Research Progress and Challenges in the Mechanism of Photodynamic Therapy for Cancer

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Abstract Photodynamic therapy (PDT) is an emerging cancer treatment modality that induces tumor cell death by utilizing photosensitizers generating reactive oxygen species (ROS) under specific wavelength light excitation, which has the advantages of high selectivity and low toxicity. This paper reviews the latest research advances and challenges in PDT for cancer treatment. It focuses on analyzing its fundamental principles and mechanisms, including Type I and Type II photodynamic reactions, the intracellular localization and mechanisms of photosensitizers, and thoroughly explores various PDT-induced cell death patterns, especially the challenges and corresponding strategies related to the tumor microenvironment (TME). Meanwhile, this paper elaborates the main mechanisms of tumor cell resistance to PDT and discusses the synergistic mechanisms to overcome these challenges through novel photosensitizers, nanocarrier technology and multimodal combined other therapies like photothermal therapy, chemotherapy, immunotherapy and others. This review aims to reveal the complexity and diversity of PDT mechanisms, assess current challenges, and look toward the future, so as to provide a deep understanding and theoretical foundation for further exploration in the field of PDT, and promote the further development and clinical application of PDT in the field of cancer treatment.

Key words Photodynamic; Anti-cancer; Reactive oxygen species; Photosensitizer; Mechanism

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Cancer, a major disease severely threatening human health, still faces multiple challenges in its treatment field, including therapeutic efficacy, precision, and complexity such as intra-tumoral heterogeneity and tumor cell plasticity[1]. Although traditional treatments like surgery, chemotherapy, and radiotherapy are widely applied and their effectiveness has been proven, they are often accompanied by adverse outcomes such as tumor recurrence and metastasis[2-4]. Photodynamic therapy (PDT) is an emerging tumor treatment modality that utilizes photosensitizers to generate toxic reactive oxygen species (ROS), such as superoxide radicals and singlet oxygen, under specific wavelength light irradiation to kill tumor cells[2,5-6]. PDT offers advantages such as high selectivity, minimally invasive nature, and reduced side effects[6-8]. Due to the selective accumulation of photosensitizers in tumor tissues combined with precise light irradiation, PDT effectively kills tumor cells without damaging surrounding normal tissues. Furthermore, the treatment process does not rely on the systemic distribution of traditional chemotherapeutic drugs, so the toxicity and side effects are relatively lower.

In recent years, PDT has demonstrated significant therapeutic efficacy in the treatment of various cancers, including esophageal, lung, breast, and skin cancers, and has been validated as an effective adjuvant cancer treatment strategy[9-12]. With deepening understanding of PDT mechanisms and advancements in novel photosensitizers and nanotechnology, the therapeutic efficacy and application scope of PDT have been significantly enhanced. Researchers have not only revealed the complex regulation of PDT-induced cell death, but also explored how to overcome challenges posed by the tumor microenvironment (TME), such as tumor hypoxia and immune suppression, to further enhance therapeutic outcomes[4,13-14]. Furthermore, integrating PDT with sonodynamic therapy to form sonodynamic photodynamic therapy (SPDT) or combining it with other methods such as chemotherapy, immunotherapy, or photothermal therapy, also provides new avenues for cancer treatment[15-19].

Despite demonstrated significant potential in cancer therapy, PDT research mechanisms still faces several bottlenecks, including the difficulty in balancing photosensitizer targeting with phototoxicity, particularly the lack of selectivity for deep tissues, and limited tissue penetration depth constrained by light physical properties and oxygen dependency, hypoxic conditions in the tumor microenvironment, and the inherent antioxidant defense mechanisms of tumor cells and their resistance to treatment[4,6,14,20-25]. This review summarizes the latest research progress related to the mechanism of PDT for cancer, and provides an in-depth discussion and analysis, aiming to provide theoretical

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support for the mechanism optimization and clinical transformation of PDT.

Basic Principles of PDT

The basic principle of PDT is based on photochemical reaction process, which includes three key elements: photosensitizer, light of specific wavelength and molecular oxygen[2,6,8,26]. When exposed by specific wavelength light, the photosensitizers transitions from ground state (S_0) to excited singlet state (S_1), followed by rapid relaxation to a lower energy, but longer-lived excited triplet state (T_1)[27]. Photosensitizers in the triplet state can react with surrounding biomolecules or oxygen via two primary pathways include Type I and Type II photodynamic reactions, thereby generating cytotoxic reactive oxygen species (ROS).

Type I and Type II photodynamic reactions

In Type I reactions, the triplet-excited photosensitizer directly undergoes electron or hydrogen atom transfer with biomolecules, generating free radicals and radical ions. These free radicals subsequently react with oxygen to produce ROS such as superoxide anion (O_2^-), hydroxyl radical ($\cdot OH$), and hydrogen peroxide (H_2O_2) (Fig. 1)[28-29]. The advantage of Type I reactions lies in their relatively low dependence on oxygen concentration, enabling them to maintain activity within the hypoxic microenvironments commonly found in tumors. This offers a potential pathway to overcome treatment challenges posed by tumor hypoxia[4,21,29]. Zhuang *et al.*[29] reported phosphoindole oxide-based Type I photosensitizers that efficiently generate Type I ROS and induce endoplasmic reticulum stress-mediated cell apoptosis and autophagy under hypoxic conditions, demonstrating their potential in overcoming tumor hypoxia. In contrast, Type II reactions represent the most prevalent mechanism in PDT, wherein excited triplet-state photosensitizers transfer their energy to ground-state oxygen molecules ($^3O_2$), thereby generating highly reactive singlet oxygen ($^1O_2$) (Fig. 1)[27,30-31]. Singlet oxygen is a potent oxidizing agent that can rapidly react with various intracellular biomolecules, causing cell membrane damage, protein oxidation, enzyme inactivation, and DNA strand breaks, ultimately leading to cell death[27,31]. Przygoda *et al.*[31] have explored in depth the key role of single-line oxygen in PDT to induce apoptosis and other cell death pathways, and emphasized its potential for precise targeting of cancer cells.

Although Type I and Type II reactions differ fundamentally in their initiation mechanisms. Type I reactions rely on electron transfer with low oxygen dependence, while Type II reactions depend on energy transfer and are currently the mainstream approach in clinical applications. Both ultimately converge through the production of reactive oxygen species that trigger oxidative damage, leading to tumor cell death[21,30,32].

Subcellular Localization and Mechanisms of Photosensitizers

The cytotoxic effects of ROS generated by PDT has specific intracellular targets, which depend on the subcellular localization of photosensitizers. The intracellular localization of photosensitizers decisively influences in its mechanism of action and the patterns of induced cell death[11,27,33]. Due to differences in physicochemical properties, various photosensitizers tend to accumulate in specific cellular organelles. Upon light activation, this leads to the localized generation of high ROS concentrations within these critical organelles, triggering initial damage.

