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| RESEARCH ARTICLE

Overcoming Tumor Hypoxia and Acidic Microenvironment to Convert Photodynamic Therapy into a Systemic Antitumor Immune Response

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| ABSTRACT

Photodynamic therapy (PDT) has become an interesting minimally invasive method of cancer treatment, which employs the use of photosensitizers to produce reactive oxygen species (ROS) that cause tumor cells to die. Nevertheless, PDT is highly inefficient in hypoxic and acidic tumor microenvironment (TME) that inhibits the production of ROS and the development of antitumor immune response. The new recent developments in nanomedicine and tumor microenvironment modulation have demonstrated an ability to overcome these barriers. Nanomaterials that generate oxygen, photoswitchable hypoxia-sensitive nanomaterials and pH-responsive nanoplatforms are some of the strategies that increase the efficacy of local PDT, at the same time overcoming immunosuppression. Besides, localized phototoxicity may be translated into a systemic antitumor immune response with combination strategies targeting immune checkpoint inhibitors and immunomodulatory nanocarriers, which potentially induces lasting tumor regression and avoids recurrence. This review critically discusses how hypoxia and acidity inhibit PDT, the nanotechnology-based approaches to address such drawbacks, and how PDT can be used to complement immunotherapy. Knowledge and control of the TME provides an avenue through which PDT can be employed to become a systemic method of anticancer therapy rather than a local treatment system.

| KEYWORDS

Photodynamic therapy (PDT), Tumor hypoxia, Acidic tumor microenvironment, Nanomedicine, Antitumor immunity, Immunotherapy

| ARTICLE INFORMATION

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1. Introduction

Photodynamic therapy (PDT) is an example of a minimally invasive treatment of cancer when photosensitizers are used in response to a specific wavelength of light and result in the formation of reactive oxygen species (ROS), which causes tumor cell apoptosis, necrosis, and immunogenic cell death (Zhang et al., 2022; Zhao et al., 2021). PDT has been of interest to researchers in the last ten years due to its capacity to selectively kill tumor tissues without killing normal cells, which has benefits over traditional treatments that include chemotherapy and radiotherapy (He et al., 2019).

The clinical efficacy of PDT is strongly reduced by the peculiarities of the tumor microenvironment (TME) as well, specifically, tumor hypoxia and acidic pH (Shen et al., 2021; Dang et al., 2017). The tumor hypoxia occurs due to the intensive tumor cells growth and maladapted vasculature, which decreases oxygen levels and inhibits the production of ROS, inhibiting the effects of PDT (He et al., 2019; Shen et al., 2021). At the same time, the buildup of lactate and other acidic metabolites reduces the extracellular pH of tumors, which further impairs the functioning of immune cell activities and leads to multidrug resistance (Zhao et al., 2021; Huang et al., 2024).

Besides having a direct impact on the production of ROS, hypoxia and acidity stimulates an immunosuppressive TME, which is typified by a decrease in cytotoxic T-cell activity, an increase in regulatory T-cell (Treg) populations, and a consequent rising in immunosuppressive cytokines (Wang et al., 2021; He et al., 2019). This environment has the effect to not only restrain the local cytotoxic outcomes of PDT however to also suppress the creation of a systemic antitumor immune response which is essential both to the long-term tumor control and the prevention of metastasis.

Recent studies have been concerned with the methods of addressing these barriers of the microenvironment and improving the antitumor immune response created by PDT. The development of oxygen-generating nanomaterials, hypoxia-adaptive photosensitizers, and pH-responsive nanoplatforms that enhance the generation of ROS and immune activation in tumors are some of the methods (Guo et al., 2018; Lu et al., 2023; Meng et al., 2023). Also, integration of PDT with immunotherapy including immune checkpoint blockers or immune-stimulating nanocarriers has shown the possibility to transform local phototoxicity into immune-wide reaction, which gives long-term tumor regression (Sun et al., 2022; Chung et al., 2020; Pan et al., 2023).

