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REVIEW

Advances in Nanomedicine-Mediated Photodynamic Therapy for Lung Cancer: Challenges and Perspectives

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Abstract: Photodynamic therapy (PDT), a precision modality based on photosensitizers, light, and oxygen, demonstrates unique advantages in lung cancer treatment. The limitations of traditional photosensitizers in clinical applications, including poor water solubility and insufficient targeting, have driven the development of nanotechnology and novel photosensitizers. Accordingly, this review elaborates on advanced strategies designed to enhance therapeutic specificity and efficacy, overcome the hypoxic tumor microenvironment (TME) and combat monotherapy resistance. These strategies include the design of various nanocarriers, active targeting ligands, novel energy transfer methods, as well as intelligent responsive systems and combination therapies. Nevertheless, despite abundant preclinical achievements, the clinical translation of nano-PDT formulations faces significant obstacles. Future efforts should focus on developing theranostic platforms to rigorously evaluate clinical safety and efficacy, enable precision treatment, and decipher immunological synergy.

Keywords: photodynamic therapy, nanomedicine, targeting ligands, responsive design, lung cancer

Introduction

Lung cancer is one of the most common malignancies with the morbidity and mortality ranking first worldwide.[1] According to the global data published in 2024, lung cancer accounts for about one in eight of the nearly 20 million new cancer cases. Among these cases, Asia accounts for 49.2% of the morbidity and 56.1% of the mortality.[2] In fact, the high incidence and mortality of lung cancer make it a major global public health problem.

The pathogenesis of lung cancer is a complex process attributed to the combined effects of heredity, environment and living habits.[3,4] However, many lung cancer patients are diagnosed at the middle or advanced stage, which poses considerable challenges to clinical treatment. The current therapies for lung cancer contain surgical resection, radiotherapy and chemotherapy.[5] But the conventional radiotherapy and chemotherapy usually cause adverse effects like myelosuppression, nausea, vomiting and hair loss. Furthermore, chemotherapy frequently induces drug resistance, thereby limiting treatment options for recurrence or metastasis and diminishing long-term survival rates. The five-year survival rate for lung cancer varies globally, from 20–30% in China and the United States to under 10% in Brazil and India, highlighting a pressing clinical challenge that necessitates the exploration of innovative treatments.[6]

Recently, PDT—a modality based on a drug-device combination—has attracted wide attention in lung cancer treatment. PDT is indicated for patients with inoperable early-stage lung cancer, as well as advanced cases requiring palliative care to alleviate symptoms.[7] Compared with conventional therapies, PDT offers distinct advantages such as minimal invasiveness, high selectivity, and compatibility with combination therapy. Its capacity for precise spatial and temporal control of light activation enables effective tumor targeting while minimizing damage to normal tissues.

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However, the clinical application of PDT is hampered by inherent limitations of conventional photosensitizers, notably poor aqueous solubility and inadequate tumor targeting specificity.[8] These shortcomings often lead to suboptimal biodistribution and reduce therapeutic efficacy. To address these challenges, the development of advanced drug carriers is pivotal for enhancing the efficacy of PDT. In this context, nanomedicine has emerged as a promising strategy, offering a protective carrier system that mitigates in vivo degradation and phagocytic clearance.[9] By enhancing photosensitizer bioavailability and biocompatibility, nanocarriers can prolong systemic circulation, reduce off-target toxicity, and improve tumor-specific accumulation, collectively elevating the overall therapeutic potential of PDT. It is hoped that the systematic analysis of challenges and strategies presented in this review will provide valuable insights to facilitate the clinical translation of PDT for lung cancer.

Photodynamic Therapy

PDT comprises three core components: light source, photosensitizers and surrounding substrates. Upon irradiation, the photosensitizers interact with surrounding substrates to generate reactive oxygen species (ROS), such as singlet oxygen ($^1O_2$), hydroxyl radical (•OH), superoxide anion radical ($•O_2^-$) and so on. In the process of PDT, the light source provides energy, and the photosensitizer absorbs within its activation spectrum, causing its transition from the ground state (PS^0) to the excited singlet state (PS^1). PS^1 can dissipate energy as fluorescene/heat or undergo intersystem crossing to the excited triplet state (PS^3). And PS^3 could also dissipate energy as fluorescene/heat, or interact with surrounding substrates via electron/energy transfer to produce ROS.

ROS generation occurs via two main pathways:

- Type I: Free radicals are produced via electron transfer or hydrogen atom transfer from substrates (eg, $•O_2^-$ from O_2, •OH from H_2O).
- Type II: $^1O_2$ is generated by energy transfer from PS^3 to ground-state oxygen (facilitated by spin compatibility).

In PDT, common light sources include laser and light-emitting diode (LED). Compared with LED, lasers feature with monochromaticity, directionality, and high energy density. So they are less absorbed by tissue hemoglobin and melanin, enabling precise energy delivery to deep tumors. Surrounding substrate molecules include O_2, H_2O, glutathione (GSH), nicotinamide adenine dinucleotide, transition metal ions, and some biological macromolecules (proteins, lipids, and nucleic acids). Substrate-photosensitizer reactions produce free radicals/ROS, which oxidize biomolecules, thus impairing cell function and metabolism.[10] And the free radicals/ROS make damage to intracellular components (eg, proteins, DNA) and induce apoptosis or necrosis.[11]

At present, clinically used photosensitizers are categorized into three generations by their development history.[12,13] First-generation photosensitizers, mainly hematoporphyrin derivatives (eg, Photofrin), have short excitation wavelengths, poor tissue penetration and long half-lives, causing severe phototoxicity. Second-generation agents (eg, 5-aminolevulinic acid, phthalocyanins) have longer excitation wavelengths, and exhibit higher selectivity in damaging tumor cells. Third-generation photosensitizers are modified with targeting structures (eg, receptors) to enhance tumor-specific targeting. Since 1995, when the first photosensitizer (Photofrin) was approved, PDT research has advanced significantly over two decades. Currently, multiple photosensitizer drugs (eg, Levulan, Foscan) are approved globally, applying in the treatment of keratosis, head and neck cancer, esophageal cancer, lung cancer, and diagnosis of bladder cancer (Table 1).

The field of photosensitizer development has witnessed substantial progress. As a novel vascular-targeted photosensitizer, Padeliporfin, a Pd-containing tetrapyrrolic compound, has been approved in regions like the European Union for treating localized prostate cancer.[14,15] Besides, the photoimmunotherapy drug Akalux has been approved in Japan for head and neck cancers, which conjugates antibodies with photosensitizers, enabling precise cancer cell destruction.[16] Several innovative photosensitizers are still undergoing clinical evaluation, such as TLD-1433,[17] a Ru-based agent for bladder cancer, and SGX301,[18] a topical gel formulation of synthetic Hypericin for cutaneous T-cell lymphoma. In addition, the FZ-P001 Sodium for Injection developed domestically in China has had its application for clinical trial accepted in 2025, which conjugates cyanine photosensitizer to the folate receptor (FR) α-specific ligands for real-time fluorescence-guided surgery in cancers such as ovarian and lung cancer.

Table 1 Approved Photosensitizer Drugs

Drug Name	Active Ingredients	Initial Approval	Company	Indications
Photofrin	Porfimer Sodium	1995	PINNACLE BIOLGS	Esophageal Cancer; Endobronchial Cancer; High-Grade Dysplasia in Barrett's Esophagus.
Levulan	Aminolevulinic Acid Hydrochloride	1999	SUN PHARM INDS INC	Minimally to moderately thick actinic keratoses of the face, scalp, or upper arms.
Foscan	Temoporfin	2001	BIOLITEC PHARMA LTD	Advanced head and neck squamous cell carcinoma.
Visudyne	Verteporfin	2000	BAUSCH LOMB IRELAND	Age-related macular degeneration inpatients with predominantly classic subfoveal choroidal neovascularization.
Metvix	Methyl Aminolevulinate Hydrochloride	2004	GALDERMA LABS LP	Non-hyperkeratotic actinic keratoses of the face and scalp.
Laserphyrin	Talaporfin Sodium	2004	MEIJI SEIKA PHARMA CO. LTD.	Early stage of lung cancer.
HiPorfin	Hematoporphyrin	2006	MLELONGE	Localization diagnosis and treatment of superficial cancers in oral cavity, bladder, bronchus, lung, digestive system and other parts of the precancerous lesions such as leukoplakia; Treatment of port wine stains.
5-ALA	Aminolevulinic Acid Hydrochloride	2007	FUDAN ZHANGJIANG	Condyloma acuminata.
Cysview	Hexaminolevulinate Hydrochloride	2010	PHOTOCURE ASA	Photodynamic diagnosis of bladder cancer.
HMME	Hemoporfin	2016	FUDAN ZHANGJIANG	Port wine stains.
Ameluz	Aminolevulinic Acid Hydrochloride	2017	BIOFRONTERA	Lesion-directed and field-directedtreatment of actinic keratoses (AKs) of mild-to-moderate severity on the face and scalp.
TOOKAD	Padeliporfin Di-potassium	2017	STEBA BIOTECH S.A	Prostatic Neoplasms.
Akalux	Cetuximab Sarotalocan Sodium	2021	RAKUTEN MEDICAL INC.	Unresectable locally advanced or locally recurrent head and neck cancer.