Mitochondrial localization

Mitochondrial localization is a defining feature of cationic or lipophilic photosensitizers such as phthalocyanine and rhodamine derivatives. As the cell power plant, mitochondria utilize their membrane potential ($\Delta\Psi m$) to drive positively charged photosensitizers to accumulate within both the inner mitochondrial membrane and matrix. When photosensitizers within mitochondria are activated, the resulting ROS directly damage the mitochondrial membrane, leading to a decrease in mitochondrial $\Delta\Psi m$, opening of the mitochondrial permeability transition pore, and increased mitochondrial outer membrane permeability (MOMP)[27,34-36]. This triggers the release of cytochrome c, thereby activating the intrinsic apoptosis pathway. Didamson *et al.*[35] demonstrated that aluminum phthalocyanine-mediated PDT kills esophageal cancer cells by inducing ATM-associated DNA damage responses and mitochondrial-mediated apoptosis. Lyu *et al.*[37] also indicated that manipulating mitochondrial function can enhance PDT efficacy and trigger tumor cell apoptosis. Liu *et al.*[38] found that a photosensitizer designed and synthesized by strong electrostatic interaction has a strong mitochondrial targeting ability, and only 10 s of light ($0.4\ J/cm^2$) can achieve 100% cell pyroptosis.

This high efficiency of induced cell death is mainly due to the release of ROS after the photosensitizer specifically targets mitochondria and activates the caspase-3/GSDME mediated apoptosis pathway[38]. Wang *et al.*[39] investigated a novel mitochondrial-targeting iridium (III) complex photosensitizer, Ir-TPE, which used aggregation-induced emission (AIE) design to assemble into nanoaggregates in aqueous solution that not only solved the problems of fluorescence quenching and decreased ROS production caused by aggregation of traditional photosensitizers, but also achieved a significant increase in the production of singlet oxygen. More importantly, the photosensitizer produced excessive ROS in mitochondria after light exposure, causing mitochondrial DNA damage and simultaneoued consumption of glutathione (GSH), which jointly triggered the two modes of cell death, ferroptosis and autophagy, showing a strong ability to kill cancer cells.

Lysosomal localization

Lysosomes are acidic organelles rich in various hydrolases in cells. Once the membrane stability of lysosomes is destroyed, enzyme leakage will occur and cell death will be caused. Damage to lysosomal membranes leads to the release of lysosomal enzymes such as cathepsins B and D into the cytoplasm. These enzymes can cleave Bid protein, thereby affecting MOMP and ultimately causing cell death[27,40]. Kessel and Reiners[40] noted that lysosomal

light damage can trigger calcium ion release, activating calpain (CAPN), which cleaves ATG5 into tATG5, and tATG5 interacts with mitochondria to enhance pro-apoptotic signaling. Lysosomal targeting is also commonly observed in weakly basic amine photosensitizers such as hypericin and quinine-conjugated porphyrins. Photosensitizers with weakly basic amino groups such as morpholinyl can be enriched in lysosomes by ion trap effect due to the acidic environment of lysosomes. Tao *et al.* [41] studied a BODIPY dimer that was localized in lysosomes by the introduction of morpholinyl groups, which could produce ROS and thermal effects simultaneously under near-infrared light irradiation, effectively blocking the protective autophagy of tumor cells and activating pyroptosis.

Furthermore, dynamic localization demonstrate enhanced complexity. Li *et al.* [42] developed a GSH-activated photosensitizer, BTF-DNBS, which is initially localized in lysosomes. However, within hours, most molecules undergo lysosomal escape, with a 78% drug escape rate occurring within four hours in lysosomes. This lysosomal escape mechanism successfully prevents degradation caused by lysosomal acidic environments and hydrolases, addressing the issue of traditional photosensitizers being degraded in lysosomes. Subsequently, specific rod-like self-assembled structures form within the Golgi apparatus, enabling spatiotemporal transfer from lysosomes to the Golgi. The molecule ingeniously exploits the GSH concentration gradient between tumor cells and normal cells, precisely targeting through disruption of photoinduced electron transfer mechanisms, ultimately triggering the Golgi-mediated cell pyroptosis pathway. This study for the first time revealed the spatio-temporal transport pattern of AIE photosensitizers from lysosomes to Golgi apparatus, providing a new paradigm for precise regulation of cell death signals.

ER localization

The endoplasmic reticulum (ER) is a key organelle for protein synthesis, folding and modification in cells. In recent years, it has attracted extensive attention as an emerging target of PDT. The photosensitizers targeting the ER can often induce ER stress and induce cell death. When photosensitizers accumulate and activate within the ER, the generated ROS can induce protein misfolding and ER stress. If ER stress exceeds the cell's tolerance threshold, it triggers the unfolded protein response (UPR), subsequently activating apoptotic pathways[27,29]. Zhuang *et al.* [29] demonstrated the importance of ER stress-mediated apoptosis and autophagy in Type I PDT. Nam *et al.* [43] designed ER-targeted iridium (III) complexes as potent PDT drugs, through ROS-mediated protein oxidation and photo-crosslinking, inducing significant protein modifications in the ER and mitochondria, ultimately leading to cancer cell death. Ma *et al.* developed a class of near-infrared photosensitizers T780T-ER by introducing dual regulatory strategies of ER targeting unit and enhanced intramolecular torsion. As a twisted-structured dimer, T780T-ER demonstrated exceptional photothermal stability and efficient ROS generation capacity, overcoming the oxygen dependency of traditional photosensitizers. Under ex vivo PDT, T780T-ER upregulates GRP78 to induce ER stress, thereby activating pyroptosis through the caspase-3/GSDME pathway while stimulating the release of inflammatory cytokines and damage-associated molecular patterns (DAMPs).

In vivo experiments showed that tumor injection of T780T-ER inhibited tumor growth and enhanced anti-tumor immune efficacy, and this effect could effectively inhibit the growth of distant tumors even under low temperature phototherapy conditions[44]. Cheng *et al.* [45] investigated the dual-omics approach using DFTBPPY (DY), an AIE photosensitizer that targets both ER and lipid droplets. This dual-targeting strategy induces mitochondrial dysfunction and lipid peroxidation through simultaneous generation of Type I and II ROS upon light activation. These coordinated effects synergistically induce both ferroptosis and pyroptosis, ultimately triggering a potent anti-tumor immune response for effective bladder cancer treatment. The dual-targeting strategy's advantage lies in its ability to disrupt multiple organelle functions simultaneously, thereby initiating a more intense lipid peroxidation cascade.

Other subcellular localizations

In addition to the above major organelles, the cell membrane, nucleus and Golgi apparatus have also become emerging research targets. Localization of photosensitizers on the cell membrane induces membrane lipid peroxidation, disrupting membrane integrity and causing ion channel dysfunction, resulting in the influx of intracellular calcium ions, ultimately leading to cell swelling and lysis, typically manifesting as necrosis or necroptotic apoptosis[27]. Nuclear targeting typically relies on ultra-small nanoparticles that enable penetration through nuclear membrane pores. Nuclear-targeted PDT directly induces DNA damage by causing strand breaks and releasing fragments into the cytoplasm, while oxidative base addition and cross-linking further result in significant genetic damage, ultimately triggering apoptosis[46]. Golgi body targeting, such as the dynamic localization photosensitizers described in "Lysosomal localization", has shown the potential to activate anti-tumor immunity by inducing cremation.