This paper is a critical review of the factors through which hypoxia and acidity inhibit the efficacy of PDT, further elaborates on the emerging strategies to surmount these challenges, and the future prospects of PDT in inducing systemic antitumor immunity. The TME is a complex system that should be understood and manipulated to make PDT a multifactorial approach to anticancer treatment.

2. Tumor Microenvironment (TME) Barriers

The tumor microenvironment (TME) is a complicated system of tumor cells, stromal cells, blood vessels, and other extra-cellular matrix factors that has a significant impact on tumor development and treatment outcome. Hypoxia, acidity and immunosuppressive conditions are some of the defining features of the cancer and a significant impediment that hinders the effectiveness of the photodynamic therapy (PDT) and other treatment therapies used in cancer treatment. The awareness of these obstacles is essential to creating measures that will lead to the improvement of PDT efficacy and induce systemic antitumor immunity.

2.1 Tumor Hypoxia

2.1.1 Causes of Hypoxia in Tumors:

Hypoxia of tumors is mainly caused by the high rate of cancer cell growth and abnormal vasculature. The growing tumor cannot supply its elevated oxygen requirements, and its poorly arranged blood vessels cannot meet the demand (Modur par. 6). Moreover, tumors have chaotic and leaky vasculature that does not distribute oxygen evenly and forms areas with severe oxygen divergence (Shen et al., 2021; Dang et al., 2017).

2.1.2 Immunologic and Metabolic Consequences on PDT efficacy and immune suppression:

During PDT, oxygen is an important substrate to the production of reactive oxygen species (ROS). The hypoxic areas in the tumor greatly inhibit the generation of ROS and this directly inhibits the killing of the tumor cells. Besides, hypoxia triggers the expression of immunosuppressive factors, including hypoxia-inducible factor 1-alpha (HIF-1), that may suppress cytotoxic T-cell functions and activate tumor survival pathways. Hypoxia, therefore, not only reduces the effects of PDT at the local level, but it also suppresses the development of a systemic immune response to tumor cells. Shen et al., 2021; Dang et al., 2017.

2.2 Acidic Microenvironment

2.2.1 Mechanisms of Acidity

The main cause of tumor acidity is the anaerobic glycolysis or the Warburg effect wherein cancer cells process glucose into lactate despite the presence of oxygen. Lactate and hydrogen ions accumulation decreases the extracellular pH to form an acidic microenvironment (Zhao et al., 2021; Huang et al., 2024).

2.2.2 Effects on PDT and Immune Cell Effect:

The acidic TME has adverse effects on PDT in a number of ways. To begin with, low PH may also influence the chemical activity of photosensitizers and decrease the production of ROS which decreases the tumor cell cytotoxic effects. Second, acidity compromises the immunity with inhibition of cytotoxic T lymphocytes and natural killer (NK) cells, required to offer an effective systemic antitumor response. Finally, acidic microenvironment enhances the mechanisms of tumor adaptation and resistance and lowers the effectiveness of therapy. Zhao et al., 2021; Huang et al., 2024.

2.3 Immunosuppressive Effects

2.3.1 Role of Hypoxia and Acidity:

Hypoxia and acidity have a synergistic effect to produce an immunosuppressive TME. Hypoxia stabilizes the HIF-1A that facilitates recruitment of regulatory T-cells (Treg) and inhibits cytotoxic T-cell activities. This is aided by acidity, which favors Tregs and myeloid-derived suppressor cells (MDSCs) that prevent the body from developing antitumor immunity against the cancer (He et al., 2019; Wang et al., 2021).

2.3.2 Additional Factor to Multidrug Resistance:

This TME suppresses the efficacy of PDT and is also responsible for the development of multidrug resistance because cancer cells in hypoxic and acidic environments increase survival pathways and excrete pumps. Such changes are increasing the resistance of tumors to conventional therapies and highlight the necessity of therapy approaches that can alter the TME so as to recover immune capabilities and increase ROS-mediated cytotoxicity.