Actually, most photosensitizers typically present certain challenges in clinical applications (Figure 1): (1) The hydrophobic molecules lead to poor water solubility and a strong tendency to aggregate under physiological conditions, which severely suppresses ROS production. And the hydrophobicity usually exhibits low bioavailability and poor tumor specificity, resulting in off-target toxicity, such as prolonged skin photosensitivity.[8] (2) The efficacy of PDT is fundamentally limited by the penetration depth of activating light in biological tissues. For most first- and second-generation photosensitizers, the visible light served as energy source could penetrate only a few millimeters, restricting PDT to superficial or endoscopically accessible tumors.[13] (3) The low-oxygen environment is a typical characteristic of solid tumors, and it deprives the dominant Type II PDT reaction of its essential reactant—oxygen. This creates a vicious, self-limiting feedback cycle, where PDT consumes the very oxygen it needs to function, further exacerbating hypoxia and diminishing its own therapeutic effect.[19] (4) Another key issue is the monotherapy resistance of PDT, which involves suboptimal tissue delivery of photosensitizers and insufficient light intensity that reduces ROS production. In these conditions, tumor cells are more susceptible to developing resistance to PDT. Furthermore, factors such as drug efflux and degradation, the activity of intracellular antioxidant enzymes and heat shock proteins of tumor cells all significantly contribute to the emergence of PDT resistance.[20,21]

In terms of these challenges, the design of composite nanocarrier delivery system has emerged as a promising development direction. Drug carriers could enhance the bioavailability and targeted delivery of photosensitizers. And the

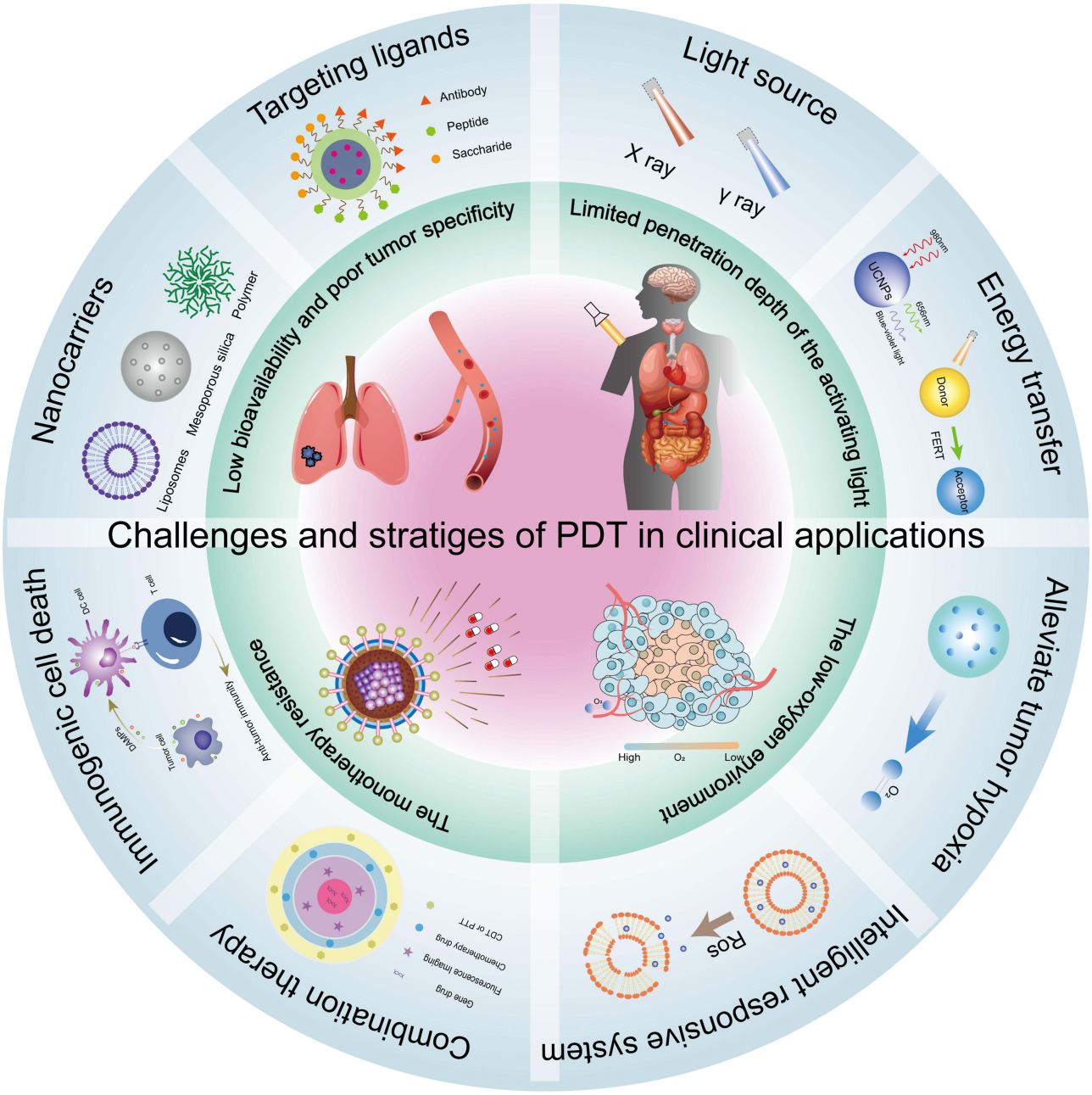

Figure 1 The challenges and strategies of PDT in clinical applications.

composite structures on the carriers could facilitate various functionalities, including optimizing light energy transfer, alleviating hypoxic environments, and enabling other combination therapies. Therefore, this review aims to discuss the application of nanomedicine in photodynamic therapy for lung cancer research, with the goal of providing new perspectives and directions for more effective strategies.

The Mechanisms of PDT in Lung Cancer

PDT achieves its anti-tumor effect chiefly through the action of ROS. This action kills cancer cells directly via oxidative damage, which consequently elicits an immune response against the tumor. At regulated levels, ROS participates in vital signaling pathways and serves as a key regulator of redox homeostasis. And ROS also induces oxidative stress and damages biomolecules at high levels. This duality underscores its potential as both a therapeutic target in lung cancer treatment.[22]

Direct Killing Effect of Oxidative Damage

The cytotoxicity of ROS initiates with the oxidation of cellular macromolecules (eg, lipids, proteins and nucleic acids), disrupting their structure and function. Specifically, ROS-mediated oxidation of unsaturated fatty acids in cell membranes causes lipid peroxidation, which alters fluidity and permeability of membranes. It also oxidizes amino acid residues (eg, cysteine and methionine) in proteins, affecting enzymatic activity in transcription or metabolism. Furthermore, ROS reacts with nucleic acids bases, inducing DNA strand breakage, cross-linking and base damage—interfering with DNA replication/transcription and ultimately leading to tumor cell death.

At the suborganelle level, excessive ROS generation triggers mitochondrial dysfunction by depolarizing the membrane potential and damaging the respiratory chain. This disrupts electron transport and leads to further ROS generation, which is described as the vicious cycle of ROS propagation in cancer.[23] Concurrently, ROS-induced membrane damage disrupts calcium ion homeostasis, resulting in calcium ion overload. This, in turn, promotes the abnormal and irreversible opening of the mitochondrial permeability transition pore.[24] This allows cytochrome C and apoptosis-inducing factors to release into the cytoplasm, where they activate apoptosis signaling pathways (eg, the caspase protein cascade reaction). Additionally, gasdermin E can be activated, leading to pyroptosis via disrupting the cell membrane's phosphoester structure.[25]

Beyond these organelle-driven pathways, ROS-mediated oxidative damage to biomacromolecules also involves in cell metabolism and function, leading to various forms of cell death such as apoptosis (triggered by low ROS doses) and necrosis (induced by high ROS doses).[26] As summarized in a review, multiple mechanisms of PDT-induced cell death are under investigation, including ferroptosis, pyroptosis and immunogenic cell death (ICD), reflecting the complex interplay between oxidative stress and cellular demise.[17]

Triggerring Immune Response

Beyond ROS-mediated direct cell damage, PDT also elicits anti-tumor immunity through ROS-driven inflammation and ICD. ROS generated by PDT initiates a potent inflammation response, which stimulates tumor-associated macrophages, activates redox-sensitive pathways (eg, nuclear factor kappa B and activator protein 1), and promotes the release of inflammatory cytokines, such as interleukin (IL), TNF and TGF-β.[23] Furthermore, ROS-damaged tumor cells release damage-associated molecular patterns (DAMPs), including HMGB1, calreticulin and ATP. These signals promote the maturation of dendritic cells (DC) and activate effector immune cells (eg, T lymphocytes and natural killer (NK) cells), thereby inducing ICD.[27] The resultant systemic immune activation not only helps suppress the distant metastasis but also provides a strong rationale for combining PDT with immunotherapy to enhance therapeutic outcomes.[28]

Fluorescence Imaging

Beyond the therapeutic role, certain photosensitizers (eg, Chlorin e6 (Ce6)[29] and IR780[30]) exhibit fluorescence properties, enabling their use in theranostic agents for imaging. The anti-tumor effect of PDT relies on photosensitizer accumulation in tumors, while the same fluorescence allows real-time monitoring of its distribution. This capability facilitates precise light irradiation areas to avoid normal tissue damage, and supports comprehensive treatment management: preoperative therapeutic localization, intraoperative dynamic adjustment of treatment schedules via fluorescence signal decay, and postoperative assessment of therapeutic response. However, a key challenge arises from the shared mechanism for imaging and therapy: insufficient tumor targeting leads to unintended phototoxicity in normal tissues during diagnostic imaging. To decouple these functions, researchers have developed lanthanide-doped upconversion nanoparticles (UCNPs) to separate imaging and therapeutic light channels. The UCNPs could convert longer-wavelength excitation light into distinct emission wavelengths—one for high-contrast imaging and another matching the photosensitizer's activation spectrum for therapy, thus preventing phototoxic reactions during imaging monitoring.[31]

Nanocarrier Strategies to Overcome Photosensitizer Delivery Barriers

Nanocarriers of Photosensitizer

Many photosensitizers—especially most natural photosensitizers and primary photosensitizers—suffer from poor water solubility, low bioavailability and off-target toxicity.[32] To address these issues, researchers often load photosensitizers

using biocompatible substances—such as polyethylene glycol (PEG),[33] hyaluronic acid (HA)[34] and human serum albumin (HSA).[27] These are either directly used as the carriers of photosensitizer or modified on the nanocarrier shells, offering good biocompatibility and excellent tumor-targeting capacity. From the first to the third generation, enhancing the tumor targeting of photosensitizers has emerged as a key direction to improve the anti-tumor efficacy of PDT. So reforming and modifying photosensitizers to effectively boost the targeting capacity to tumor cells is the critical approach from the drug delivery perspective.