In summary, PDT efficiently generates ROS through the synergistic interaction of photosensitizers, light, and oxygen. These ROS target various organelles within cells, triggering a cascade of reactions that act on different initial targets to regulate subsequent complex cellular biological responses. This mechanism lays the foundation for designing specific cell death patterns as needed, ultimately leading to tumor cell death. A deep understanding of these core mechanisms serves as the basis for optimizing photosensitizer design, enhancing PDT efficacy, and overcoming therapeutic challenges.

PDT-Induced Cell Death Mechanisms

PDT induces multiple forms of tumor cell death through ROS generation, which is closely related to the subcellular localization of photosensitizers described above. Traditionally, PDT-induced cell death has been categorized into three primary types such as

apoptosis, necrosis, and autophagy[10,27,47-48]. However, with the continuous advancement in understanding cell death mechanisms, recent studies have found that PDT can also induce multiple novel cell death pathways, such as ferroptosis, immunogenic cell death, and pyroptosis[47,49-50]. It is very important to clarify the internal mechanism of different death modes and its correlation with localization for optimizing PDT treatment and overcoming drug resistance.

Apoptosis

Apoptosis is a programmed cell death, characterized by cell volume shrinkage, chromatin condensation, DNA fragmentation, and the formation of apoptotic bodies, which are ultimately cleared by phagocytes without inducing inflammatory responses. PDT-induced apoptosis is one of its primary antitumor mechanisms, typically initiated through endogenous (mitochondrial) and extrinsic (death receptor) pathways[11,27,48].

The activation of the endogenous apoptosis pathway is usually closely related to the localization of the mitochondrial photosensitizer. When such photosensitizers are enriched in mitochondria, ROS produced by PDT directly damages the mitochondrial membrane, resulting in decreased mitochondrial ΔΨm and increased MOMP, which then promotes the release of cytochrome c and other pro-apoptotic factors into the cytoplasm[27,34-35]. Subsequently, cytochrome c and APAF-1 and procaspase-9 form an apoptotic body, activate caspase-9, and then activate downstream effector caspase-3 and caspase-7, and finally execute the apoptosis program[27,34]. Didhamson *et al.*[34] demonstrated that mitochondrial-targeted aluminum phthalocyanine-mediated PDT effectively induced apoptosis in human esophageal carcinoma cells through mechanisms including increased ROS, reduced ΔΨm, enhanced cytochrome c release, and activation of caspase-3/7 (Fig. 2a). Similarly, Mei *et al.*[51] reported that the novel mitochondrial-targeted photosensitizer ATPP-DTPA-mediated blue light PDT significantly inhibited colorectal cancer cell growth and induced apoptosis by generating excessive ROS and activating the p38-MAPK signaling pathway.

The activation of the extrinsic apoptosis pathway may be more significantly associated with the localization of photosensitizers in the cell membrane. ROS generated by PDT can also directly or indirectly activate cell surface death receptors such as Fas and TNF receptors, leading to the formation of the death-inducing signaling complex (DISC) and subsequently activating caspase-8. Activated caspase-8 can directly activate effector caspases-3 and -7, or generate truncated Bid (tBid) by cleaving Bid protein. tBid functions on mitochondria to promote cytochrome c release, thereby linking the intrinsic apoptosis pathway (Fig. 2b)[27].

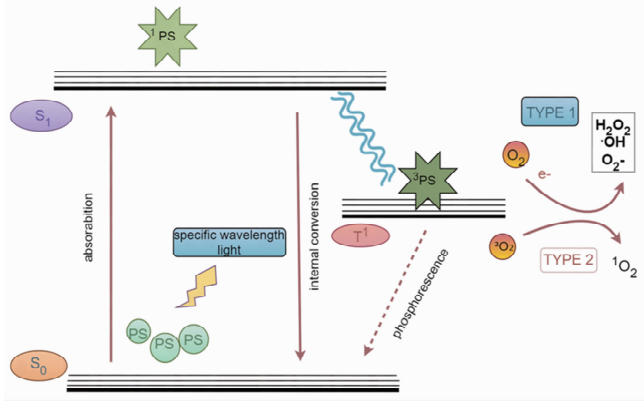
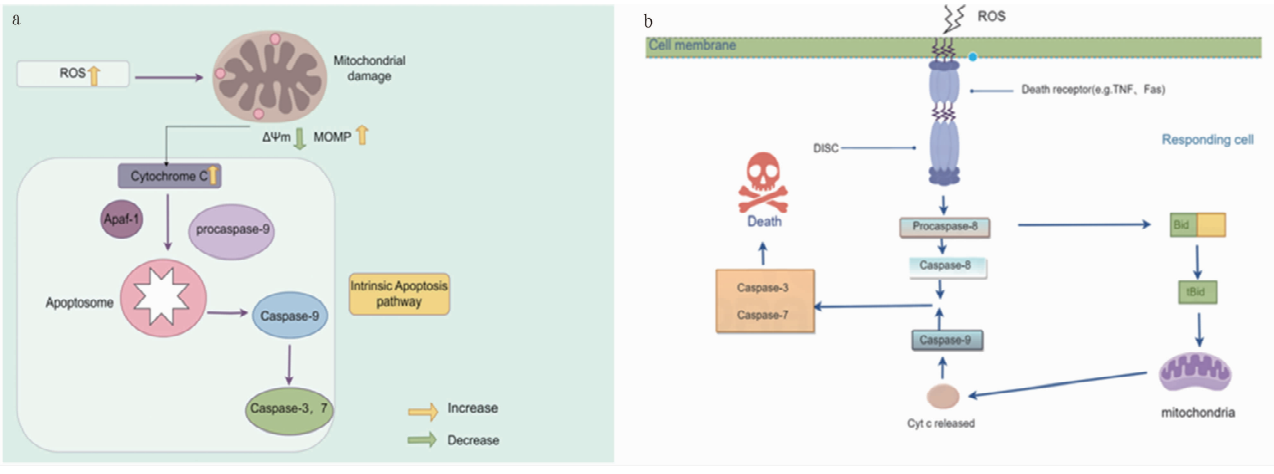


Fig. 1 Schematic diagram of type I and type II photodynamic reaction principles



(a) Mechanism diagram of the intrinsic apoptosis pathway; (b) Mechanism diagram of the extrinsic apoptosis pathway.

Fig. 2 Schematic diagram of apoptosis

Autophagy

Autophagy is a cellular "self-eating" process that maintains intracellular homeostasis and responds to stress by forming autophagosomes that engulf damaged organelles or proteins and transport them to lysosomes for degradation. In PDT, the role of autophagy is complex, and its specific effect is closely related to the subcellular localization of photosensitizers. When the photosensitizer is localized in mitochondria, ROS generated by PDT can

induce mitochondrial damage. This triggers autophagy as a cellular protective mechanism to eliminate damaged mitochondria, thereby helping cells resist ROS-induced injury and enhance survival. However, excessive or dysregulated autophagy may lead to cell death through autophagic necrosis, or synergistically promote cell death when combined with apoptosis[10,27,35,40,47,52].

