

Passive and Active Tumor Targeting in Photodynamic Therapy of Cancer: Mini-Review

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Abstract. Photodynamic therapy (PDT) is a minimally invasive treatment procedure that utilizes a light of specific wavelength and a chemically nontoxic drug photosensitizer (PS) to generate reactive oxygen species (ROS) that can selectively destroy cancer cells or other targeted tissues. However, to increase the efficiency and application of PDT, several issues still need to be resolved. One of the main challenges in PDT is ensuring that the photosensitizing agent accumulates specifically in cancer cells and not in healthy tissues. This is particularly challenging for solid tumors, which have a complex microenvironment and poor vascularization. Passive and active targeting are two strategies in PDT that aim to improve treatment outcomes by enhancing the selective accumulation of PS in tumors thereby improving the cancer therapeutic outcome. These strategies play a critical role in optimizing the efficacy and safety of PDT for cancer treatment. Passive and active targeting strategies have their advantages and limitations. In this mini-review, we focus on the advantages and disadvantages of each method and discuss the role of stimuli-responsive changes in PS delivery. © 2024 Journal of Biomedical Photonics & Engineering.

Keywords: passive and active targeting; photosensitizers; photodynamic therapy; stimuli-response; cancer.

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1 Introduction

Photodynamic Therapy (PDT) has been used as an alternative therapeutic option to treat various diseases including cancer. Oscar Raab discovered PDT more than a hundred years ago; however, the photodynamic reaction term was first coined by Von Tappeiner [1]. Even though PDT was discovered a hundred years ago, its widespread use started in late 1970s [2]. PDT works based on the utilization of light-sensitive photochemical molecules they are nontoxic in the dark and are called photosensitizers (PSs). The other two important components of PDT are light and oxygen. Due to their specific photochemical properties and cellular uptake efficiency, only a limited number of PSs have received approval to be used in clinics [3]. PS are photoactive molecules that aid their wide use as therapeutic agents in PDT as well as possess fluorescence, which properly enables their use in imaging and photodiagnosis of tumor

cells. PDT-induced cell destruction involves different mechanisms of action [3, 4]. The extent of tissue damage and cell death mechanisms are dependent on various factors, such as the type of PS used, doses, subcellular localization, etc. PSs absorb specific wavelengths of light, triggering photochemical or photophysical reactions. A high degree of chemical purity, high photochemical reactivity, stability at room temperature, minimal dark toxicity, easy solubility, availability, and high selectivity for cancer cells are the important characteristics of an ideal PS. Ideal PS also should have minimum absorption in the range of 400 nm to 600 nm and a light absorption maximum between 600 nm and 800 nm [5–7].

In 1970s, Dougherty introduced PSs for the treatment on a commercial scale with the use of hematoporphyrin derivative (HpD). HpD is considered as a first-generation PS, obtained by purification and chemical modification

of the hematoporphyrin which is the first porphyrin used as PS. The first-generation PSs show minimal chemical purity and tissue penetration which leads to the accumulation in skin. These disadvantages lead to the development of second-generation PS with better chemical purity, higher singlet oxygen production, and better tissue penetration. Still, the low water solubility is a limiting factor. The third generation PS invention solves many of these drawbacks by developing PS with high affinity to tumor with reduced damage to nearby healthy tissues. Third generation PS developed by conjugation of second-generation PS with targeting entities or moieties [8, 9].

One of the biggest challenges in PDT is ensuring that the photosensitizing agent accumulates specifically in cancer cells and not in healthy tissues. This is particularly challenging for solid tumors, which have a complex microenvironment and poor vascularization [10–12]. Recently the drug delivery has become an important aspect of cancer research. Compared to the conventional drugs, nanoparticles-based drugs enhance the efficacy of drug delivery process due to its easy preparation, minimal toxicity and tumor targeting efficacies. Passive and active targeting are two ways to enhance the consequent PDT outcomes. Furthermore, passive and active targeting are two complementary approaches in PDT that aim to improve treatment outcomes by enhancing the selective accumulation of PSs in tumor tissues. These strategies play an important role in optimizing the efficacy and safety of PDT for cancer treatment [12–14]. In this mini-review we focus on advantages and disadvantages of each method and we also highlighted the limitations and recent developments in the area of tumor targeting.