The nano drug delivery system (NDDS) has been extensively investigated and applied in drug delivery, demonstrating the potential of nanotechnology in this field.[35] Nanocarriers, a core component of NDDS, are well-recognized for enhancing therapeutic efficacy and reducing adverse effects. They achieve those by improving drug solubility and bioavailability, as well as optimizing drug pharmacokinetics and biodistribution.[36] In PDT, NDDS are frequently employed to mitigate the phototoxicity of photosensitizers and enhance their targeting capability. Based on their composition, nanocarriers used in PDT can be primarily categorized into several types, including lipid-based nanoparticles (eg, liposomes), polymeric nanoparticles, metal-based nanoparticles, and inorganic nonmetallic materials (Figure 2). In this review, various nanocarriers of photosensitizer delivery for PDT research in lung cancer are summarized and classified as follows.

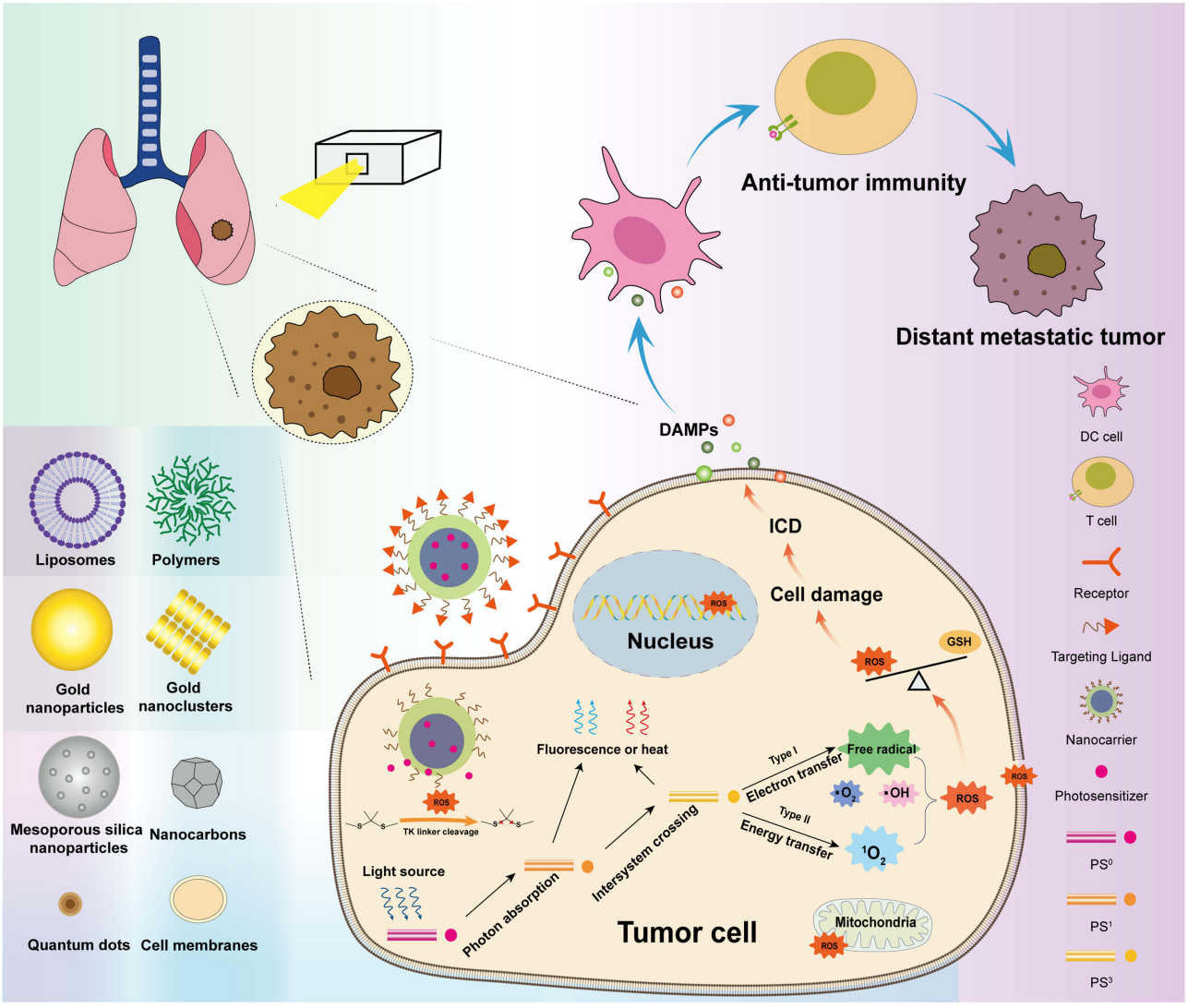

Figure 2 The mechanism of PDT in lung cancer.

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Lipid Based Nanoparticles

Lipid based nanoparticles, including solid lipid nanoparticles (SLNs) and liposomes, are widely used as nanocarriers. The phospholipid bilayer structure of liposomes is particularly advantageous, allowing for the co-encapsulation of both hydrophilic and hydrophobic drugs. For instance, one study encapsulated the photosensitizer betanin with liposomes, which could protect the water-soluble drug against rapid degradation and facilitate the anticancer effect.[37] Conversely, SLNs possess a solid lipid core ideal for trapping hydrophobic agents. This characteristic has been leveraged to deliver photosensitizers like purpurin-18-N-propylimide methylester, enhancing their bioavailability and therapeutic performance in PDT.[38] Despite offering excellent biocompatibility and versatility for drug loading, the application of lipid-based nanoparticles is limited by low stability, drug leakage, and limited loading capacity.

Polymer-Based Nanoparticles

Polymer-based nanoparticles are extensively investigated in NDDS due to their excellent biocompatibility and high tunable chemical structures. Common polymeric nanoparticles include natural polymers (eg, polyose, polypeptides, albumin) and synthesis polymers (eg, poly(lactic-co-glycolic acid) (PLGA) and polyethylene glycol (PEG)[39]). Compared with lipid-based nanocarriers, polymeric nanoparticles typically possess a more robust structural framework. A key advantage of polymers lies in their customizable design, allowing for precise control over sizes, architecture, and surface chemistry, which can be further functionalized with targeting ligands or responsive moieties.[40]

This versatility is exemplified in several studies. Wang et al synthesized water-soluble nonlinear random copolymers via reversible addition-fragmentation chain transfer polymerization, conjugating the side chains with water-insoluble fullerene (C_{60}) through amine addition reactions for potential application in PDT against lung cancer cells.[41] Another strategy involves designing sophisticated block copolymers or composite structures for multifunctionality. For instance, another study developed core-shell nanoparticles, with a cationic polymer core and a HA shell, where the photosensitizer Ce6 was linked via a thioether linker and the chemotherapeutic drug afatinib was—achieving the combination of PDT and chemotherapy.[42] While the biodegradable structure of polymeric nanoparticles allows for controlled drug release and PEGylation enhances circulation, the potential toxicity from acidic degradation byproducts remains a concern.

Metal-Based Nanoparticles

Metal-based nanoparticles have garnered significant interest in PDT due to their excellent stability, surface modifiability and strong light-absorption capacity.[43] Notably, various metal nanomaterials, such as precious metal nanomaterials and transition metal sulfide materials, can absorb light energy and convert it into heat under light irradiation. Their efficient photothermal conversion, enabling their use as both carriers and active agents for combining photothermal therapy (PTT) with PDT.[44] Beyond PTT, certain metal ions (eg, Fe, Mn, Cu) can catalyze Fenton-like reactions, facilitating chemodynamic therapy (CDT). This multi-mechanism potential makes them versatile platforms for synergistic treatment strategies, as exemplified by PEG-coated CuS nanoparticles that function simultaneously in PTT and PDT.[45]

Additionally, their optical properties are exploited for diagnostic imaging. For instance, Xia et al synthesized a theranostic photosensitizer nanoprobe based on gold nanostars (GNSs). The GNSs were surface-coated with bovine serum albumin and functionalized with matrix metalloproteinase (MMP)2 polypeptides, serving as carriers of photosensitizer IR-780 while enabling PTT and photoacoustic imaging.[46] Thus, metal-based nanoparticles represent integrative theranostic platforms combining photothermal conversion, imaging capabilities, and catalytic functions. However, their translation is tempered by concerns regarding potential long-term toxicity, bioaccumulation, and high material costs.