Song *et al.*[53] found that m-THPC, which is mainly located in the ER, and vitilopofen-mediated PDT in mitochondria induced autophagy-mediated cell death in colorectal cancer cells by activating the ROS/JNK signaling pathway, and that inhibiting autophagy significantly reduce the anticancer effects of PDT. Dai *et al.*[52] proposed that inhibiting autophagy could further enhance PDT efficacy. They developed a biomimetic nanoplatform to co-deliver the lysosome-targeting photosensitizer PCN-224 and the autophagy inhibitor chloroquine (CQ), by suppressing autophagy to intensify ROS-induced lethal effects, achieving precise synergistic therapy combining PDT with autophagy inhibition. Similarly, Xie *et al.*[54] constructed a carrier-free nanodrug Ce6@ CQ that mainly targets lysosomes and ER Through the self-assembly of photosensitizer Ce6 and autophagy inhibitor CQ, the autophagy pathway was blocked, the PDT effect was enhanced, and the ICD was synergistically triggered, thus effectively treating breast cancer. Zhu *et al.*[41] also demonstrated that chloroquine-mediated autophagy inhibition significantly enhanced apoptosis induced by Sinoporphyrin Sodium-mediated PDT in human colorectal cancer cells, as well as tumor size was observed to reduction or even complete regression in the *in vivo* models. Kessel and Reiners[40] noted that autophagy may exert a cytoprotective effect when mitochondria are the primary target, whereas lysosomal damage may enhance photodynamic killing by inhibiting mitochondrial autophagy. Yao *et al.*[35] indicates that PDT mediated by Elsinochrome A, a natural photosensitizer mainly targeting mitochondria, induced apoptosis and autophagy in melanoma cells through ROS/Atg/Parkin pathway.

Necrosis and necroptosis

Necrosis is a non-procedural cell death, usually caused by severe cellular damage, characterized by cell swelling, cell membrane rupture and release of cellular contents, which leads to inflammatory response. In PDT, when the photosensitizer is located in the lysosome and produces a large amount of ROS, it will destroy the stability of the lysosomal membrane, resulting in the release of various hydrolytic enzymes into the cytoplasm. These enzymes further digest various components in the cell, and eventually cause the rupture of the cell membrane and necrosis when the repair ability of the cell exceeds[27,47-48]. However, with the deepening understanding of death mechanisms, many cell deaths previously classified as necrosis are now redefined as forms of death such as necroptosis. Necroptosis is mediated by proteins like receptor-interacting protein kinase 1 (RIPK1), RIPK3, and mixed lineage kinase domain-like protein (MLKL). It functions as a backup death mechanism in cells where the apoptosis pathway is impaired. When PDT causes mitochondrial or plasma membrane damage while caspase-8 activity is suppressed, necroptosis may occur[47,49].

Immunogenic cell death

Immunogenic cell death (ICD) is a specialized form of cell death that not only directly kills tumor cells but also releases specific damage-associated molecular patterns (DAMPs), such as ATP, high-mobility group box protein B1 (HMGB1), and calreticulin (CRT). These DAMPs act as "danger signals" that can be recognized by antigen-presenting cells (APCs), such as dendritic cells, promoting the uptake, processing, and presentation of tumor antigens, thereby activating T cell-mediated adaptive immune responses and forming long-term immune memory (Fig. 3)[13,47,55-58]. PDT is considered to be one of the effective means to induce ICD, and its effect is closely related to the subcellular localization of photosensitizers.

Photosensitizers located in the ER or plasma membrane are more likely to cause CRT exposure and HMGB1 release, thus enhancing ICD[13,15,47,59-60]. The combination of PDT with immune therapies such as immune checkpoint inhibitors can further enhance the antitumor effect. Gong *et al.*[55] showed that the combination of PDT and anti-PD-1 could significantly inhibit the tumor growth of NSCLC and increase the infiltration of CD8 + T cells. Lin *et al.*[56] designed a self-delivery translatable nanosystem that synergistically activated host immune responses and durable immune memory by enhancing PDT and incorporating immunomodulators, significantly inhibiting breast cancer growth and metastasis. The induction of ICD makes PDT not only a local treatment, but also empowers it to activate systemic anti-tumor immunity.

Ferroptosis

Ferroptosis, as an iron-dependent lipid peroxidation-mediated form of programmed cell death, is characterized by the accumulation of lipid peroxides. It is closely linked to intracellular iron metabolism, lipid metabolism, and GSH metabolism[47]. PDT and ferroptosis have a natural synergistic effect. ROS produced by photosensitizers targeting mitochondria or lysosomes not only directly kill tumor cells, but also promote ferroptosis by consuming GSH and degrading GPX4. This dual action can break the redox homeostasis in cells and significantly enhance the therapeutic effect[61-64]. In addition, as an important site of lipid synthesis, the ER may also promote ferroptosis by interfering with lipid metabolism through its targeted photosensitizers[47]. Ya *et al.*[65] designed a nanoplatform to deliver photosensitizers and ferroptosis inducers simultaneously by disrupting the intracellular redox homeostasis, which showed excellent effects in tumor therapy.

Other cell death modes

With the deepening of understanding of cell death mechanisms, in addition to traditional apoptosis, necrosis and autophagy, PDT has been found to induce a variety of emerging cell death patterns in recent years, which provide a new perspective for the study of PDT mechanism and the development of therapeutic strategies[47,49].

Pyroptosis is a highly inflammatory form of programmed cell

death, characterized by cell swelling, vesicle formation, and membrane rupture, accompanied by the release of inflammatory mediators such as IL-1β and IL-18. Zhou *et al.* [70] reported a mitochondria-targeted PDT approach using the photosensitizer IR700DX-6T, which triggered pyroptosis in colorectal cancer cells via ROS generation, p38 phosphorylation, and caspase-3-mediated GSDME cleavage. This pyroptosis not only directly killed tumor cells but also induced host anti-tumor immune responses and enhances sensitivity to PD-1 blockade therapy (Fig. 4). In addition, the ER-targeted photosensitizer T780T-ER described in Chapter 2 can activate caspase-3/GSDME pathway by inducing ER stress to effectively induce Pyroptosis. Similarly, the dynamic localization photosensitizer located in the Golgi body also played a role through GSDME-mediated Pyroptosis pathway[42-44].

Paradapoptosis is a non-caspase-dependent form of cell death, characterized by vacuolation of mitochondria and the ER, without the activation of caspases[40,47]. Kessel and Reiners[40] pointed out that light damage from photosensitizers localized to the ER can also initiate paraproapoptosis, a death pathway that is effective even in cell types with impaired apoptosis and appears to be unaffected by autophagy.