3. Strategies to Overcome Hypoxia

One of the most severe hindrances to the efficiency of photodynamic therapy (PDT) is tumor hypoxia. Since oxygen is a prerequisite to the formation of reactive oxygen species (ROS), hypoxia alleviation or independence of oxygen is an important research topic. The recent developments in nanomedicine have allowed implementing new approaches to locally replenishing oxygen supply, adjusting PDT to hypoxic environments, and controlling the tumor microenvironment (TME) to reestablish therapeutic efficacy and immune activation.

3.1 Nanomaterials that generate Oxygen

3.1.1 Nanoparticle Based Systems Catalase Loaded: MnO 2 Catalase based and Catalase Loaded Nanoparticles

Oxygen-generating nanomaterials are some of the most direct ways to overcome tumor hypoxia. Such systems normally take advantage of the excessive concentrations of endogenous hydrogen peroxide (H_2O_2) in tumors. Nano-catalase-loaded nanoparticles are used to break down H_2O_2 into water and oxygen in the region and thus enhance the oxygen concentration locally. On the same note, nanomaterials made of manganese dioxide (MnO_2) react with the H_2O_2 in acidic tumor conditions to generate oxygen and, at the same time, alleviate hypoxia (Guo et al., 2018; Liu et al., 2018).

3.1.2 Local Oxygen Release Enhancing Mechanism of PDT

Localized production of oxygen is directly beneficial to PDT as it is able to restore the formation of ROS when photosensitizers are activated by light. The availability of more oxygen enhances the formation of singlet oxygen, which results in superior killing of tumor cells. Also, the nutrients such as oxygen lead to reversal of immune suppression caused by hypoxia, leading to infiltration of immune cells and encouraging immunogenic cell death caused by PDT. Subsequently, oxygen-producing nanomaterials are able to enhance local performance of PDT in addition to triggering the development of systemic antitumor immunity. Guo et al., 2018; Liu et al., 2018

3.2 Photosensitizers Reacting to Hypoxia

3.2.1 Photoactive Organizations Occupying the Type I Group:

The use of Type II photochemical reactions that are very oxygen-sensitive is the traditional PDT. To treat hypoxia, Type I photosensitizers have been established, which produce ROS generation via electron or hydrogen transfer reactions and yield less reliant free radicals on molecular oxygen. Such photosensitizers are not deactivated by hypoxia, and PDT can still be effectively performed even in regions of tumor that lack oxygen (Lu et al., 2023).

3.2.2 Hypoxia-responsive Adaptive Nanoplatforms:

Refined nanoplatforms have been developed to react to hypoxic signals in tumors. Such systems have the capability of activating or releasing photosensitizers in hypoxic areas and increasing tumor specificity with reducing off-target effects. Synergistic therapies, including combined photothermalphotodynamic therapy and immunotherapy, are also achieved with the help of hypoxia-responsive nanocarriers that increase the production of ROS and stimulates immune activation (Meng et al., 2023). These kind of adaptive platforms are a good future approach in defeating the inherent oxygen constraint of the traditional PDT. Lu et al., 2023; Meng et al., 2023

3.3 Tumor Microenvironment Modulators.

3.3.1 Decomposition of H 2 O 2, pH Control, and IDO Block

Besides direct provision of oxygen, the other viable move would be to titrate the tumor microenvironment to diminish hypoxia and immunosuppression. Decomposing nanomaterials of H2O 2 do not only produce oxygen, but also mitigate oxidative stress-induced resistance mechanisms. Also, pH-altering agents have the potential to reduce tumor acidity, which indirectly enhances the use of oxygen and the work of immune cells. Immune tolerance has also been reverted by preventing the synthesis of indoleamine 2,3-dioxygenase (IDO) which is increased in hypoxic environments and this inhibits immune responses in PDT (Xing et al., 2019).