Inorganic Nonmetallic Materials

Inorganic nonmetallic materials constitute another major class of drug nanocarriers, primarily encompassing nanocarbon and nanosilicon materials. Nanocarbons materials—such as nanoscale activated carbon (NAC),[47] nanodiamond (ND),[48] graphene, and C_{60}[41]—possess excellent optical and thermal properties. They can absorb infrared light energy to generate photothermal effects and, in some cases, directly serve as photosensitizer of PDT, thus functioning as either carriers or active therapeutic agents. For example, iron-doped nanodiamonds have been demonstrated to act as dual-function

carriers: the doped iron catalyzes Fenton-like reactions within the TME to produce highly cytotoxic •OH for CDT, while the nanodiamond itself provides intrinsic fluorescence for imaging probe.[48]

Among nanosilicon carriers, mesoporous silica nanoparticles (MSNs) are the most prevalent due to their highly porous structure and readily modifiable surfaces. This versatility is illustrated in a study by Zhou et al, who designed zinc protoporphyrin (ZnPP)-loaded MSNs for non-small cell lung cancer spinal metastasis (NSCLC-SM), with RGDyK (Arg-Gly-Asp-d-Tyr-Lys) modified to achieve precisely targeting. The system specifically binds to β3-integrin (significantly overexpressed in NSCLC-SM) and simultaneously inhibits the integrin which prevents programmed death ligand 1 (PD-L1) degradation.[49]

Beyond these, quantum dots (QDs) are emerging as promising agents in PDT. These nano-semiconductor crystals (typically 2–10 nm in size) composed of II–VI or III–V elements exhibit good biocompatibility and photostability. Upon photoexcitation, they undergo electronic transitions and emit size-tunable fluorescence.[50] Owing to these luminescence properties, QDs show great potential for both bioimaging and as PDT agents. For example, Liu et al fabricated $CoFe_2O_4$-QDs as promising photosensitizers. The $CoFe_2O_4$-QDs have been shown to enhance ROS generation and induce apoptosis in NSCLC cells, demonstrating combined PTT and PDT effects.[51] Collectively, inorganic non-metallic nanocarriers offer advantages such as high surface areas and substantial drug-loading capacity. However, a key translational challenge is their generally poor biodegradability, which raises concerns regarding potential long-term retention in vivo.

Cell Membrane-Based Materials

Furthermore, cell membrane-based materials represent a promising bio-inspired drug delivery platform, characterized by intrinsic tumor targeting, efficient delivery, hight biocompatibility and self-protection against degradation. Unlike synthetic liposomes that merely mimic the phospholipid bilayer, endogenous cell membrane (eg, cancer cell membrane (CCM), mesenchymal stem cell (MSC) membrane, platelet membrane, macrophage, NK cell membrane) retains functional surface glycoproteins and glycolipids which are crucial for complex biological communication, enabling true active targeting.[52]

Consequently, nanocarriers coated with endogenous cell membranes have been extensively explored. They synergize the customizable properties of a synthetic core with the sophisticated biological functions of a natural membrane.[53] Liu et al prepared the macrophage membrane-hybridized liposomes to deliver verteporfin, leveraging the membrane's targeting ability.[54] Another study engineered macrophage membranes (embedded with photosensitizers) with fusogenic virus glycoprotein to enhance membrane fusion, thereby anchoring photosensitizers onto tumor cell membranes. This system can achieve synergistic therapy of PDT and calcium ion overload for lung cancer.[24] In a different approach, gold nanostar-based nanoparticles coated with $CaCO_3$ and loaded with Ce6, were encapsulated into NK cells to achieve synergistic PTT, PDT and immunotherapy effects.[55]

While these platforms exhibit superior targeting and immune evasion, their clinical translation becomes significantly constrained by complex, costly manufacturing processes that hinder scalable production. As summarized in Table 2, which outlines the key nanocarrier types and their trade-offs, the core challenge for successful clinical translation is to balance high therapeutic efficacy with long-term safety.

Targeting Ligands

Nanoparticle carriers enable passive targeting and enrichment in tumor tissues via the enhanced permeability and retention (EPR) effect.[68] The EPR effect is a unique physiological phenomenon of tumor tissues, characterized by

Table 2 Summary of Nanocarrier Systems for PDT

Type of Nanoparticles	Advantages and Limitations	Nanocarrier	Photosensitizer	Ref
Lipid based nanoparticles	• High biocompatibility; suitable for hydrophilic or hydrophobic drugs • Low stability and drug leakage issues; limited drug loading capacity	Liposomes SLNs Liposomes	Betanin Purpurin-18-N-propylimide methylester IR-780	[37] [38] [56]

(*Continued*)

Table 2 (Continued).

Type of Nanoparticles	Advantages and Limitations	Nanocarrier	Photosensitizer	Ref
Polymer-based nanoparticles	• Biodegradable structure and controlled drug release; PEGylation improves circulation time • Potential toxicity and acidic degradation byproducts	PLGA	Curcumin	[32]
		Water-soluble copolymer	C_{60}	[41]
		Poly (L-lysine)	Ce6	[42]
		Polymeric nanoparticle	ICG	[57]
		HA	Photosensitive protein (KillerRed)	[58]
		D-α-tocopheryl polyethylene glycol 1000 succinate	Ce6	[59]
		PEG	Hypericin	[60]
		Graft copolymer based core-shell micelles	5,10,15,20 tetrakis pentafluorophenyl-21H,23H-porphine, Au	[61]
		Oil-core polyelectrolyte	Verteporfin	[62]
Metal-based materials	• Excellent photothermal conversion; multimodal imaging capability; intrinsic catalytic activity • Potential long-term toxicity and bioaccumulation; high material cost	Au nanobipyramid	IR780, Au	[30]
		Hollow gold nanoshells	Gold	[63]
		Plasmonic CuO/Cu_2O truncated nanocube	CuO/Cu_2O	[64]
		Iron oxide nanoparticles	Ce6	[65]
		Gold nanoparticles	Protoporphyrin IX	[66]
Inorganic nonmetallic materials	• High surface area and drug loading capacity • Poor biodegradability and risk of long-term retention	NAC	ZnPc, NAC	[47]
		ND	Fe-doped ND	[48]
		QDs	$CoFe_2O_4$-QDs	[51]
		MSNs	IR-780	[67]
Cell membrane-based materials	• Innate immune evasion and targeting ability; high biocompatibility • Complex and costly fabrication; difficult large-scale production.	Functionalized cell membranes	Meso-tetra(4-aminophenyl) porphyrin	[24]
		NK cells	Ce6, GNSs	[55]

high permeability and prolonged retention of tumor blood vessels. Tumor cells secrete abundant vascular growth factors to promote new blood vessel formation, but these new vessels have structural and functional defects (eg, large vessel wall gaps, high permeability), enabling easier penetration of circulating macromolecules and nanoparticles into the TME. Additionally, dysplastic lymphatic vessels and poor lymphatic reflux in tumors prevent clearance of infiltrated macromolecules or nanoparticles, leading to their long-term retention in tumor tissues. While the EPR effect is a foundational concept in nanomedicine, a large body of clinical evidence now shows it to be highly heterogeneous and unreliable in human patients, contributing to the failure of many nanomedicines in clinical trials.[69,70] Therefore, nanocarriers often employ more advanced active targeting strategies, which involve decorating the nanocarrier surface with ligands (eg, peptides, antibodies, saccharides) that bind to receptors overexpressed on lung cancer cells.

For nanomedicines, targeting ligands are primarily engineered to bind receptors overexpressed on lung cancer cells, including the FR, albumin receptor, integrin receptor, epidermal growth factor receptor (EGFR), CD44 receptor, and immune checkpoint molecules such as PD-L1. For instance, folate is utilized to target the FR on tumor cells.[71] Wang et al developed self-assembled phthalocyanine-albumin nanoparticles to inhibit lung metastasis of cancer cells, which the albumin deemed to target the albumin receptor on tumor vessels and the albumin-binding proteins on tumor cells.[72] And tumor-targeting peptides (eg, TFA (Gly-Arg-Gly-Asp-Ser),[73] RGD (Arg-Gly-Asp)[63] and other peptide derivatives[49]) are frequently conjugated to nanocarriers to target integrin receptors, which are key regulators of tumor cell migration and proliferation. For cancers overexpressing specific biomarkers, precision targeting can be achieved with corresponding

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ligands, such as the amino-terminal fragment (ATF) of urokinase plasminogen activator (uPA) for targeting the uPA receptor on H1299 cells,[74] or monoclonal antibodies for targeting EGFR on H69AR cells.[64] Besides, a promising PDT agent for lung cancer was designed to enhance targeting efficiency, GNPs@PEG/Ce6-P, leveraging the binding function of PD-L1 targeting peptide modified on the surface of GNPs.[75]

Beyond peptides and antibodies, natural polysaccharides could serve as effective targeting moieties. Chondroitin sulfate (CS)[76] and HA[77] can be functionalized on nanocarriers to specifically bind to CD44 receptor, which are overexpressed on many lung cancer cells, thereby enhancing tumor accumulation and cellular uptake. In addition, P-selectin of platelet membrane can also target and bind to CD44 receptors of cancer cells, facilitating targeted delivery of photosensitizers.[78]