The mechanisms of PDT-induced cell death are diverse and closely related to the subcellular localization of photosensitizers. A deeper understanding of these complex cell death pathways and their interactions is crucial for optimizing PDT protocols, achieving precision therapy, and enhancing anti-tumor immune responses.

Challenges and Strategies in the TME for PDT Efficacy

The tumor microenvironment (TME) is a complex ecosystem composed of tumor cells, stromal cells, immune cells, blood vessels, and extracellular matrix. Its unique characteristics such as hypoxia, low pH, high antioxidant capacity, and immunosuppression, have significantly influence on tumor initiation, progression, metastasis, and treatment response[1,4,28]. These features also present novel targets and strategies for optimizing PDT.

Challenges and strategies in tumor hypoxia

Hypoxia within the TME is a critical factor affecting the efficacy of PDT. During PDT treatment, substantial oxygen is consumed to generate cytotoxic singlet oxygen. Concurrently, the vaso-occlusive effect further exacerbates hypoxia in tumor tissues. Consequently, the hypoxia environment will severely limits ROS production efficiency, thereby diminishing therapeutic outcomes[4,29,66-69].

To overcome tumor hypoxia, researchers have proposed various innovative strategies. For instance, through nanocarriers, oxygen-producing substances or catalysts are delivered locally to tumors, generating oxygen within the tumor to alleviate hypoxia[4,67]. Song *et al.* [67] developed a DNA/upconversion nanoparticle composite, in which G-quadruplex/hemoglobin DNA mimics horseradish peroxidase (HRP), enabling catalysis of endogenous H_2O_2 to generate O_2 and thus overcome tumor hypoxia. Lyu *et al.* [37] also proposed a multi-enzyme-like MOF (PyroFPSH) with peroxidase-mimetic activity that sustainably generates ROS to overcome hypoxia and enhance PDT (Fig. 5). Oxygen delivery via exogenous oxygen carriers, which directly transport oxygen to the tumor site and release it upon illumination, effectively alleviates tumor hypoxia[4,18]. Xavierselvan *et al.* [18] demonstrated photoacoustic nanodroplets as triple carriers for oxygen, photosensitizers, and indocyanine green, triggering the spatial and temporal delivery of oxygen to the tumors through light, significantly enhanced PDT efficacy, with a 9.1-fold increase in tumor oxygen content observed in the *in vivo* models. Alternatively, Type I photosensitizers with reduced oxygen dependency have been developed, such as the phosphoindole oxide Type I photosensitizer reported by Zhuang *et al.*, which can efficiently generate ROS under hypoxic conditions[29]. Kuznetsov *et al.* [69] explored combining PDT with photoactivated chemotherapy (PACT), that PACT operate independently of oxygen and can compensate for PDT's limitations under hypoxic conditions. By inhibiting mitochondrial respiration, targeting the mitochondrial electron transport chain or the HIF-1α pathway, tumor cells' oxygen consumption is reduced, indirectly increasing oxygen concentration[2,19]. Chen *et al.* [70] and Rui *et al.* [71] developed oxygen-autotrophic nano-system such as BC-PDA/HA to improve tumor hypoxia, and combine these with drugs like bufalin to inhibit the HIF-1α pathway, which could significantly enhances PDT efficacy.

Challenges and strategies for antioxidant defense mechanisms

To resist PDT-induced oxidative stress, tumor cells often develop robust antioxidant defense mechanisms, including upregulating the activity of superoxide dismutase (SOD), catalase (CAT), GSH, heme oxygenase-1 (HO-1)[8,31,72]. These enzymes effectively scavenge ROS generated by PDT, thereby reducing therapeutic efficacy and leading to tumor cell resistance to PDT.

Researchers have proposed the following countermeasures against the antioxidant defense mechanisms of tumor cells. For instance, the combined use of specific antioxidant enzyme inhibitors can weaken the antioxidant capacity of tumor cells, making them more sensitive to the ROS generated by PDT and thereby enhancing therapeutic efficacy[8,72]. Udomsak *et al.* [8] conducted an in-depth analysis of ROS detoxifying enzymes, including SOD, CAT, GSH redox cycle, and HO-1 in interfering with PDT-induced cell death. They emphasized the potential of employing antioxidant enzyme inhibitors as a strategy to reduce tumor cell antioxidant activity and improve PDT efficacy. Przygoda *et al.* [31] revealed a self-amplifying mechanism involving secondary singlet oxygen generation and CAT inactivation, offering prospects for enhancing PDT efficacy, which by targeting the Nrf2 signaling pathway, knocking down or inhibiting Nrf2 using gene editing technologies such as CRISPR-Cas9 can reduce tumor cell antioxidant capacity and increase their sensitivity to ROS. Song *et al.* [67] demonstrated that DNA/UCNPs complexes enhanced synergistic PDT effects by sensitizing cancer cells to ROS through CRISPR-Cas9-mediated cleavage of the antioxidant regulator Nrf2 (Fig. 6). Wang *et al.* [28]

proposed photocatalysis induced NADH oxidation to damage the mitochondrial electron transport chain, which is a novel PDT mechanism that disrupts tumor cell energy metabolism and redox balance, thereby enhancing PDT efficacy.

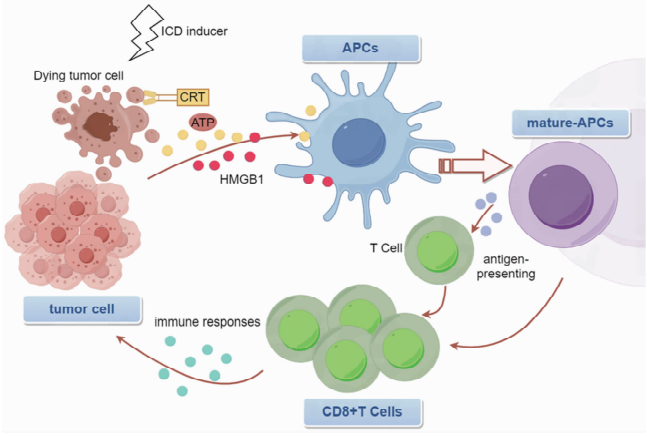


Fig. 3 Schematic diagram of immunogenic cell death mechanisms

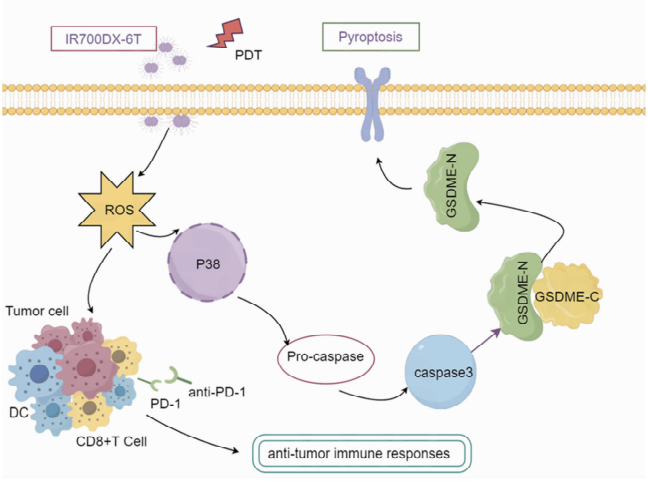


Fig. 4 Schematic diagram of the pyroptosis mechanism induced by photosensitizer IR700DX-6T in colorectal cancer cells