2 Drug Delivery in Nanotechnology

Nanoparticles are typically designed to carry drugs and release them in a controlled manner, allowing for targeted and efficient drug delivery. There are various types of nanoparticles used in drug delivery, including liposomes, polymeric nanoparticles, dendrimers, and carbon nanotubes [15, 16]. These nanoparticles can be engineered to have specific properties such as size, shape, surface charge, and surface functionalization, which can influence their interactions with cells and tissues. One of the key advantages of using nanotechnology for drug delivery is the ability to enhance the therapeutic efficacy of drugs while minimizing their side effects [17]. Nanoparticles can improve drug solubility, stability, and bioavailability, allowing for better drug absorption and distribution in the body. Additionally, nanoparticles can be designed to target specific cells or tissues, such as tumor cells, by incorporating targeting ligands on their surfaces [18, 19]. This targeted drug delivery approach can increase drug accumulation at the desired site while reducing systemic toxicity. Nanoparticles can also be engineered to release drugs in a controlled manner, either through passive diffusion or by responding to specific

stimuli such as pH, temperature, or enzymes. This controlled release mechanism can prolong the drug's therapeutic effect and reduce the frequency of drug administration [20–22].

2.1 Passive and Active Targeting

Recent research has shifted towards targeted drugs, which offer significantly improved efficiency in cancer treatment compared to traditional chemotherapeutic drugs, thus becoming the mainstream therapy for cancer. Imatinib, the first tyrosine kinase inhibitor, was approved by the Food and Drug Administration (FDA) in 2001. Since then, increased number of small molecules for targeting chemotherapeutic drugs have been established for various types of cancer treatments. Targeted chemotherapeutic drugs can be small molecules or macromolecules such as antibody, peptide, antibody drug conjugate, nucleic acid etc. [23].

The advantages of targeted drug delivery systems include safeguarding healthy cells from drug molecules that can cause cytotoxicity, a reduction in dose-limiting unpleasant side effects, and killing of tumor cells that are resistant to treatment and relapse. Because of the specific cellular uptake mechanisms, nanoparticles (NPs) act as drug delivery systems to the targeted sites in active form, in adequate doses and reduce the levels that settle down in healthy cells [24–26]. The tumor uptake increased due to Enhanced Permeability and Retention (EPR) effect, that refers to the increased permeability of abnormal tumor blood vessels, allowing for enhanced drug delivery to tumor tissues while reducing systemic side effects, thereby achieving the improved PDT efficacy. The lack of normal lymphatic drainage in cancer cells leads to the retaining of NPs in cancer cells. Small molecule medicines, which have a short circulation time and quick clearance from cancer tissue. As a result, encapsulating small molecule drugs in nanosized drug carriers improves their pharmacokinetic characteristics to extend systemic circulation, provides cancer selectivity, and lowers the adverse side effects. Although it lacks a ligand for precise tissue binding, this sort of passive tumor targeting depends on the features of carrier molecules, such as size, circulation time, and tumor biology [27, 28].

Active targeting has the potential to greatly improve the amount of drug delivered to the target cells as compared to free drug or passively targeted nanocarriers. This can be achieved by the modification/addition of the nanocarrier sides with ligands binding to specific receptors upregulated on the cancer cells. This method will enhance the affinity of NPs to cancer cell surface and increase the drug diffusion. Most of the tumor cell targeting is achieved using nanocarriers that enhance the drug penetration. Numerous peptides, antibodies, and other small molecules are utilized often in targeted therapies [29]. In Fig. 1, it has been demonstrated how PS delivery can be targeted passively and actively with special reference to liposome mediated drug delivery. Fig. 1 also depicts three different drug loading strategies.

