as shown in Figure 2.

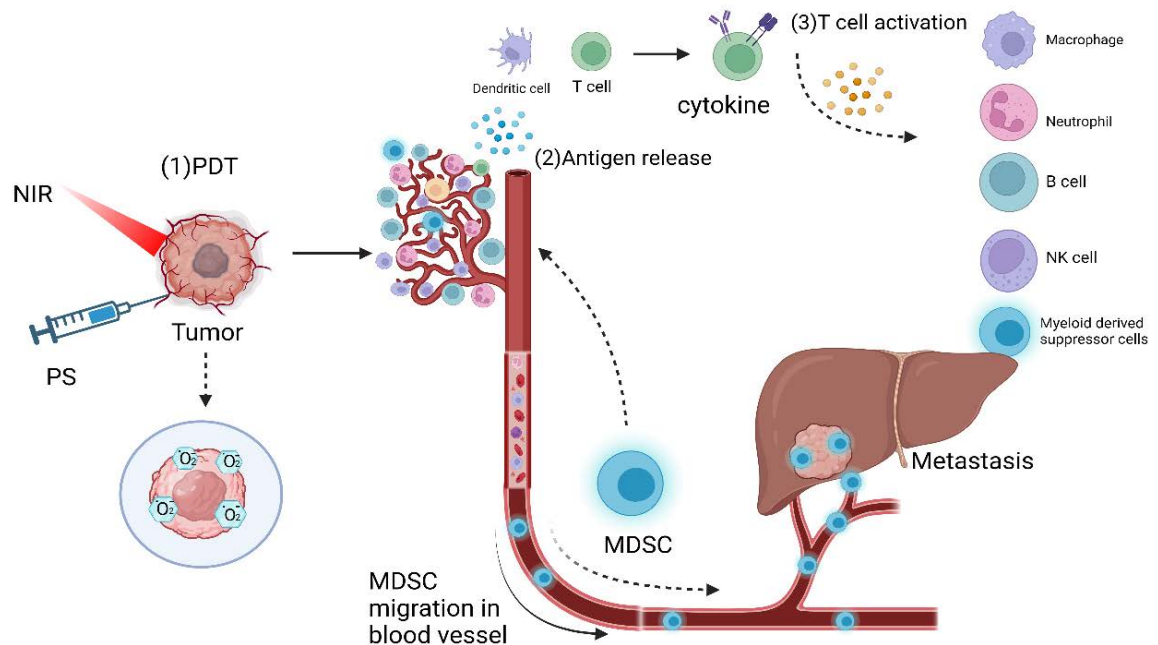


Fig. 2 Schematic diagram of PDT bidirectional therapy

4. Application of PDT

4.1 Skin Cancer

Skin cancer is one of the earliest and most successful cancer types in which PDT has been applied. For non-melanoma skin cancers (e.g., basal cell carcinoma and squamous cell carcinoma), PDT has shown highly effective therapeutic effects, especially in early stage cancer treatment and superficial tumors. PDT not only effectively controls the disease, but also preserves more healthy tissues and reduces scars left by the surgery. It has been shown in Wang that the combined use of ALA and hematoporphyrin derivatives intravenously administered with near-infrared light irradiation followed by PDT, produced better efficacy in skin cancer and reduced the chances of postoperative scarring [8]. The combination therapy also significantly reduced the phototoxic effects of photosensitizers, resulting in a much shorter time for patients to recover after surgery [9].

4.2 Head and Neck Cancer

PDT has also been used in the treatment of head and neck cancers, especially for patients who have difficulty with surgery or wish to preserve organ function. Studies have shown that PDT has potential advantages in the treatment of early oral cavity and laryngeal cancers, effectively reducing tumor volume and improving patients' quality of life. The study reported on mesotetrahydroxyphenyl chloride-mediated adjuvant PDT in 54 patients with postoperative squamous head and neck cancer who were not suit-

able for other adjuvant therapies [10]. The results showed that patients had a 2-year progression-free survival rate of 30%, a disease-free survival rate of 28%, and an overall survival rate of 51%. Recurrent squamous head and neck cancer usually has a poor prognosis, with a 2-year progression-free survival rate of 36.4% after surgery (except for patients with early stage laryngeal carcinoma) [11].

4.3 Bile Duct Cancers

The use of PDT in the treatment of cholangiocarcinoma is mainly for cases that cannot be surgically resected, especially for those patients who cannot undergo surgery due to the location of the tumor, its size, or the patient's health status. PDT can be used as a palliative treatment to help alleviate symptoms, such as jaundice, and to improve the quality of life by decreasing the tumor burden. PDT can also be used as a treatment to improve the quality of life by decreasing the tumor burden. A Meta-analysis that included 55 studies (2146 patients) in which 1149 patients received PDT in combination with stenting, 545 received radiofrequency ablation (RFA) in combination with stenting, and 452 received stenting only, resulted in overall survival of 11.9, 8.1, and 6.7 months in the three groups, respectively [12]. Compared with the RFA group, the PDT-combined stent group had lower 30- and 90-day mortality rates and demonstrated better stent patency rates of 6.1 months compared with 5.5 months in the RFA group, and the combined duration of stent patency in the stent-only group was 4.7 months [12]. However, cholangitis was observed in 23.4% of patients in the PDT combined stent group, while it was relatively lower in the

RFA group and the stent-only group, at 9.5% and 15.5%, respectively; furthermore, the probability of concomitant hepatic abscess in the three groups was 5%, 2.6%, and 2.1%, respectively, and it was slightly higher in the PDT combined stent group than in the other two groups [12]. Therefore, it is shown that PDT can prolong the stent patency time and improve the quality of life of patients in palliative care.