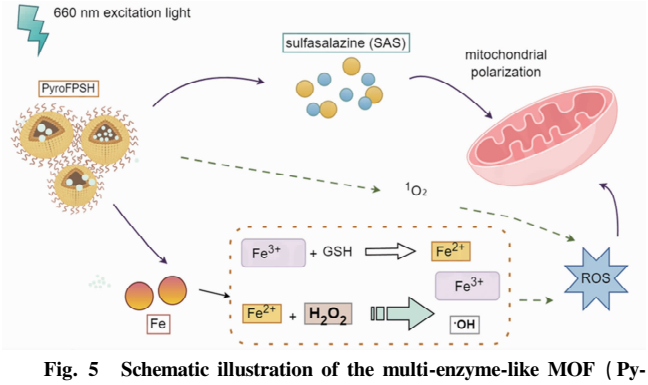


Fig. 5 Schematic illustration of the multi-enzyme-like MOF (PyroFPSH) simulating the continuous generation of reactive oxygen species by catalase and glutathione peroxidase

Challenges and strategies in the immunosuppressive microenvironment

The TME typically exhibits an immunosuppressive state, characterized by regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs), and tumor-associated macrophages (TAMs), which suppress effector T cell activity, hindering effective antitumor immune responses[13,60]. This immunosuppression is a major obstacle for cancer immunotherapy and also limits the potential of PDT to induce immune responses.

To further enhance the immune-activating effects of PDT, researchers are exploring multiple strategies to overcome TME immunosuppression, such as combining PDT with immune checkpoint inhibitors like PD-1/PD-L1 inhibitors to release T cell suppression and enhance antitumor immune responses[13,59,66]. *In vivo* studies by Gong *et al.* and Zhou *et al.*[59,66]. have both validated the efficacy of this combination strategy. Alternatively, co-delivery of photosensitizers and immunomodulators via nanocarriers can directly modulate immunosuppressive cell populations or enhance the activity of immune cells[4,60]. Lin *et al.*[60] developed a nanosystem that co-delivered metformin and sunitinib to alleviate tumor immune suppression through multiple mechanisms. Xie *et al.*[54] enhanced PDT efficacy and synergistically triggered ICD by blocking the autophagy pathway, achieving effective treatment of breast cancer.

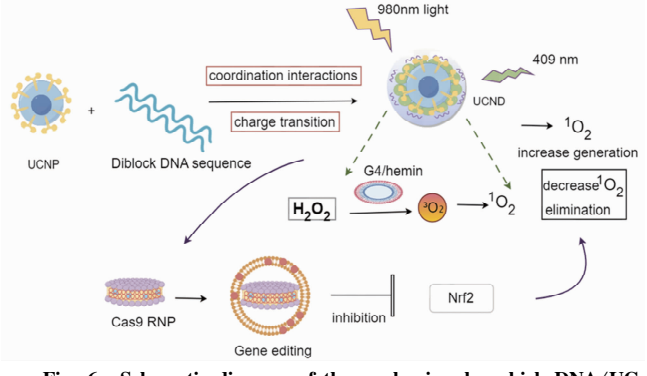


Fig. 6 Schematic diagram of the mechanism by which DNA/UCNPs complexes counteract antioxidant defense

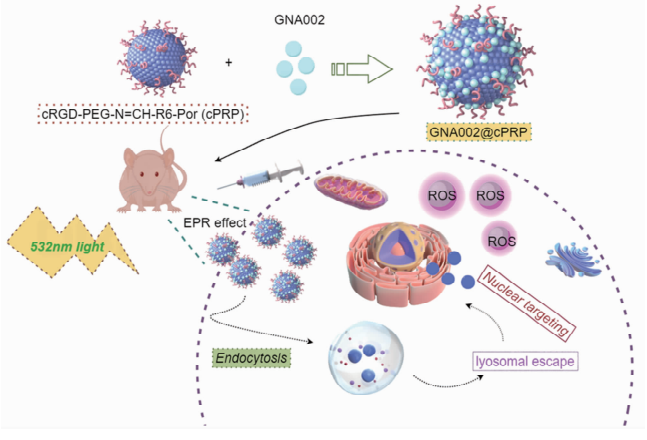


Fig. 7 Schematic illustration of GNA002@cPRP nanoparticle formation and nuclear-targeted delivery mechanism

In summary, the interaction between PDT and the TME is a complex and dynamic process. Deepening our understanding of how PDT overcomes tumor hypoxia, counters antioxidant defenses,

and modulates immunosuppressive microenvironments is crucial for realizing its full potential in cancer immunotherapy. Nanocarrier deliverysystems and combination therapy strategies are particularly important in this context.

Challenges and Strategies in PDT Resistance Mechanisms

Despite the immense potential of PDT in cancer treatment, tumor cell resistance to PDT remains a key challenge limiting its clinical application and therapeutic efficacy[8,14,72]. Understanding these resistance mechanisms and developing corresponding overcoming strategies are crucial for enhancing PDT efficacy.

Challenges in PDT resistance mechanisms

Tumor cell resistance to PDT results from the combined effects of multiple factors and pathways. For instance, the properties of photosensitizers and their distribution and accumulation within tumor tissue are critical determinants of PDT efficacy. Many conventional photosensitizers exhibit limited penetration and distribution within tumor tissue due to their hydrophilic nature or large molecular weight, leading to insufficient photosensitizer concentration in deep tumor regions and consequently affect therapeutic outcomes[14]. Non-specific distribution of photosensitizers may cause damage to healthy tissues, limiting their usable dose while reducing specific killing of tumor cells[6]. Tumor cells may develop resistance by upregulating efflux pumps such as P-glycoprotein to accelerate photosensitizer efflux and reduce effective intracellular concentrations[25,68]. Mossakowska *et al.*[68] investigating PDT resistance mechanisms in vulvar carcinoma found that resistant cells accumulated and effluxed less porphyrin, suggesting drug transport may contribute to resistance. Alternatively, tumor cells may activate DNA damage repair pathways to repair such damage and evade cell death. Mossakowska *et al.*[68] also observed increased activity of the DNA repair protein apurinic/apyrimidinic endonuclease 1 (APE1) in PDT-resistant vulvar carcinoma cells. They further demonstrated that inhibiting APE1 activity significantly reduced the survival rate of PDT-resistant cells, suggesting a critical role for APE1 in PDT-mediated DNA damage repair. Tumor cells may resist PDT by modulating cell death pathways. In some cases, PDT-induced autophagy may function as a cellular protective mechanism to help cells eliminate damaged organelles and thus resist ROS induced damage[40,53]. Song *et al.*[53] found that inhibiting autophagy significantly enhances the anticancer effect of PDT in colorectal cancer cells, suggesting autophagy may exert a protective role during PDT. Tumor cells may suppress apoptosis by upregulating anti-apoptotic proteins such as Bcl-2 or downregulating pro-apoptotic proteins such as Bax or through mechanisms like caspase inhibitors, thereby avoiding cell death by PDT[25].