Beyond targeting tumor surface receptors, strategies have been developed from direct nanocarriers to specific intracellular organelles or to exploit tumor metabolic pathways. Mitochondrial targeting, for example, is achieved by conjugating cationic molecules like triphenylphosphine (TPP) to nanocarriers, leveraging the mitochondria's negative membrane potential.[56,79] Another approach involves conjugating glucose to nanocarriers to capitalize on the enhanced glucose metabolism of tumor cells, promoting the targeted accumulation of photosensitizers.[65]

The previously mentioned endogenous cell membrane carriers also have promising applications in tumor targeting. For example, the CCMs exhibit targeting homing effects to homologous tumor cells, and their immunosuppressive molecules help drug carriers escape from the immune system—facilitating drug accumulation in tumor tissues.[80] MSCs are attracted by chemokins released by tumor tissues, showing their prominent tumor-homing ability. A study proposed a Trojan horse delivery strategy against lung melanoma metastasis that MSC membranes enable the delivery of photosensitizers for PDT.[81] In another study, Yan et al constructed platelet membrane-coated nanoparticles (PCDD NPs) with tumor-targeting function, which utilized overexpressed P-selectin on platelet membranes to bind to the CD44 receptor on tumor cells.[78] As components of the immune system, macrophage membranes and NK cell membranes also exhibit intrinsic tumor-targeting abilities. The surface chemokine receptors are attracted by chemokines in the TME, and the surface ligands can recognize and bind to receptors on tumor cells.[82,83] Researcher have designed and fabricated delivery systems based on THP-1 macrophage membranes[25] and human NK cell membranes[55] for delivery and targeting system of photosensitizers. These systems exhibit efficient tumor-targeting ability and excellent therapeutic efficacy toward lung cancer.

In summary, the evolution of targeting in nanomedicine has progressed from reliance on the passive EPR effect to sophisticated active and bio-inspired strategies. These strategies encompass: (1) active targeting to overexpressed surface receptors using small molecules, peptides, antibodies, or polysaccharides; (2) subcellular targeting to organelles like mitochondria; (3) metabolic targeting; and (4) the use of endogenous cell membranes as multifunctional, biologically derived targeting platforms. Collectively, these diverse and complementary approaches are paving the way for more efficient and personalized nanotherapeutics for lung cancer treatment.

Emerging Strategies for Improve Energy Transfer Efficiency

Novel Energy Sources

To overcome the limited tissue penetration of visible light, innovative energy sources have been explored. The onizing radiation (eg, X-rays, γ-rays) has been studied as a new energy source, termed radiodynamic therapy.[84] For example, X-ray-responsive photosensitizers like $NaCeF_4$:Gd,Tb Scintillator could absorb energy from secondary electrons from secondary electrons, generating electron-hole pairs that subsequently produceROS like $\bullet O_2^-$ and •OH.[85] Similarly, Chen et al found that hafnium-doped hydroxyapatite nanoparticles can be activated by γ-rays to induce ROS.[86] In a study, Wang et al reported the MC540-SAO:Eu@$mSiO_2$ nanoparticles, which exert dual radiotherapy-PDT effects under X-rays and offer a potential strategy against radioresistant tumors.[87]

Beyond ionizing radiation, sonodynamic therapy (SDT) represents another strategy for deep-seated tumors. SDT employs ultrasound—which offers superior tissue penetration and minimal energy attenuation—to activate sonosensitizers. The acoustic cavitation effect triggered by ultrasound leads to the formation of free radicals (eg, •OH) that induce tumor cell death.[76,88] Collectively, these advancements in energy source technology—leveraging ionizing radiation and ultrasound—significantly enhance energy delivery to deep-seated tumors, thereby improving the efficiency and broadening the applicability of PDT-based treatments.

Optimization of Energy Transfer

Natural photosensitive substances like curcumin,[32] betanin[37] and hypericin[89] typically exhibit absorption spectra within the visible light range (400–600 nm). The visible light offers high photon energy and potent phototoxicity suitable for superficial applications but suffers from limited tissue penetration. In contrast, conventional photosensitizers (eg, Porphyrins, Phthalocyanines) are generally activated by first near-infrared (NIR) light at 600–900 nm, offering deeper penetration. However, a significant challenge arises because the optimal window for high-resolution fluorescence imaging lies within the second NIR spectrum (NIR-II, 1000–1400 nm), which does not overlap with the activation spectra of most available photosensitizers.

To bridge this gap, UCNPs have attracted considerable interest. UCNPs can transform low-energy NIR light into high-energy visible or ultraviolet emissions through processes such as excited-state absorption, energy transfer upconversion, and photon avalanche mediated by lanthanide ions. This allows deep-penetrating NIR light to activate photosensitizers that otherwise require visible-light excitation.[90] The optical characteristics of UCNP-based nanocarrier in PDT are summarized in Table 3. A representative example is the hybrid mesoporous MnO_2-UCNPs system developed by Han et al,[73] which emits up-conversion luminescence at 980 nm (converting to 656 nm for photosensitizer excitation in PDT) and down-conversion luminescence at 730 nm (converting to 1064 and 1332 nm for NIR imaging). This temporal separation of therapeutic and imaging signals minimizes off-target activation and reduces potential damage to normal tissues. Similarly, Yue et al prepared multifunctional Ce6-CPT-UCNPs, which the UCNP emission under 980 nm irradiation overlaps with absorption spectrum of Ce6, enabling simultaneous imaging and PDT activation.[29]

Another strategy to enhance energy transfer is fluorescence resonance energy transfer (FRET), a process in which energy is non-radiatively transferred from a donor fluorophore to an acceptor moiety through dipole–dipole interactions.[92] Upon photoexcitation, the donor transfers its energy to the nearby acceptor, which then emits fluorescence or generates reactive species. For example, Zhao et al loaded the photosensitizer 5, 10, 15, 20-tetraphenylphorphyrin onto a light-harvesting polymer, poly[N,N "-bis(4-butylpheny)-N,N" -bis(phenyl)benzidine], achieving enhanced fluorescence imaging and PDT efficacy through efficient FRET.[93] In another study, Chen et al innovatively designed a TME-responsivefluorescent probe in which the photosensitizer and the quencher are linked via a cleavable linker. In normal tissues, the quencher suppresses fluorescence; and in the TME, linker cleavage restores fluorescence, enabling tumor-specific imaging while reserving PDT activity for the target site.[94] Collectively, these advanced energy-transfer strategies—UCNP-mediated wavelength conversion and FRET-based energy harvesting—significantly improve the efficiency of light utilization in PDT. They not only overcome the inherent penetration limits of traditional light sources but also enhance targeting precision, thereby mitigating off-target effects while enabling deeper and more effective therapeutic outcomes.

Table 3 Optical Characteristics of UCNPs in PDT

Composition of UCNPs	Activated Wavelength	Converted Wavelength	Photosensitizers That Accept Converted Light	Mechanisms of Photosensitizers	Ref
$NaErF_4$@$NaYF_4$ @$NaYF_4$:5%Nd@$NaYF_4$	980 nm laser	656 nm light	Ce6	PDT	[73]
$NaYF_4$:60%Yb, 0.5%Tm@$NaYF_4$ core-shell nanoparticles	980 nm laser	Blue-violet light	Non-pathogenic Escherichia coli carrying a photoactivatable transcriptional promoter	Upregulate the expression of respiratory chain enzymes, and blue-violet light activates enzymes to continuously produce H_2O_2.	[91]
Organosilica-shelled β-$NaLuF_4$: Gd/Yb/Er nanoprobes	980 nm laser	-	β-carboxyphthalocyanine zinc or rose Bengal	PDT Dual-modal imaging	[74]
(Ln^{3+})-doped nanocrystals	980 nm laser	645 nm-675 nm light	Ce6	PDT Fluorescence imaging	[29]
$SrAl_2O_4$:Eu	X rays	Green photoluminescence	MC540	PDT	[87]

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Nanotechnological Approaches to Mitigate Tumor Hypoxia for Enhanced Therapy

Improvement of Tumor Environment for PDT

In most solid tumors, the hypoxic microenvironment—caused by overproliferation of tumor tissues and abnormal tumor angiogenesis (leading to imbalance oxygen supply and demand)—becomes a main problem, which significantly impacts the PDT efficacy.[95] Therefore, researchers focus on improving the intratumoral oxygen levels to enhance the PDT efficacy, including (1) the oxygen-carrying agents like hemoglobin[27] and nanoperfluorocarbon[96] that directly deliver oxygen to tumors; (2) oxygen-generating catalysts (eg, manganese ions[89] and platinum nanoparticles[54]) that decompose endogenous hydrogen peroxide (H_2O_2) or water to produce oxygen; and (3) oxygen-consumption inhibitors, such as respiratory chain inhibitor atovaquone (ATO), which reduce cellular oxygen demand.[30]

Beyond oxygen supply, the TME presents other modifiable chemical features. Notably, elevated levels of H_2O_2—resulting from dysregulated mitochondrial metabolism and oncogenic signaling—provide both a challenge and an opportunity.[97] H_2O_2 can serve as a substrate for the Fenton or Fenton-like reactions, which reacts with metal ions (eg, ferrous ions, ferric ions, manganese ions, copper ions) to generate highly cytotoxic •OH. This process, known as CDT, can be synergistically combined with PDT.[98,99] Deng et al designed a polymer nanoparticle incorporating a photosensitizer, glucose oxidase and iron oxide, which glucose oxidase could catalyze glucose to produce H_2O_2, thereby achieving combined PDT and CDT.[100] Another study developed engineered bacteria that express respiratory chain enzyme II to continuously produce H_2O_2, simultaneously alleviating hypoxia and supplying substrate for CDT.[91] Obviously, increasing H_2O_2 levels is an effective strategy to enhance the efficacy of PDT or CDT.[101]

Conversely, the TME is often characterized by elevated levels of reducing substances, particularly GSH. Tumor cells upregulate GSH synthesis to maintain redox homeostasis, which confers resistance to oxidative therapies like PDT by scavenging ROS.[102–104] Therefore, depleting intratumoral GSH represents a critical strategy to potentiate PDT including the GSH-responsive nanomedicines.[105] This has prompted the rational design of responsive nanoparticles that can remodel the TME to enhance the efficacy of PDT.