Liposome Based Drug Delivery

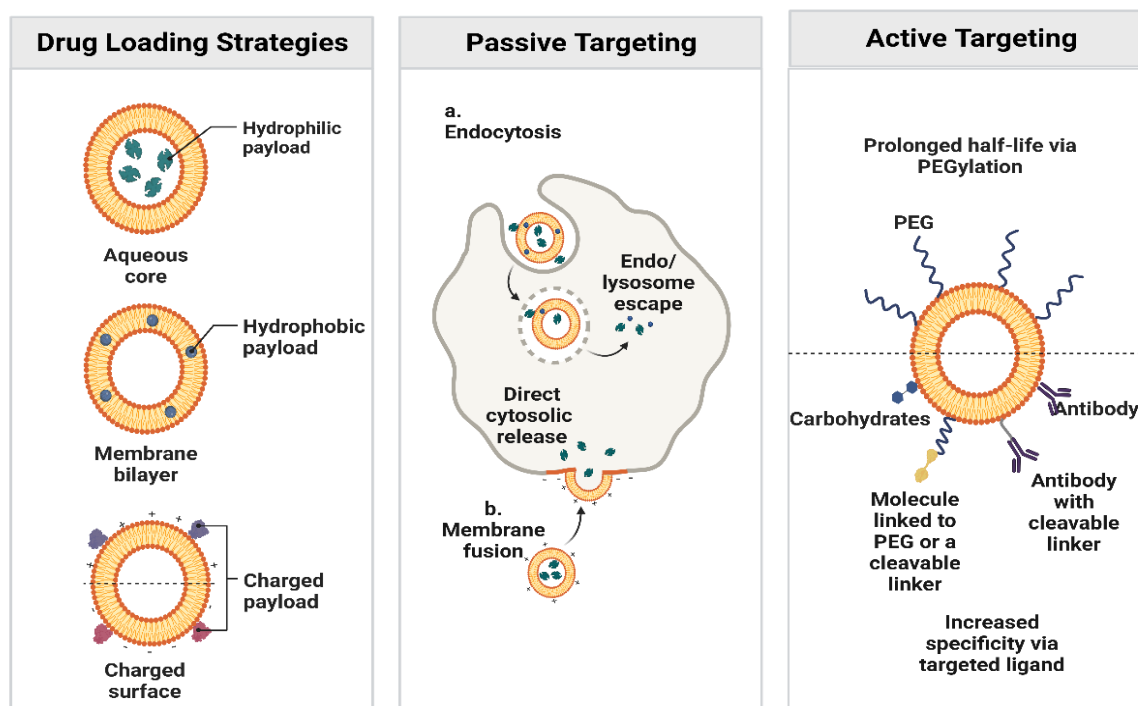


Fig. 1 Schematic representation of the hydrophilic and hydrophobic drugs loading on liposome for passive and active targeting application in cancer cells during PDT. During passive targeting liposomes can merge into cells via (a) Endocytosis and (b) Membrane fusion, while during active targeting, conjugating ligands and antibody can increase specificity of drug delivery in cells.

Recent studies in PDT have directed on many innovative methods to enhance the targeting of cancer cells using anticancer drugs and photosensitizers. An essential strategy involves combining a photosensitizing agent with folic acid (FA), potentially enhancing the targeting efficiency of folate receptors, which are often excessively expressed on the surface of numerous tumor cells. Stallivieri et al, synthesized different folic acid (oligo(ethylene glycol)) OEG conjugated photosensitisers and studied the photophysical properties for possible *in vitro* and *in vivo* applications. They found that introducing an OEG does not notably enhance the hydrophilicity of the FA-porphyrin. However, all FA-targeted photosensitisers synthesized exhibit favorable to excellent photophysical characteristics, with Chlorin e6 (Ce6) emerging as the most promising option [30]. Yan et al. conducted a study showcasing polydopamine (PDA)-FA-PS nanomedicine as an exceptionally potent and targeted anticancer solution. Additionally, they proposed a strategy to mitigate the metabolic and specificity challenges associated with clinical photosensitisers [31].