3.3.2 Normalization of TME by Nanomedicine usage:

Nanomedicine allows accurate delivery of TME modulating agents to the tumors reducing systemic toxicity. These nanosystems are known to normalize TME by acting concurrently on hypoxia, acidity, and immunosuppressive pathways. Such normalization boosts the efficacy of PDT, facilitates the immune cell invasion, and enables the transformation of local destruction of tumor by PDT into systemic antitumor immune response (Shen et al., 2020).

4. Strategies to Overcome Acidic Microenvironment

Acidic tumor microenvironment (TME) is a characteristic of solid tumors and constitutes one of the greatest barriers to successful photodynamic therapy (PDT). Tumor acidity not only suppresses the production of reactive oxygen species (ROS) but also inhibits the activity of immune cells and induces resistance to therapeutic actions. To overcome these obstacles, scientists have created pH-dependent nanoplatforms and buffering mechanisms that selectively act in acidic tumor cells, which induce an improved effect of PDT and antitumor immunity.

4.1 Nanoparticle based pH-Responsive Nanoplatforms.

4.1.1 Nanobubbles and Polymeric Micelles on the Basis of Acidity:

PH-responsive nanoplatforms are aimed at taking the advantage of acidic pH of tumor microenvironment to release drugs and activate their sites. Such nanobubbles as nanobubbles, in turn, can stay stable at regular physiological conditions but convert to a phase transition or structural destabilization at acidic pH and allow controlled release of photosensitizers and oxygen-promoting agents directly into tumors (Zhao et al., 2021).

On the same note, any polymerized micelles that have acid sensitive conjugates break down in low-pH conditions, which enhances the concentration of therapeutic agents locally. Such systems enhance the efficiency of PDT by modifying the release of photosensitizers to be concentrated on the tumor and not in the normal tissues (Yang et al., 2018).

4.4.2 PDT and Immune Activation: Improvement.

The selective response of pH-responsible nanoplatforms towards tumor acidity increases the production of ROS during PDT and decreases systemic toxicity. In addition, PDT-induced tumor cells death that is localized encourages immunogenic cell death, which allows the release of antigens and activation of immune system. Therefore, pH-reactive systems are useful both to enhance the accuracy of PDT and to promote the antitumor immune response in the body. Zhao et al., 2021; Yang et al., 2018.

4.2 Buffering and pH Modulation

4.2.1 Alkalizing Agents Tumor-Targeted Delivery:

Buffering and pH modulation is the other solution that has been effective in counteracting the acidity of tumors. Replacement of acidic microenvironment with alkalizing agents can occur by targeting tumor with alkalizing agents, which would increase physiological pH, promoting the creation of ROS and the performance of immune cells. They may be contained in nanocarriers to guarantee a preference of these agents to tumor tissues and reduce off-target consequences (Huang et al., 2024).

4.2.2 Nano-carriers, which are pH-sensitive to normalize the microenvironment:

High-level pH-sensitive nanocarriers do not only release therapeutic molecules in acidic environments, but they also actively control the TME by overturning acidosis. Stabilization of tumor pH increases cytotoxic T-cell response, oxygen consumption and inhibits immunosuppressive signaling. Consequently, buffering mechanisms complement PDT in order to increase local tumor cell destruction and promote the formation of systemic antitumor immunity. Huang et al., 2024

Table1: Strategies to Overcome the Acidic Tumor Microenvironment for Enhanced Photodynamic Therapy

Strategy Category	Representative Nanoplatforms / Approaches	Mechanism of Action	Benefits for PDT and Immunity	Key References
pH-Responsive Nanoplatforms	Acid-sensitive nanobubbles	Under acidic pH, nanobubbles undergo phase transition, releasing photosensitizers and oxygen-enhancing agents selectively in tumors	Improves local ROS generation; enhances PDT selectivity; reduces off-target toxicity	Zhao et al., 2021
	Polymeric micelles with acid-labile linkers	Micelle disassembly in low pH releases encapsulated photosensitizers at tumor sites	Increases intratumoral drug accumulation; enhances PDT efficacy	Yang et al., 2018
Buffering and pH Modulation	Alkalizing agent-loaded nanocarriers	Neutralization of tumor acidity through targeted delivery of buffering agents	Restores immune cell function; improves ROS stability and PDT effectiveness	Huang et al., 2024
	Ultra-acid-sensitive nanocarriers	Rapid degradation under acidic conditions while modulating extracellular pH	Normalizes tumor microenvironment; enhances immune infiltration and PDT-induced immunogenic cell death	Huang et al., 2024