Intelligent Responsive Nanoparticles Based on Endogenous Stimuli

Numerous studies have explored responsive designs about exogenous stimuli such as heat, ultrasound, and magnetic field, particularly photo-responsive nanodrugs for PDT, which are the subject of this review.[106] In addition, exploiting the characteristics of TME to design intelligent tumor-responsive delivery systems holds great potential, including low pH, hypoxia, high GSH and so on.[107] Intelligent responsive designs offer distinct advantages over traditional nanomedicines. They could provide precise spatiotemporal control of drug release, and consume excessive substances in the TME, which obviously makes sense to enhance the efficacy of PDT.[108] For instance, Linderman et al presented mechanisms of some tumour-responsive nanomaterials, including pH-sensitive, reduction, enzymatic cleavage and so on.[109] Below, we will introduce intelligent responsive designs for PDT nanoedicine based on endogenous TME stimuli.

GSH-Responsive

As PDT relies on ROS to kill tumor cells, the high GSH levels in the TME can scavenge these ROS, diminishing therapeutic efficacy and contributing to treatment resistance. Therefore, many PDT drug carriers are designed to incorporate with GSH-responsive structures. This not only achieve triggered drug release at the tumor site but also actively deplete intratumoral GSH, thereby preserving the cytotoxic ROS generated by PDT. For example, the TCFI nanoplatform, coordinating Cu/Fe-based Fenton-like reactants with 3,3'-dithiobis-propionohydrazide that contains the disulfide bonds, consumes GSH via metal ion redox and disulfide-thiol exchange reactions.[110] Han et al synthesized UCNP/Ce6@mMnO_2/DSP-TFA, where the MnO_2 shell reacts with H_2O_2, GSH and H^+ in the TME, thereby releasing cisplatin drugs (DSP) for chemotherapy and Mn^{2+} ions that catalyzes the production of oxygen, to alleviate hypoxia and synergistically enhance PDT efficacy.[73]

ROS-Responsive

The intrinsic generation of ROS during PDT provides a built-in trigger for engineering intelligent, stimuli-responsive nanomedicines. By incorporating ROS-labile chemical bonds, nanocarriers can be designed to undergo controlled structural disassembly precisely where and when ROS is produced, releasing co-loaded agents. This "self-amplifying" drug release strategy enhances therapeutic synergy. For example, novel platelet membrane-coated nanoparticles were designed for which the platelet membrane ruptures under ROS conditions, facilitating release of internal drug.[78] Additionally, Yue et al synthesized the ROS-responsive nanoparticles, including ZnPc/CPT-TPP NPs and Ce6-CPT-UCNPs, which Zinc phthalocyanine (ZnPc) and Ce6 absorb light to generate ROS and then cleaves the thioketal (TK) linkers to release chemotherapy drugs camptothecin (CPT).[29,79] Besides, another study prepared a ROS-sensitive nanoplatform—indocyanine green (ICG) NPs—via self-assembly of ROS-sensitive oligomer dihydrolipoic acid, which contains the TK bonds.[57] Diao et al developed a dual-activatable nano-immunomodulator (DIR NPs) for photodynamic immunotherapy, which ROS cleaves the TK linker and enables drug release.[111]

Hypoxia-Responsive

Notably, the inherent hypoxia of the TME presents a fundamental challenge for oxygen-dependent PDT. To convert this barrier into a triggering mechanism, Tseng et al designed a sophisticated delivery system. They engineered self-assembling nanoparticles from hyaluronic acid (HA), 2-nitroimidazole derivatives, and lactate oxidase (LOX), which were used to carry a viral vector encoding photosensitive proteins. The design leverages the high lactate concentration in the TME. The LOX catalyzes lactate oxidation and exacerbates oxygen consumption. This intensified hypoxia then stimulates the bioreduction of the 2-nitroimidazole components, leading to the dissociation of the carrier and the subsequent release of the viral vector.[58] This strategy exemplifies an enzyme-amplified hypoxia-responsive design, where LOX activity dynamically lowers oxygen levels to activate the release mechanism.

Enzyme-Responsive

The TME highly overexpresses a variety of enzymes (eg, hyaluronidase (HAase), cathepsin, Caspase 3, MMP enzymes), which provide precise biological triggers for designing enzyme-responsive nanocarriers with degradable structures. A representative strategy employs enzyme-cleavable linkers to control theranostic functions. For instance, a NIR fluorescent probe (CyA-P-CyB) was designed based on FRET mechanism. In this design, a fluorescent donor (CyA) and a quencher (CyB) are linked by a cathepsin B-activated peptide (Gly-Phe-Leu-Gly).[94] A clever point is that in the intact state, fluorescence would be quenched; and after enzymatic cleavage of the peptide, the separation of CyA and CyB restores fluorescence, enabling tumor-specific imaging. Additionally, to enhance responsiveness, dual-responsive carriers are being actively explored. Zhang et al synthesized enzyme-ROS dual-responsive nanoparticles (HPGBCA) with an HA shell and a thioether-linked inner core. In this system, HAase in the TME degrades the HA shell, while ROS generated by light-irradiated Ce6 triggers the core disintegration, jointly promoting drug release.[42]

pH-Responsive

The acidic milieu in the TME acts as a powerful immunosuppressive driver.[112] It suppresses the cytotoxic function of tumor-infiltrating immune cells, such as T cells and NK cells, and indirectly promotes tumor progression by recruiting and activating immunosuppressive populations, including myeloid-derived suppressor cells and regulatory T cells. Besides, the well-defined pH gradient in vivo provides a robust foundation for designing stimuli-responsive drug delivery systems. From normal physiological conditions (pH 7.35–7.45) to the acidic TME (pH 6.2–7.1), and further to the more acidic endo/lysosomal compartments (pH 5.0–5.5), this descending pH profile offers multiple triggers for the precise and accelerated release of agents.[113,114] Several covalent bonds (eg, hydrazone, imine, acetal, oxime, amide, and ester bonds) are unstable under acidity.[106] For example, the pyropheophorbide and vorinostat-bound BSA nano hydrogel (PVBN) is a dual-prodrug nanogel, and the ester linkages enable lysosomal drug release. Besides, pH-sensitive anti-tumor prodrug nanoparticles (eg, Ce6-GNCs-DOX NPs, TCAD@Ce6 NPs) contain cis-aconitic anhydride (CA)-modified doxorubicin (DOX), where the pH-sensitive cis-acontityl linkage between DOX and CA would be hydrolyzed.[59,115] Additionally, some acid-sensitive carriers such as $CaCO_3$ and hydroxyapatite (HAp) dissolve under acidity, causing carrier disintegration and drug release.[55,86]

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Furthermore, some acid-sensitive metal ion compounds like CuS are also used in smart responsive nanomedicins: CuS could release copper ions under acidic conditions to promote CDT.[45,68] Wang et al designed an acid-responsive theranostic photosensitizer by incorporating morpholine into phthalocyanine. The N atom in the imidazole structure is easily protonated under acidity, reducing photoinduced electron transfer and aggregation-caused quenching under acidic TME—enabling tumor-targeted PDT and low-background fluorescence imaging.[72]

Heat-Responsive

The integration of PDT with PTT has motivated the development of heat-responsive nanocarriers. These systems leverage the localized temperature rise from PTT to trigger drug release. For example, Li et al developed a gold nanoshell-based nanoplatform (RGD@siRNA@HAuNs), where photothermally induced heating cleaves the thiol-gold bonds, and trigger subsequent release.[63] Similarly, thermosensitive liposomes have been engineered using lipids like 1,2-Dipalmitoyl-sn-glycero-3-phosphocholine (DPPC), which has a phase transition temperature near 42°C.[56] Upon light irradiation, the IR-780, a molecule with both photosensitive and photothermal properties, generates sufficient heat to disrupt the liposomal bilayer, enabling controlled payload release.

Given that the design and function of complex intelligent responsive nanoparticles are highly dependent on the TME, the reliable activation and precise efficacy in the highly heterogeneous human body are paramount. It is therefore imperative to employ advanced clinically relevant disease models that better mimic human TME conditions for evaluation, like immunocompetent orthotopic models, representing a key challenge in their clinical translation.