2.2 In Vitro and in Vivo Studies in PDT

Photosensitisers (PSs) have been loaded in various methods such as physical loading in self-assembled NPs for hydrophobic drugs and chemical conjugating of PSs to drug delivery and each procedure has advantages and drawbacks [32, 33]. In passive targeting the size and

surface properties play critical role to PS delivery, while NPs have been coated with a number of ligands that attach to cell surface receptors to enable active targeting [34–36]. Tumor vascular network in contrast to normal tissue, has leakage endothelial layer and impairment of lymphatic drainage, so during passive targeting intravenous injection of PSs leads to accumulation in tumor [36]. In this area, Huang et al. examined human serum albumin (HSA) NP loading paclitaxel and sinoporphyrin as PS on 4T1 breast cancer cells. Their findings showed albumin has excellent potential to PS delivery, more uptake and long half-time in blood circulation [37]. A similar study in passive targeting area conducted by Gong et al, used hyaluronidase (HAase) which breaks down hyaluronan by extracellular matrix of tumor in chlorine e6 (NM-Ce6) nanocomplex on 4T1 cells *in vitro* and *in vivo*. They found that tumor uptake increased due to the EPR effect, thereby leads to improved PDT efficacy [38].

Several studies regarding active targeting therapy in PDT have been carried out. For instance, Naidoo et al., designed and synthesized an antibody-metallated phthalocyanine-polyethylene glycol-gold NP drug conjugate in PDT of A375 melanoma cells *in vitro*. They showed that the bio-active antibody PS drug targeting enhanced the PDT efficiency in A375 cancer cells [39]. Moreover, Yoo et al. reported some ligands such as proteins, polysaccharides, aptamers, peptides can be employed in active targeting of NPs stature [40].

Table 1 Some studies in passive and active targeting of PSs agents in PDT.

References	Year	Nanocomplex or drug	Passive/Active targeting	Cell line	<i>In vitro/in vivo</i>
Y. Zhang et al. [37]	2020	HSA-NPs	Passive targeting via increasing temperature and cells permeability	4T1	<i>In vitro</i> and <i>in vivo</i>
H. Gong et al. [38]	2016	chlorine e6 (NM-Ce6)	Passive targeting (enhanced permeability and retention (EPR) effect)	4T1	<i>In vitro</i> and <i>in vivo</i>
C. Naidoo et al. [39]	2019	ZnPcS4 PS	Active targeting via conjugating specific antibody on gold nanoparticles	A375	<i>In vitro</i>
T. Qi et al. [41]	2019	TPP-PS	Passive targeting via pH-activatable of nanoparticle in tumor environment and increasing cell uptake	HO8910	<i>In vivo</i>
N. Iqbal et al. [42], J. Koval' et al. [43]	2014, 2010	hypericin (HY)	Active targeting via HY delivery by conjugating of Human epidermal growth factor receptor 2 (HER2) inhibitor	SKBR-3 cells	<i>In vitro</i>
H. J. Hah et al. [44]	2011	MB-conjugated PAA	Active targeting via coating with F3 peptides on PAA photosensitizer	9L, MDA-MB-435, and F98	<i>In vitro</i>
L. Zeng et al. [45]	2015	FA-NPs-DOX	Passive targeting via DOX-loaded on NaYF ₄ :Yb/Tm-TiO ₂ (FA-NPs-DOX)	MCF-7	<i>In vitro</i>
Gavrina et al. [46]	2018	Ce6-PVA	Passive targeting via permeability of cells and cell uptake	CT26	<i>In vitro</i> and <i>in vivo</i>

Qi et al. reported that pH-activatable and mitochondria-targeted of Pyropheophorbide-a (PPa) conjugated with triphenyl phosphonium (TPP-NH₂) shows high contrast in tumor imaging and remarkable suppress of HO8910-tumor progression without obvious toxicity *in vivo*. They concluded that the active targeting of PPa conjugated with TTP increases the enhanced uptake of the photosensitizer drug [41]. Human epidermal growth factor receptor 2 (HER2) in some cancers including breast and gastric has been targeted for active therapy [42]. Koval' et al. for the first time showed hypericin (HY) in combination with AG 825 can target HER2 in SKBR-3 breast cancer cells *in vitro* and increased apoptotic cell death and total degradation of HER2 via the high uptake of HY[43]. Another study by Hah et al., synthesised Methylene blue(MB)-conjugated polyacrylamide (PAA) NPs for PDT aimed on various cell lines such as 9L, MDA-MB-435, and F98. They coated the NPs with F3 peptides, which give specific targeting for 9L, MDA-MB-435, and F98 cancer cells *in vitro*. Finally they reported high uptake of NPs in all cell lines lead to increase the PDT efficiency with minimum cytotoxicity [44]. Furthermore, Zeng et al.

synthesized Doxorubicin (Dox)-loaded NaYF₄:Yb/Tm-TiO₂ inorganic PSs (FA-NPs-Dox) to overcome resistant MCF-7/ADR cells in PDT. Their findings indicated that the presence of folic acid (FA) in FA-NPs-Dox facilitated the targeted cellular uptake and rapid release of Dox in drug-sensitive MCF-7 cells [45]. Some studies about passive and active targeting of PS agents in PDT have been summarized in Table 1.