5. Enhancing Systemic Antitumor Immune Response

Although photodynamic therapy (PDT) was first designed as a localized curative treatment of tumors, increasing evidence indicates that appropriately optimized PDT has the potential to induce a systemic antitumor immunologic reaction. With the PDT-induced tumor destruction enabling the overcoming of hypoxia and acidity in the tumor microenvironment (TME), the immune-mediated process can be converted to attacking tumors at a distance and in metastasis. This part addresses the significant mechanisms and strategies that allow PDT to be used as an immunotherapeutic modality.

5.1 PDT Induced Immunogenic Cell Death (ICD)

5.1.1 Cell Death Immunogenicity Mechanisms:

Immunogenic cell death (ICD) is a special type of regulated cell death which triggers adaptive immune response. The induction of ICD by PDT is strong in the presence of adequate reactive oxygen species (ROS). The damage-associated molecular patterns (DAMPs) released by tumor cells during PDT-induced ICD include calreticulin, ATP, and high-mobility group box 1 (HMGB1). The signals are danger signals that enhance the maturation of dendritic cells and antigen presentation (Zhang et al., 2022).

5.1.2 Tumor-Associated Antigen Liberation and Immune Activation:

Besides the DAMPs, tumor destruction by PDT results in the release of tumor-associated antigens, which are taken up by antigen presenting cells and given to T lymphocytes. This activates cytotoxic T-cell reactions which are capable of identifying and destroying the residual tumor cells and remote metastases. Nevertheless, the size of ICD strongly depends on the level of oxygen and TME, and hypoxia and acid modulation are necessary to achieve the full potential of PDT-induced immune stimulation (Sun et al., 2022).

5.2 Combination with Immunotherapy

The combination with Immunotherapy 7.2 Immunotherapy Observations Immunotherapy and Thiazide In combination, Immunotherapy and Thiazide Immunotherapy and Prednisone Immunotherapy and Prednisone Thiazide Immunotherapy and Prednisone Immunotherapy and Burbrop Thiazide Immunotherapy and Burbrop Immunotherapy and Lamotrigine Immunotherapy and Lamotrigine Immunotherapy and Stimulus Control Immunotherapy and Stimulus Control Immunotherapy and Vitamin D Immunotherapy and Vitamin D Thiazide Immunotherapy and Isonia

5.2.1 Immune Checkpoint Inhibitors (PD-1/PD-L1 and CTLA-4):

PDT may promote immune responses in a body, but the immune checkpoint pathways tend to restrain their power. PD-1/PD-L1 and CTLA-4 immune checkpoints have been demonstrated to induce immune exhaustion and deactivate T-cell functions in tumors. The use of PDT with checkpoint blockade enables PDT-produced tumor antigens and ICD signals to be converted to neutral systemic immune responses (Wang et al., 2021).

5.2.2 Interaction of Hypoxia-Controlled PDT and Immunotherapy:

The alleviation of hypoxia is a great step towards maximizing the interaction between PDT and immunotherapy. Hypoxia-controlled PDT enhances the generation of ROS and the release of antigens, and immunotherapy maintains the activation of T-cells and immune escape. It has been shown that oxygen-generating or hypoxia-sensitive PDT platforms used together with immune checkpoint inhibitors lead to better tumor regression and metastasis prevention than monotherapies (Chung et al., 2020). This interaction highlights the need to have combined treatment measures that help to address both the TME and immune checkpoints.

Multi-pronged nanoplatforms represent highly promising nanocrystalline structures with remarkable capabilities for biodegradation (Shahari, 2001).<|human|>Multi-pronged Nanoplatforms Multi-pronged nanoplatforms are very promising nanocrystalline structures with an impressive biodegradation capability (Shahari, 2001).