Synergistic Strategies for Combating Monotherapy Resistance

PDT often induces resistance in tumor cells, through mechanisms such as nitric oxide generation, overexpressed EGFR mRNA, and upregulated anti-apoptotic Bcl-2 family proteins.[67] To counter the problem of resistance, PDT is frequently combined with other modalities, including PTT, CDT, chemotherapy, and immunotherapy. These combinations not only enhance antitumor efficacy but also mitigate the development of resistance inherent to monotherapy. Consequently, a central paradigm in nanomedicine is the design of integrated platforms that converge active targeting, stimuli-responsive drug release, and multimodal combination therapy. A summary of recent nano-designs incorporating these strategies for lung cancer PDT is provided in Table 4.

Combination with Direct Cytotoxic Modalities

PDT + PTT/CDT

PDT is frequently combined with other modalities to overcome its limitations and enhance the efficacy, with PTT and CDT being two prominent synergistic strategies. The synergy between PDT and PTT is based on mutual sensitization. PTT induces localized hyperthermia, which damages tumor cell membranes and increases their permeability. This structural disruption not only directly kills cells but also enhances the cellular uptake of concurrently delivered photosensitizers, thereby amplifying subsequent ROS generation during PDT. Conversely, the oxidative stress inflicted by PDT weakens cellular repair mechanisms and reduces thermal tolerance, rendering cancer cells more susceptible to PTT-induced damage. For instance, photosensitizers like IR-780 exhibit both photosensitive and photothermal properties, enabling simultaneous and synergistic action of PTT and PDT.[56] Similarly, the metal-materials with PTT effects like GNSs can also serve as nanocarriers to deliver photosensitizer,[75] and the photosensitizer like CuS has both PTT and CDT effects.[45]

While both PDT and CDT rely on ROS generation to damage cells, their mechanisms are distinct and complementary. PDT primarily consumes oxygen in tumor tissues to produce $^1O_2$, whileas CDT uses Fenton or Fenton-like reactions catalyzed by metal ions to convert H_2O_2 in the TME into highly toxic •OH. The distinct ROS types synergistically act on tumor cells, significantly enhancing cytotoxicity. Notably, the hypoxic condition in the TME limits PDT for its reliance on oxygen as common material. In contrast, CDT's Fenton reaction primarily consumes H_2O_2 and the weakly acidic TME accelerates this reaction to produce ROS—greatly compensating for PDT's oxygen limitation. Combining PDT and CDT allows PDT to work under oxygen-sufficient regions on the tumor surface, while CDT functions in the hypoxic deep tumor tissues, overcoming PDT's hypoxic-induced limitation.

Table 4 Multifunctional Nanoparticles for Targeting, Responsiveness, and Combination Therapy

Nanoparticles	Targeting Ligand	Responsive Mechanisms	Combination Therapy	Tumor Cells	Ref
HCNP	Macrophage membrane	–	–	H1299 lung cancer cells	[25]
Ce6-CPT-UCNPs	-	ROS	Chemotherapy Fluorescence imaging	NCI-H460 lung cancer cells	[29]
C16-K(PpIX)-PEG8-KDEVD-IMT	-	Enzyme	Immunotherapy	Lung melanoma metastasis of CT26 colon carcinoma cells	[33]
HA-ADH-Ce6	HA	Enzyme	Fluorescence imaging and photoacoustic imaging	A549 lung cancer cells	[34]
HPGBCA	HA	Enzyme and ROS	Targeted therapy	A549 lung cancer cells	[42]
CuS-PEG nanoparticles	-	pH	CDT	Lung adenocarcinoma SPC-A-1 cells, Gefitinib-resistant cell lines	[45,68]
ZnPP@MSN-RGDyK	RGDyK peptide	-	Immunotherapy	A549 lung cancer cells	[49]
GNS@$CaCO_3$/Ce6-NK	NK cells	pH	PTT Immunotherapy Fluorescence imaging and photoacoustic imaging	A549 lung cancer cells	[55]
NanoPcM	Albumin	pH	Immunotherapy	Lung metastasis model of 4T1 breast carcinoma cells	[72]
UCNP/Ce6@mMnO_2/DSP-TFA	TFA peptide	H_2O_2, GSH, and pH	Chemotherapy CDT Fluorescence imaging	A549 lung cancer cells	[73]
DOX@siRNA@HAuNs	RGD peptide	Heat	Chemotherapy Gene therapy	EML4-ALK mutation H2228 lung cancer	[63]
UCNP@ROS-ZnPc-COOH	The ATF of uPA	-	PTT	H1299 lung cancer cells	[74]
Anti-EGFR-CuO/Cu_2O TNCs	Monoclonal anti-EGFR moieties	-	PTT Multimodal imaging	H69AR small-cell lung cancer cells	[64]
GNPs@PEG/Ce6-PD-L1 peptide	PD-L1 peptide	-	PTT Fluorescence imaging	HCC827 lung cancer cells	[75]
CS-ADH-Rh-LA	CS	-	Chemotherapy	A549 lung cancer cells	[76]
DHU-MSNs-DOX-HA	HA	pH	Chemotherapy	A549 lung cancer cells	[77]
PCDD NPs	Platelet membrane	ROS	Chemotherapy	Lung metastasis model of B16F10 melanoma cells	[78]
IL-TTSL	TPP	Heat	Adjuvant therapy PTT Fluorescence imaging	LL/2 mouse Lewis Lung Carcinoma cells	[56]
ZnPc/CPT-TPPNPs	TPP	ROS	Chemotherapy	NCI-H460 lung cancer cells	[79]
IO-PG-GLU-Ce6	Glucose	-	-	Lewis lung cancer cells	[65]
Lp-KRCCM-A	4T1-Fluc cell membranes	-	Chemotherapy	Lung metastasis model of 4T1-Fluc cells	[80]
MSC-PDA-Ce6	MSCs	-	PTT	Lung melanoma metastasis of B16F10 melanoma cells	[81]
Hf:HAp nanoparticles	-	pH	-	A549 lung cancer cells	[86]
CyA-P-CyB	-	Enzyme	Fluorescence imaging	U87-MG glioblastoma cells and A549 lung cancer cells	[94]
TCFI Nanoparticles	-	GSH	CDT	Lung metastasis of B16F10 melanoma cells	[110]

(*Continued*)

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Table 4 (Continued).

Nanoparticles	Targeting Ligand	Responsive Mechanisms	Combination Therapy	Tumor Cells	Ref
ICG NPs	-	ROS	Gene therapy	H1299 lung cancer cells	[57]
DIR NPs	3,5-dioxocyclohexanecarboxylic acid	ROS	Immunotherapy	Lung metastasis model of 4T1 cells	[111]
HA-6-(2-nitroimidazole)-hexylamine-AAV2-LOX	HA	Enzyme and hypoxia	-	H1975 lung cancer cells	[58]
Ce6-GNCs-DOX NPs	MMP2-cleavable polypeptide	pH	Chemotherapy Fluorescence imaging	A549 lung cancer cells	[59]
TCAD@Ce6 NPs	-	pH	Chemotherapy	A549 lung cancer cells	[115]
PVBN	-	pH	Adjuvant therapy	A549 cells and B16F10 cells	[116]
APPF prodrug hydrogels	-	ROS	Immunotherapy	Lung metastasis model of 4T1 cells	[117]
OPeH	-	ROS and pH	CDT	Lung metastasis model of 4T1 cells	[118]

PDT + Chemotherapy

Common chemotherapy drugs include DSP,[73] docetaxel (DTX),[76,78] CPT,[29,79] DOX.[59,77,115] The chemotherapy drugs could damage DNA structure and inhibit cell proliferation, but they are lack of targeting ability, causing side effects like gastrointestinal reactions and bone marrow suppression. Co-delivering photosensitizers with chemotherapeutic agents via targeted nanocarriers enable spatial-temporal overlap of therapeutic actions. This approach reduces the required systemic drug doses, minimizes off-target toxicity, and attacks cancer cells through concurrent mechanisms—DNA damage/proliferation inhibition and oxidative stress—thereby overcoming single-mechanism resistance. In another study, Jiang et al proposed a novel and promising strategy for efficient photochemotherapy in their study: a dual-prodrug nanogel combining Vorinostat (a histone deacetylase inhibitor that activates tumor suppressor genes) and Pyropheophorbide (light-activated to generate ROS for PDT).[116]

Combination with Biological Interventions

PDT + Targeted Therapy

Beyond chemotherapeutics, integrating targeting agents with photosensitizers, such as afatinib (AFT), which could target and inhibit EGFR tyrosine kinase, allows for the dual targeting of oncogenic signaling and direct tumor killing effect. For example, in the design of a carrier modified with the enzyme-ROS double-responsive HA shell, HA targets CD44 receptors on tumor cells, while tumor-overexpressed HAase enables intelligent response to the carrier.[42] Additionally, ROS released by the photosensitizer reacts with the carrier's thioether linker, switching the carrier from hydrophobic to hydrophilic. This structural change triggers the release of AFT and the photosensitizer.

PDT + Gene Therapy

Furthermore, gene therapy has also been combined with PDT for addressing specific genetic drivers of cancer. Nanoplatforms can co-deliver photosensitizers with nucleic acids, such as siRNA to silence oncogenes or mRNA to restore tumor suppressor function. The spatial coupling of PDT-induced DNA damage with genetic correction or silencing creates a powerful synergistic effect, offering a precise approach for genetically defined lung cancer subtypes.