Strategies to overcome PDT resistance

To enhance PDT efficacy, researchers have developed multiple innovative strategies to overcome tumor cell resistance. Novel photosensitizers with higher water solubility, better targeting, deeper tissue penetration, and higher ROS quantum yield have been developed to enhance accumulation at tumor sites and photochemical efficiency[6,14]. Novel photosensitizers such as Aza-BODIPY and its derivatives are being explored to enhance tissue penetration[14]. Designing "Smart" photosensitizers responsive to the tumor microenvironment, which are activate only at tumor sites, thereby improving specificity and safety[24,70]. Ilhan *et al.*[73] reported nitric oxide (NO)-activated PDT based on BODIPY-copper complexes, leveraging elevated NO concentrations in the tumor microenvironment for targeted activation. Sun *et al.*[74] highlighted carbon dots as novel carbon-based nanomaterials exhibiting excellent photosensitization activity and efficient ROS generation, playing a significant role as photosensitizers or carriers in tumor therapy. Combining PDT with DNA repair inhibitors, such as APE1 inhibitors, can prevent tumor cells from repairing PDT-induced DNA damage, thereby enhancing PDT's killing efficiency[72]. Premji *et al.*[75] indicated that in photothermal or PDT, tumor cells upregulate heat shock protein (HSP) production to resist treatment. By using HSP inhibitors or reducing intracellular ATP levels, the production of HSP can be suppressed, thereby enhancing PDT efficacy. Combining PDT with other anticancer therapies can achieve synergistic effects, overcoming the limitations and resistance of single therapies[15-17].

By deepening our understanding of the molecular mechanisms underlying PDT resistance and integrating novel photosensitizers, advanced nanocarrier technologies, and multimodal combination therapies, we can significantly enhance the efficacy of PDT in cancer treatment.

Research on Synergistic Mechanisms in Combination Therapy

Monotherapy in cancer treatment often faces challenges such as drug resistance, recurrence, insufficient light penetration for deep tumors, and limited efficacy against metastatic tumors. Therefore, combining PDT with other therapeutic strategies to achieve multi-targeted, multi-mechanistic synergistic effects has become a key direction for improving cancer treatment outcomes[4,28,76]. This combination therapies not only overcome the inherent limitations of PDT but also enhance the efficacy of other therapies.

Photodynamic-photothermal combination therapy

Photothermal therapy (PTT) utilizes photothermal conversion materials to generate heat under near-infrared light irradiation, directly killing tumor cells through thermal effects[72]. The combination of PDT and PTT can achieve a dual killing mechanism, which is a promising therapeutic strategy[15,17,57,75]. ROS generated by PDT and heat produced by PTT can independently or synergistically induce tumor cell death. Heat increases cell membrane permeability, enhancing photosensitizer uptake and ROS diffusion while boosting tumor tissue blood flow, thereby improving oxygen supply, alleviates tumor hypoxia, and facilitates the progress of PDT[17]. ROS can also exacerbates thermal damage, leading to more thorough tumor clearance. PTT can also overcome tumor cell

resistance to heat by suppressing HSP production, while PDT can compensate for potential limitations of PTT in certain tumor types[75]. Premji *et al.* [75] explored how functionalized nanomaterials enhance PTT/PDT and combined therapy efficacy by inhibiting ATP-dependent HSP.

Photodynamic-chemotherapy combination

Chemotherapy drugs directly kill tumor cells through distinct mechanisms but often carry severe systemic toxicity and resistance issues. The combination of PDT and chemotherapy can make use of the locality and selectivity of PDT to reduce systemic chemotherapy doses and side effects while synergistically enhancing therapeutic efficacy[15,24-25,69,76]. PDT-induced ROS can damage DNA, leading to cell cycle arrest and enhancing the cytotoxicity of chemotherapeutic agents. Simultaneously, chemotherapeutic drugs can also enhance PDT efficacy by inhibiting cell proliferation, disrupting the cell cycle, suppressing DNA repair, or inducing oxidative stress, thereby creating a more favorable therapeutic environment for PDT[24]. Hong *et al.* [16] and Rajan *et al.* [15] both highlighted the potential of PDT combined with chemotherapy to enhance apoptotic responses and suppress resistance mechanisms. Li *et al.* [24] developed a pH-cascade-responsive micellar nanoplatform for co-delivery of photosensitizers and the novel anticancer drug GNA002, enabling nuclear-targeted chemo-photodynamic synergistic therapy that demonstrated potent anticancer activity both *in vitro* and *in vivo*. PDT can overcome tumor resistance to chemotherapeutic agents by disrupting tumor vasculature, altering the tumor microenvironment, or inducing immune responses. Conversely, chemotherapeutic drugs can enhance PDT sensitivity by inhibiting tumor cell proliferation or inducing apoptosis[15-16]. Multidrug resistance (MDR) is a primary cause of chemotherapy failure. PDT kills cells via non-MDR-related mechanisms, so combining with chemotherapy can effectively overcomes MDR. Bhattacharya *et al.* [25] reviewed the application of PDT in the fight against MDR cancer and emphasized the potential of a new generation of photosensitizers based on nanomaterials to overcome MDR.

Photodynamic-nanocarrier conjugates

Nanocarriers play a crucial synergistic role in photodynamic combination therapy. By encapsulating photosensitizers within nanocarriers, that can significantly improve their pharmacokinetic properties, tumor targeting, deep tissue penetration, and biocompatibility[6,15,57,77-80].

The size of nanocarriers enables them to enter the tumor stroma through leaky blood vessels within tumor tissue and become retained due to impaired tumor lymphatic drainage, known as the EPR effect, thereby achieving passive targeted accumulation of photosensitizers at tumor sites[6,79-80]. By modifying the surface of nanocarriers with specific ligands such as antibodies, peptides, or folate, they can recognize and bind receptors overexpressed on tumor cell surfaces, enabling more precise targeted delivery[6,52,60,70]. Li *et al.* [24] constructed a pH-cascade-responsive micellar nanoplatform featuring active targeting via cyclized RGD peptide (cRGD) modified polyethylene glycol (PEG) and combined with the cell-penetrating peptide hexarhein, it forms the copolymer cPRP and binds with GNA002 to create GNA002@cPRP nanoparticles, enabling targeted delivery to the cell nucleus (Fig. 7). Chen *et al.* [52] and Dai *et al.* [57] discussed the advantages of cell membrane mimetic nanomedicines, which by coating nanoparticle surfaces with tumor cell membranes or immune cell membranes, nanocarriers can gain immune evasion capabilities, prolong circulation time *in vivo*, enhance biocompatibility, and enable homogenous targeting or immune activation, significantly boosting PDT's antitumor efficacy. Rajan *et al.* [15] highlighted the advantages of nano-enhanced PDT in optimizing drug delivery, selectivity, and ROS generation, while exploring the potential of NE-PDT combination with chemotherapy, immunotherapy, and targeted therapies. Mohanty *et al.* [80] reviewed the application of nanoparticle-assisted PDT in skin cancer treatment, encompassing polymeric nanoparticles, metallic nanoparticles, and lipid nanocarriers, as well as advanced carriers like quantum dots, microneedles, and cubes. They highlighted the role of nanoparticles in improving skin penetration and enhancing PDT therapeutic efficacy. Kwiatkowski *et al.* [81] also noted that the combination of nanomaterials with photosensitizers can increase PDT efficiency and reducing side effects.