5.3 Multifunctional delivery via single Nanoplatforms

Recent innovations in the field of nanomedicine have resulted in the creation of multi-pronged nanoplatforms that are able to offer oxygen sources, photosensitizers and immunomodulatory agents at the same time. It is these integrated systems that are meant to work in concert with a variety of TME barriers, which allow the efficient ROS production, the elevated PDT effect, and the activation of the immune system in the context of the same therapeutic platform (Zou et al., 2025).

5.3.1 Increasing of ROS and Immune Activation:

Multi-pronged nanoplatforms enhance the production of ROS and the long-term activation of the immune response by co-delivering oxygen-generating components and immunostimulatory molecules. These systems boost the maturation of dendritic cells, cytotoxics T cells and prolonged immune memory that results in the long-term antitumor responses. These platforms are a prospective approach to systems transplanting localized PDT into a systemic antitumor immunotherapy (Pan et al., 2023).

6. Challenges and Limitations

Although the vast progress has been achieved concerning the overcoming of tumor hypoxia and acidity to improve photodynamic therapy (PDT) to induce systemic antitumor immunity, scientific, technical, and translational challenges still exist. These limitations are critical issues that should be tackled to make hypoxia- and pH-modulated PDT strategies successful in clinical implementation.

6.1 The Tumor Microenvironment is not simple and uniform, but instead a complex and heterogeneous environment

Among the main issues, it is the strong spatial and temporal heterogeneity of the tumor microenvironment (TME). The distribution of oxygen, pH, distribution of immune cells is not only different between different types of tumors but also within a given tumor. This heterogeneity makes it difficult to design globally efficient nanoplatforms because tumor area strategies should be less effective in other tumor areas (Zheng et al., 2022). This means that it is still challenging to achieve homogenous oxygenation, normalization of pH and immune stimulation throughout the tumor mass.

6.2 Biosafety, Biodegradability and Long-Term Toxicity.

A lot of oxygen-generating and pH-sensitive nanomaterials are based on inorganic components MnO 2 or intricate polymeric systems. Although it works well in preclinical models, there are still concerns on the long-term biosafety, biodegradability, and accumulation in major organs. The partial absence of the clearance of nanomaterials might result in chronic intoxication or spontaneous immune responses. Strict testing of pharmacokinetic, metabolic, and long-term safety is thus needed prior to clinical translation (Hong et al., 2022).

Figure 1: The Below diagram show the PDT Immunotherapy

PDT Immunotherapy

Pros

1 Systemic immunity

PDT induces systemic immunity, attacking tumors at a distance and in metastasis.

2 Immunogenic cell death

PDT triggers immunogenic cell death, enhancing dendritic cell maturation and antigen presentation.

3 Checkpoint blockade

Combining PDT with checkpoint blockade neutralizes immune exhaustion and activates T-cells.

4 Hypoxia control

Hypoxia-controlled PDT boosts ROS generation and antigen release, improving immunotherapy effectiveness.

5 Multifunctional platforms

Multifunctional nanoplatforms deliver oxygen, photosensitizers, and immunomodulators simultaneously.

Cons

1 TME heterogeneity

TME heterogeneity complicates nanoplatform design, limiting uniform treatment effectiveness.

2 Biosafety concerns

Biosafety concerns arise from inorganic nanomaterials, requiring strict safety testing.

3 Light penetration

Light penetration limits PDT to superficial tumors, hindering deep-seated tumor treatment.

4 Immune side effects

Immune-related adverse events, like inflammation, can limit treatment tolerability.

5 Clinical barriers

Clinical barriers include animal model discrepancies and regulatory hurdles, delaying clinical approval.