For example, H2228 cells (harboring the echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase (EML4-ALK) mutation) respond poorly to common EGFR inhibitors. Li et al devised and synthesized the nanoplatform DOX@siRNA@HAuNs, which loaded siRNA sequences to inhibit the mRNA of ALK.[63] Additionally, many lung cancer patients exhibit dysfunctional p53 gene, which is one of the key tumor suppressor gene, and the low

p53 gene expression prevents its tumor-suppressive role after DNA damage, allowing cancer cells survival and proliferation. Thus, Zhou et al constructed a co-delivery system of ICG and p53 mRNA—ICG induces ROS damage via PDT, while p53 mRNA restores p53's tumor-suppressive function and triggers apoptosis of cancer cells.[57] Other studies use viral vectors to deliver photosensitizer-expressing genes to tumor cells, enabling sustained, stable production of endogenous photosensitizers.[58] This achieves precise, long-lasting effects with low immunogenicity, overcoming the poor delivery and limited timeliness of traditional photosensitizers. Therefore, combining gene therapy and PDT also synergistically enhances the anti-tumor efficacy and reduces resistance from single therapeutic mechanism.

PDT + Immunotherapy

Numerous studies have shown that PDT induces ICD, so combining immunotherapy with PDT could synergistically enhance anti-tumor efficacy and reduce tumor cell metastasis. This process kills tumor cells and releases tumor antigens and DAMPs. These released signals are then recognized by DCs, which subsequently activate T cells to initiate a potent, systemic anti-tumor immune response. To amplify this inherent immunogenic effect, researchers have developed co-delivery systems that simultaneously load photosensitizers and immunotherapeutics. These immunomodulators primarily include immune checkpoint inhibitors (eg, PD-L1 antibodies,[117] β3-int-specific RGDyK[49]—both block PD-L1 receptors—and IMT,[33] a metabolic immune checkpoint inhibitor that inhibits the tryptophan metabolic pathway to relieve TME immunosuppression) and Toll-like receptor activators (eg, R848,[111] which directly stimulate antigen-presenting cells to enhance their activity).

This combination strategy achieves a powerful synergy: PDT eradicates the primary tumor and generates a personalized "in situ vaccine" through ICD, while the co-delivered immunomodulator concurrently unleashes the immune system. This one-two punch transforms immunologically "cold", non-responsive tumors into "hot" tumors that are highly susceptible to immune attack. Consequently, the activated immune system can systematically identify and eliminate any remaining local or antigen-matched metastatic cancer cells throughout the body, thereby significantly reducing the risk of metastasis. As an illustrative example, Diao et al developed dual-activatable DIR nanoparticles formed through the self-assembly of the immunomodulator R848 and the photosensitizer DIR.[111] This nanoplatform demonstrates a remarkable ability to potentiate the synergistic efficacy of photodynamic therapy and immunotherapy in a spatiotemporally controlled manner.

Auxiliary and Diagnostic Combinations

PDT + Adjuvant Metabolic Therapy

Besides, several adjuvant antineoplastic agents are also combined with PDT, including lonidamine[56] (inhibiting hexokinase and influence mitochondrial adenine nucleotide translocase to induce apoptosis), and ATO[30] (targeting tumor cell energy metabolism systems). Mitochondria are key producers of cellular ROS. Mitochondrial inhibitory drugs block the electron transport chain, promoting mitochondria to generate more ROS. When combined with PDT, this synergistically enhances oxidative stress damage to tumor cells. Additionally, mitochondrial inhibitors directly block mitochondrial energy production, while PDT destroys mitochondrial structure by damaging mitochondrial membrane—further cutting off energy supply. Together, they synergistically activate apoptotic pathways to promote tumor cell apoptosis.

PDT + Imaging

Moreover, PDT is often combined with imaging diagnosis, as photosensitizer like Ce6 exhibits fluorescence imaging capabilities.[34] Furthermore, some metal-based carriers such as gold nanoparticles possess stable light absorption properties and sensitive light-activated signal intensities, enabling their use in photoacoustic imaging.[46] By leveraging photosensitizer's fluorescence emission or other imaging principles, this combination not only provides precise diagnostic and localization information for tumors but also monitors photosensitizer's tissue distribution and tumor enrichment. This further guides PDT operational parameters including the irradiation range and duration, and assesses PDT's tumor-killing efficacy.

The combinatorial strategies outlined above leverage multi-modal mechanisms to significantly enhance the efficacy of PDT against lung cancer while curbing resistance. The integration of these approaches, smart nanoplatforms represents the forefront of oncological nanomedicine. However, the clinical translation of these complex systems requires a deeper mechanistic understanding of the synergies at the molecular and immunological levels. Future research must prioritize

elucidating these interactions to rationally design safer, more effective combination regimens and to identify predictive biomarkers for patient stratification.

Conclusions and Perspectives

NDDS exhibits unique advantages in delivering anti-tumor drugs. Efficient and precise targeted delivery via NDDS can greatly reduce PDT-related adverse reactions while increasing photosensitizer accumulation in tumor tissues to enhance anti-tumor efficacy. In this review, the mechanism of PDT for lung cancer and the research progress of NDDS in photosensitizer delivery for lung cancer treatment are comprehensively discussed—covering carrier types, targeting and responsive designs, enhancement of light source and combination strategies. Despite demonstrating powerful potential in countless preclinical studies, nano-PDT formulation for lung cancer has not yet reached clinical practice, primarily halted by formidable translational barriers. Researchers need to pay more attention on standardized material characterization, sufficient nanotoxicity assessment (both acute and long-term), and the use of clinically relevant disease models (eg, orthotopic, patient-derived xenograft, or immunocompetent models of lung cancer), to promote a paradigm shift from a technology-driven to a clinically driven approach. The applications in diagnostic imaging of PDT have also been highlighted in this review. So we can see that the inherent optical properties of PDT has strong potential for imaging. And even the future of clinical nano-PDT likely lies in nanotheranostics-integrated platforms that combine therapeutic and diagnostic capabilities within a single nanoparticle. Theranostic systems would allow clinicians to non-invasively image nanocarrier accumulation in a specific patient's tumor before administering the light-based therapy. This would enable the pre-selection of patients most likely to respond (ie, those with high nanocarrier uptake), addressing the critical issue of patient heterogeneity that plagues many cancer therapies.

While the synergy between nano-PDT and immunotherapy is promising, our understanding of the underlying mechanisms is still in its infancy. It is imperative to unravel the complex interface between nanocarriers, PDT-induced ICD, and the host immune system. In addition to elucidating the underlying mechanisms, researchers must also delve into optimizing clinical dosing regimens for PDT-immunotherapy combinations, and investigating how the intrinsic physicochemical properties of the nanocarrier itself (size, charge, surface chemistry) influence the type and magnitude of the resulting immune response. By refocusing research on solving these specific clinical challenges, the field can mature beyond proof-of-concept and translate its potential into tangible clinical benefits for lung cancer patients. Ultimately, the future of this field lies not merely in developing new materials, but in architecting intelligent, clinically driven platforms that seamlessly integrate diagnosis, targeted treatment, and immune activation. By relentlessly focusing on solving the tangible clinical problems of regulatory approval, precision theranostics, and therapeutic resistance, we would bridge the translational gap and finally deliver the profound potential of nano-PDT to the patients who need it most.

Abbreviations

PDT, photodynamic therapy; TME, tumor microenvironment; ROS, reactive oxygen species; $^1O_2$, singlet oxygen; •OH, hydroxyl radical; $•O_2^-$, superoxide anion radical; LED, light-emitting diode; GSH, glutathione; FR, folate receptor; ICD, immunogenic cell death; IL, interleukin; DAMPs, damage-associated molecular patterns; DC, dendritic cells; NK, natural killer; Ce6, Chlorin e6; UCNPs, upconversion nanoparticles; PEG, polyethylene glycol; HA, hyaluronic acid; HSA, human serum albumin; NDDS, nano drug delivery system; SLNs, solid lipid nanoparticles; PLGA, poly(lactic-co-glycolic acid); PEG, polyethylene glycol; C_{60}, fullerene; PTT, photothermal therapy; CDT, chemodynamic therapy; GNSs, gold nanostars; MMP, matrix metalloproteinase; NAC, nanoscale activated carbon; ND, nanodiamond; MSNs, silica nanoparticles; ZnPP, zinc protoporphyrin; NSCLC-SM, non-small cell lung cancer spinal metastasis; PD-L1, programmed death ligand 1; QDs, quantum dots; CCM, cancer cell membrane; MSC, mesenchymal stem cell; EPR, enhanced permeability and retention; EGFR, epidermal growth factor receptor; uPA, urokinase plasminogen activator; ATF, amino-terminal fragment; CS, chondroitin sulphate; TPP, triphenylphosphine; SDT, sonodynamic therapy; NIR, near-infrared; FRET, fluorescence resonance energy transfer; H_2O_2, hydrogen peroxide; ATO, atovaquone; DSP, cisplatin drugs; ZnPc, Zinc, phthalocyanine; TK, thioketal; CPT, camptothecin; ICG, indocyanine green; LOX, lactate oxidase; HAase, hyaluronidase; CA, cis-aconitic anhydride; DOX, doxorubicin; HAp, hydroxyapatite; DPPC, 1,2-Dipalmitoyl-sn-glycero-3-phosphocholine; DTX, docetaxel; AFT, afatinib; EML4-ALK, echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase.

Disclosure

The authors report no conflicts of interest in this work.

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