Gavrina et al. investigated the effectiveness of PDT utilizing chlorin e6 (Ce6) formulated with polyvinyl alcohol (PVA) compared to Ce6 alone and the clinical drug Photodithazine *in vivo*. Their research indicated that encapsulating Ce6 in PVA shows promise in enhancing selectivity and PDT efficacy. They delved into the photoactivity of Ce6-PVA through a tryptophan oxidation model reaction, examined polymer-Ce6 interaction using fluorescence spectroscopy and atomic-force microscopy, and assessed phototoxicity *in vitro*. Fluorescence imaging *in vivo* revealed that injecting Ce6 in a PVA formulation into mice resulted in a higher tumor-to-normal ratio and more significant photobleaching compared to Ce6 alone or Photodithazine. Tumor growth analysis and histological

examination of CT26 tumors demonstrated rapid, consistent tumor regression and increased necrosis following PDT with Ce6-PVA. The heightened photoactivity of the Ce6-PVA complex was validated in a tryptophan oxidation model reaction and in cultured cells [46].

3 Advantages and Disadvantages of Passive and Active Targeting in PDT

Active targeting and passive targeting are two different approaches used in PDT to deliver PSs to the desired site for effective treatment. A comparison between active and passive targeting and highlights their advantages and disadvantages are shown in Table 2. Active targeting involves the use of specific ligands or antibodies that can recognize and bind to specific receptors or biomarkers on the surface of target cells or tissues. Ligands or antibodies are usually attached to the PS, allowing for selective delivery to the desired site. Passive targeting takes advantage of the unique characteristics of tumor tissues, such as leaky blood vessels and impaired lymphatic drainage. PSs are designed to have certain physicochemical properties that allow them to accumulate passively in tumor tissues through EPR effect [47, 48].

The decision between passive and active targeting procedures depends on the application and properties of the target tissue, both of which have advantages and disadvantages.

4 Role of Stimuli-Responsive Changes in PS Delivery

Ramin et al. conducted an extensive review focusing on stimuli-responsive drug delivery systems for active

and/or passive targeted cancer chemotherapy, activated by physical and chemical cues. These systems represent a new paradigm in disease understanding at the molecular level, classified into physical and chemical categories. Stimuli-responsive materials undergo alterations in response to external triggers, offering precise control over drug release. This approach holds significant promise in nanomedicine and nanotechnology, facilitating controlled and targeted drug delivery. Stimuli-responsive drug delivery systems serve as innovative tools for oncotargeted therapy, enabling drug release through mechanisms such as EPR, interaction with overexpressed oncoreceptors, and theranostic applications [56].

Stimuli-responsive changes in PS delivery play an important role in drug release and enhancement of PDT outcomes. These changes involve the use of stimuli, such as light, temperature, pH, or enzymes, to trigger the release or activation of PSs at the target site [57, 58]. For instance, Yang et al. created hypoxia-responsive HSA based NPs for PDT. In this study, they described how to create a special kind of hypoxia-responsive HSA-based nanosystem (HCHOA) by cross-linking the PS, Ce6-conjugated HSA (HC), and oxaliplatin prodrug-conjugated HSA (HO) molecules of hypoxia-sensitive azobenzene groups. Their findings showed with a size of 100–150 nm, the HCHOA nanosystem is stable under ambient oxygen partial pressure. When exposed to the hypoxic tumor microenvironment, the nanosystem can quickly split into ultrasmall HC and HO therapeutic NPs with a diameter less than 10 nm, considerably enhancing their improved intratumoral penetration. However, with the help of this straightforward approach, it is possible to boost tumor penetration and therapeutic impact by dissociating the hypoxic-responsive nanosystem [59].