6.3 Minimal Light Infiltration and Tumor Availability.

Light penetration distance also limits the effectiveness of PDT inherently limiting its use by superficial or available tumors. Even though near-infrared (NIR) photosensitizers and the latest optical technologies have helped in dealing with this problem to some degree, the deep-seated tumors are very difficult to deal with. The lack of light delivery may lead to an inefficient production of ROS, the elimination of tumor cells, and the induction of immunogenic cell death (Zheng et al., 2022).

6.4 Immune- Related Adverse Effects and Overactivation.

Although one of the primary objectives is to boost systemic antitumor immunity, the excess of immune activation which can occur with the combination of PDT and immune checkpoint inhibitors, may result in immune-related adverse events. They are systemic inflammation and autoimmunity that can restrict the treatment tolerability. Another important issue is the need to balance powerful immune stimulation and safety, particularly in multi-pronged nanoplatforms, which deliver immunomodulators along with PDT agents (Hong et al., 2022).

6.5 Analytical and Clinical Barriers.

The majority of the hypoxia-/acidity-based PDT approaches remain at preclinical phases with most of them elucidated in murine tumor models. Disagreements between animal models and human tumor including complexity of the immune system, size of the tumor, and vasculature architecture are significant obstacles to clinical translation. Also, multifunctional nanoplatforms complicate the production process and regulatory barriers, delaying the process of obtaining clinical approval (Zheng et al., 2022).

7. Future Directions

The generation of intelligent tumor microenvironment (TME) modulation, clinical translatability, and precision of immuno-oncology integration should be considered in future studies of photodynamic therapy (PDT)-induced systemic antitumor immunity. The interdisciplinary strategies based on nanotechnology, immunology, and clinical oncology will be needed to overcome the current limitations.

7.1 Design of Intelligent and Adaptive Nanoplatform

The future nanoplatforms are likely to develop to more intelligent and adaptable systems that can dynamically respond to real-time TME variations (e.g., varying oxygen concentration, pH conditions, and immune status). Hypoxia sensing, pH responsive, and controlled drug delivery nanocarriers Multi-stimulus-responsive nanocarriers with the ability to control the generation of ROS and activation of immune responses by precise spatiotemporal regulation might be a solution. These platforms may be able to maximize the PDT efficacy with reducing off-target effects (Pan et al., 2023; Zou et al., 2025).

7.2 The PDT with Personalized Immunotherapy can be integrated.

The future of PDT is on its combination with individual immunotherapy approaches. Future developments in tumor genomics and immune profiling could enable the PDT regimens to be personalised based on the immune phenotype of an individual tumour. Hypoxia-regulated PDT in combination with immune checkpoint inhibitors, cancer vaccines, or adoptive cell therapies would lead to improved systemic antitumor response and less tumor recurrence. The individualization of patients is likely to enhance safety and therapeutic results (Wang et al., 2021).

7.3 Deep-Tissue and Image-Guided PDT Technologies: Development.

In order to eliminate light penetration shortcomings, future studies on PDT must focus on deep-tissue activation methods, such as second near-infrared (NIR-II) photosensitizers, X-ray-activated PDT, and light conversion with upconversion nanoparticles. Also, it can be possible to incorporate image-guided systems that enable real-time monitoring of oxygen concentration, ROS formation, immune stimulation, and better treatment planning and outcome evaluation (Zhang et al., 2022).

7.4 Stress on Biodegradable and Clinically safe Materials.

To move PDT nanomedicine to clinical practice, changes to biodegradable, FDA-approved and clinically scalable materials are needed. The ease of nanoplatform design without compromising on multifunctionality will be especially important in the process of approval by the authorities. Long-term safety assessments, standardized production, and large-scale production should be the focus of future research (Hong et al., 2022).

The Committee suggests using a combination of drugs in a combination trial to determine the efficacy of that combination (Murray, 2011).<|human|>9.5 Trials on Clinical Translation and Combination Therapy: A combination trial consists of drugs administered in combination to determine the efficacy of the combination (Murray, 2011).