4.4 Cervical Squamous Intraepithelial Lesions.

The use of PDT in the treatment of HSIL has increased with advances in photosensitizer and light source technology. The cervical canal was irradiated with the semiconductor laser therapeutic instrument LD-600C fiber, and the surface of the cervix was irradiated with the LED-IIB photodynamic therapy instrument, with an energy density of 80~150 J/cm², a power density of 80 mW/cm², and an illuminating time of 30 min±5 min every 7~14 d for 6 times [13]. Qu et al. showed that among the patients with HSIL treated with photodynamic therapy, the total. The total lesion regression rate was 89.58% in patients with HSIL treated with photodynamic therapy [13]. Li et al. found that PDT had a higher regression rate and lower recurrence rate than other therapies (CO₂ laser, surgery, freezing, etc.) [13].

5. Strengths and Limitations of PDT

Compared with other treatment methods (radiation, chemotherapy, etc.), PDT has the advantage of a relatively small trauma surface, which allows patients to reduce the area of secondary trauma during treatment. It is highly selective, non-invasive and reproducible, capable of targeting and destroying diseased tissues with less damage to the surrounding healthy tissues. Moreover, compared with traditional surgery, PDT is a non-invasive treatment method, with fast recovery for the patient and fewer side effects, and it can be carried out as many times as necessary, which is especially useful for recurrent lesions. The limitations of PDT, on the other hand, are the restricted depth of light penetration, which limits the ability to treat deep tissues or large tumor volumes. And while appropriate photosensitizer selection and administration is critical to treatment outcomes, the variety of photosensitizers currently available is relatively limited. Precise control of light conditions, including wavelength, dose, and duration of exposure, is also required to optimize therapeutic efficacy and minimize side effects. To overcome its limitations, consider the direction of development of PDT.

(1) Improved photosensitizer design, using biomarker-directed technology, to develop photosensitizers that specifically recognize and anchor to disease cells, reduc-

ing the impact on healthy tissue and achieving enhanced targeting. Novel photosensitizers can be created through chemical modification or bioengineering that can excite higher yields of reactive oxygen species at lower doses, resulting in enhanced efficacy. Development of photosensitizers responsive to near-infrared (NIR) light, which can make it possible to treat deep tissue lesions with PDT, due to better tissue penetration of NIR light. Penetration is optimized.

(2) Innovations in light source technology and the development of advanced light systems capable of precisely controlling the intensity and duration of light as well as its coverage, in order to achieve more precise treatment. Advancing the miniaturization and flexibility of light source equipment to make it more suitable for treating hard-to-reach body parts while enhancing the patient's treatment experience. Matching multi-wavelength technology: Utilizing advanced light sources capable of emitting multiple wavelengths of light in conjunction with photosensitizers of different characteristics to target diverse treatment needs.

(3) Comprehensive therapeutic strategy: Combined with targeted therapy, develop targeted drugs that work in conjunction with PDT so that they are specifically localized to the specific biomarkers of the tumor cells, and enhance the killing effect of PDT by inhibiting the key signaling pathways of tumor growth. Co-application of immunomodulators so that PDT and ICIs or immune activators are combined to activate the immune system's ability to recognize and clear tumors through tumor antigens released by PDT-induced tumor cell death. Application of chemotherapy to synergize chemotherapeutic agents with PDT, selecting chemotherapeutic agents that can produce a synergistic killing effect with PDT, a combination that destroys tumor cells through different mechanisms and reduces the probability of tumor cell resistance to a single treatment modality. Application of nanotechnology to develop nano delivery systems capable of carrying both PDT photosensitizers and other therapeutic agents (e.g., chemotherapeutic drugs, targeted drugs, or immunotherapeutic agents) through nanodelivery systems to achieve precise localization and controlled release and to enhance therapeutic efficacy. Gene editing technology (e.g., CRISPR-Cas9) can also be applied to target and correct key disease-causing genes in tumor cells, which can be used in combination with PDT to improve the relevance and efficiency of treatment. Integration of radiotherapy and PDT, combining radiotherapy with PDT, radiotherapy can destroy the DNA of tumor cells, while PDT destroys the cell structure by generating reactive oxygen species, and the combination of the two can improve the rate of tumor control. And monitoring and personalized adjustment

during the treatment process, real-time imaging monitoring and customized treatment, combined with high-resolution imaging technology, such as photoacoustic imaging or fluorescence imaging, to monitor photosensitizer distribution and reactive oxygen species production, to achieve real-time regulation of the treatment process. Through in-depth analysis of patient-specific biomarkers and disease characteristics, personalized PDT protocols are designed to improve the relevance and effectiveness of treatment.

6. Conclusion

As an innovative therapeutic approach, PDT has demonstrated its unique advantages in several medical fields. This paper analyzes the mechanism of action of PDT, its application in immune cells and microenvironmental alterations. It is shown that PDT has been researched in several disease treatment fields and has been initially recognized in the clinical treatment of some diseases. The efficacy of PDT is relatively impressive, and even palliative treatment can significantly improve the quality of life, thus making it clear that PDT can achieve the purpose of less trauma, less toxicity and good efficacy in cancer treatment. Although there are some therapeutic limitations, such as the lack of oxygen in the location of some tumor cells, the photosensitizer can not be fixed, the killing mechanism of the tumor is not completely clear, the lack of efficacy assessment, etc., so far, most of the research in the direction of PDT is still confined to in vitro studies or animal experiments. However, with continuous technological innovation and the development of new photosensitizers, the application scope and effect of PDT are expected to be further enhanced. Through interdisciplinary cooperation and the integration of the latest research results in chemistry, biotechnology, physics, engineering and medicine, future PDT research will develop in the direction of more efficient, safer and wider application, providing patients with better treatment options.

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