Photodynamic-immunotherapy combination

PDT is recognized as an effective inducer of immunogenic cell death (ICD), which can activate the host antitumor immune responses, providing a robust foundation for the combination of PDT and immunotherapy[4,15,55-57,59-60].

PDT-induced ICD releases damage-associated molecular patterns (DAMPs) such as ATP, HMGB1, and CRT to recruits and activates dendritic cells (DCs), thereby promoting tumor antigen presentation and initiating T cell-mediated antitumor immune responses[13,54-56]. Thiruppathi *et al.* [13] emphasized that the PDT-triggered cascade can "heat up" the TME and induce tumor antigen presentation to immune cells via ICD, thereby enhancing immunotherapy efficacy. Aebisher *et al.* [56] pointed out ROS-induced adaptive immune responses and highlighted PDT's ability to activate the adaptive immune system to destroy tumor lesions and establish immune memory. PDT-activated antitumor immune responses can synergize with anti-PD-1/PD-L1 antibodies to release tumor suppression of T cells, thereby enhancing T cell-mediated tumor killing[13,59,60,66,82]. The studies by Zhou *et al.* [66] and Gong *et al.* [59] respectively demonstrated the synergistic antitumor effects of PDT combined with anti-PD-1 therapy in non-small cell lung cancer and colorectal cancer. The adaptive immune response induced by PDT can produce long-term immune memory, which can effectively inhibit tumor recurrence and metastasis[56,60]. Lin *et al.* [60] successfully activated robust host immune responses and persistent immune memory by combining PDT with immunomodulators via self-delivery nanosystems, which significantly inhibiting tumor growth and metastasis.

Photodynamic-other therapy combination

Beyond the primary combination therapies mentioned above,

PDT has also been combined with various other treatment modalities. For instance, PDT combined with PACT, gene therapy, starvation therapy, magnetothermal therapy, and sonodynamic therapy, effectively enhancing tumor killing[57,67,69,75,81]. PACT is a strategy that uses light to activate prodrugs, releasing cytotoxic drugs at tumor sites. Kuznetsov *et al.*[69] proposed that combining PDT with PACT overcomes the oxygen dependency limitation of PDT. Song *et al.*[67] demonstrated the potential of integrating CRISPR-Cas9 gene editing technology with PDT. By CRISPR-Cas9 knockout of antioxidant genes such as Nrf2, which can enhance tumor cell sensitivity to PDT-induced ROS, thereby boosting therapeutic efficacy. Premji *et al.*[75] noted that delivering glucose-depriving agents such as glucose oxidase (GOx) in combination with starvation therapy can indirectly suppress HSPs and enhance the efficacy of PTT/PDT. The nanohybrid material developed by Curcio *et al.*[81] integrates magnetothermal therapy, PTT, and PDT, by inducing heat via magnetic fields synergistically with photothermal and photodynamic effects, it achieves multimodal tumor killing. Chen *et al.*[57] highlighted the potential of cell membrane-mimetic nanomedicines for synergistic therapies in cancer phototherapy, such as combining them with PDT.

These diverse combination therapy strategies offer broad prospects for overcoming complex challenges in cancer treatment by integrating the advantages of different therapies to attack tumors at molecular, cellular, and immune levels. Future research will continue exploring more efficient and safer combination approaches while elucidating their molecular mechanisms of synergy.

Conclusion and Prospect

PDT has achieved significant progress in oncology as a highly promising cancer treatment strategy. This review comprehensively examines and thoroughly discusses recent advancements in the core mechanisms of PDT for cancer treatment, the induction and regulation of multiple cell death pathways, interactions with the TME, challenges and strategies for overcoming resistance mechanisms, and synergistic mechanisms between PDT and other therapies.

Research indicates that the basic principle of PDT lies in the generation of ROS, particularly singlet oxygen, by photosensitizers upon light exposure, which induces cellular damage. The subcellular localization of photosensitizers is crucial for the pattern of cell death they induce, with targeting key organelles such as mitochondria, ER, and lysosomes can precisely regulate diverse cell death pathways, including apoptosis, autophagy, and pyroptosis[27,29,31,66]. In recent years, deepening insights into ICD has revealed the great potential of PDT to activate the host anti-tumor immune response, which makes it expand from local treatment to a strategy with systemic anti-tumor effect[47,55-56].

However, PDT still faces numerous challenges in clinical application. These primarily include tumor hypoxia, insufficient penetration and accumulation of photosensitizers at tumor sites, antioxidant defense mechanisms of tumor cells, and activation of DNA damage repair pathways as resistance mechanisms[4,8,14,72]. Researchers have developed various innovative strategies, such as creating novel photosensitizers and utilizing nanocarrier technologies, to develop Type I photosensitizers that can efficiently generating ROS under hypoxic conditions, designing nanoscale systems that can generation oxygen in situ or delivery oxygen, and developing adjuvant drugs or nanocarriers that suppress tumor cell antioxidant defense mechanisms[8,18,28-29,37,67]. Additionally, biomimetic nanomedicines for cell membranes have significantly enhanced PDT's therapeutic efficacy and application potential by amplifying the EPR effect, enabling active targeting, alleviating tumor hypoxia, and improving deep tissue penetration[15,57,79-80]. Furthermore, immune suppression within the TME limits PDT-induced antitumor immune responses, so combination therapy with immune checkpoint inhibitors has demonstrated significant synergistic effects[59-60,66]. Moreover, integrating PDT with multiple modalities such as chemotherapy, immunotherapy, and photothermal therapy, that demonstrates enhanced antitumor efficacy and potential for overcoming drug resistance through synergistic multi-target and multi-mechanism actions[16-17,59,66-67].

Although a more comprehensive understanding of PDT-induced cell death patterns has been gained, the interactions and conversion mechanisms between different cell death pathways, as well as their roles in tumor progression and treatment response, require further investigation. Moreover, it is still an important challenge to translate the experimental research results into clinical application, and to realize personalized precision treatment of PDT based on patients' individual differences and tumor characteristics. In summary, PDT demonstrates immense potential and broad prospects in cancer treatment. With deepening understanding of its mechanisms and ongoing technological innovation, PDT is expected to become an indispensable component of future cancer treatment strategies, offering patients more effective and safer therapeutic options.

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