To confirm the effectiveness and safety of hypoxia- and acidity-controlled PDT approaches, it is important to design clinical trials. The future clinical trials need to explore the best dosing, light administration regimens, and regimens used with immunotherapies. Besides, the discovery of predictive biomarkers, which may be signs of immune activation or hypoxia, may be used to select patients and monitor their treatment, which will speed up the adoption of the clinical solution (Zheng et al., 2022).

Table 3: Future Directions in Tumor Microenvironment–Modulated Photodynamic Therapy for Systemic Antitumor Immunity

Future Direction	Key Focus	Technological / Scientific Approaches	Expected Impact on PDT and Immunity	Representative References
Intelligent Adaptive Nanoplatforms	Dynamic response to TME heterogeneity	Multi-stimuli–responsive nanocarriers (hypoxia-, pH-, ROS-responsive); real-time TME sensing	Optimized ROS generation; precise immune activation; reduced off-target toxicity	Pan et al., 2023; Zou et al., 2025
Personalized PDT–Immunotherapy Integration	Patient-specific immune modulation	Tumor immune profiling; combination with ICIs, vaccines, or adoptive cell therapy	Enhanced systemic antitumor immunity; reduced recurrence and resistance	Wang et al., 2021
Deep-Tissue and Advanced Light Activation	Overcoming limited light penetration	NIR-II photosensitizers; X-ray–activated PDT; upconversion nanoparticles	Expanded treatment depth; improved efficacy for solid and deep tumors	Zhang et al., 2022
Image-Guided and Theranostic PDT	Real-time monitoring and precision treatment	Imaging-integrated nanoplatforms (oxygen, ROS, immune biomarkers)	Improved treatment planning; real-time efficacy evaluation	Zhang et al., 2022
Biodegradable and Clinically Translatable Materials	Safety and regulatory feasibility	FDA-approved materials; simplified nanostructures; scalable manufacturing	Accelerated clinical translation; reduced long-term toxicity	Hong et al., 2022
Clinical Trials and Biomarker Development	Validation and patient stratification	Combination therapy trials; hypoxia and immune-response biomarkers	Evidence-based optimization; personalized treatment selection	Zheng et al., 2022

8. Conclusion

Photodynamic therapy (PDT) has come out as a potential modality of treating cancer because it is spatially and temporally localized and has low systemic toxicity. Its clinical performance is, however, greatly impaired by the hostile tumor microenvironment (TME), especially hypoxia, acidic and immunosuppressive signals, which jointly inhibit the production of reactive oxygen species (ROS) and antitumor immune responses. It is necessary to overcome these barriers in order to realize the complete therapeutic and immunological potential of PDT.

The present review underscores the new developments in tumor microenvironment-responsive PDT by placing a strong focus on emerging technologies to address hypoxia and acidity in favor of oxygen-generating nanomaterials, hypoxia-responsive photosensitizers, pH-sensitive nanoplatforms, and TME normalization methods. Such strategies do not only augment the production of ROS, but also promote the PDT-induced immunogenic cell death (ICD), which promotes the release of tumor-associated antigens and danger-associated molecular patterns to activate systemic antitumor immunity.

Notably, the combination of PDT and immunotherapeutic agent, including immune checkpoint modulators, is an effective synergistic method of immune activation and sustained tumor control. Multi-pronged nanoplatforms that can concurrently deliver oxygen, photosensitizers, and immunomodulators have a lot of potential in re-engineering the TME to become an immunosuppressive environment into an immunostimulatory environment.

In spite of such improvements, there are still issues concerning clinical translation, biosafety, scalability and personalization of treatment. Future studies should focus on the creation of biodegradable and clinically compatible nanomaterials, more tissue penetrating light activation technologies, and powerful biomarkers to stratify patients. Properly designed clinical trials will play a major role in establishing the efficacy of therapy and the expedited use in the real world.

Conclusively, PDT was used as a combination therapy with immunotherapy but the tumor microenvironment was modified to achieve a transformative approach in the treatment of cancer and the resultant systemic antitumor immunity as well as better patient outcomes. Further interdisciplinary cooperation will be needed in order to translate these potential strategies out of bench and bedside.

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