Table 2 Advantages and disadvantages of passive and active targeting in PS delivery.

Types of PS delivery	Advantages	Disadvantages	References
Passive delivery	Relatively simple and does not require specific ligands or antibodies. It relies on the natural properties of tumor tissues, making it applicable to a wide range of tumors.	Passive targeting may not achieve high specificity compared to active targeting. The EPR effect can vary among different tumors and even within the same tumor, leading to inconsistent accumulation of PSs. Normal tissues may also accumulate PSs to some extent, potentially causing side effects.	[47–52]
Active targeting	Active targeting offers higher specificity and selectivity. This approach can enhance the accumulation of PSs at the target site, leading to improved therapeutic outcomes.	Achieving high targeting specificity while maintaining stability and functionality of the PS can be challenging. The biological environment is complex, and potential interactions with non-targeted components may affect the efficacy of active targeting.	[53–55]

Moreover, Zhang and colleagues in another study utilized a ROS-responsive linker for the managed release of PSs [60]. They created a block copolymer that reacts to $^1\text{O}_2$ (POEGMA-*b*-P(MAA-co-VSPpaMA)) to improve PDT by precisely controlled release of PSs. Pyropheophorbide-a (Ppa) could be controllably released via the trigger of $^1\text{O}_2$ generated by a short duration light irradiation once NPs synthesized by the block copolymer were accumulated in tumor and taken up by cancer cells. By controlling the release of Ppa with Near Infrared (NIR) illumination to enhance the sensitization of Ppa, a self-amplified PDT could be effectively realized by taking advantage of the $^1\text{O}_2$ -responsiveness of POEGMA-*b*-P(MAA-co-VSPpaMA) block copolymer. This may offer new insight into the design of precise PDT. Some key points regarding the role of stimuli-responsive changes in PS delivery have been discussed here:

1. *Controlled release*: Stimuli-responsive systems can be designed to encapsulate PSs and release them in a controlled manner upon exposure to specific stimuli. For example, light-responsive systems can be designed to release PSs when illuminated with a specific wavelength of light. This allows for precise control over the timing and location of PS release, improving treatment outcomes.

2. *Enhanced selectivity*: Stimuli-responsive changes can help improve the selectivity of PS delivery by ensuring that the release or activation occurs only at the desired site. For instance, pH-responsive systems can be designed to release PSs in the acidic environment typically found in tumor tissues, minimizing off-target effects and reducing side effects on healthy tissues.

3. *Overcoming biological barriers*: Stimuli-responsive changes can also help overcome biological barriers that may hinder effective PS delivery. For instance, temperature-responsive systems can be designed to undergo phase transitions in response to mild hyperthermia, which can enhance the penetration and accumulation of PSs in tumor tissues.

4. *Combination therapy*: Stimuli-responsive changes can be combined with other therapeutic modalities to achieve synergistic effects. For example, combining PDT with chemotherapy or radiation therapy can enhance the overall treatment efficacy. Stimuli-responsive systems can be designed to release PSs in response to specific conditions created by these combination therapies, further improving treatment outcomes.

Overall, stimuli-responsive changes in PS delivery offer opportunities to improve the effectiveness and selectivity of PDT. By utilizing these changes, researchers and clinicians can enhance the therapeutic potential of PDT and contribute to the development of more targeted and personalized cancer treatments.

5 Future perspectives

Recent developments in enhancing passive and active targeting delivery of PSs in PDT have focused on the use of nanocarriers, active targeting ligands, stimuli-

responsive systems, and multifunctional platforms. These advancements hold great promise for improving the efficacy and specificity of PDT in cancer treatment. Passive targeting relies on integrating the therapeutic agent into a macromolecule or nanoparticle, allowing it to reach the target organ passively. The efficacy of passive targeting hinges on the drug's circulation time, which is attained by enveloping the nanoparticle with a coating of some form. The active targeting strategy involves the binding of the antitumor agent, either covalently or non-covalently, to a molecule capable of selectively interacting with specific molecules on the surface of target cells. Here, we have summarized some suggestions and strategies to develop passive and active targeting of PSs.

- 1) Exploration of novel nanocarriers, 2) Targeting ligand optimization: Further research can be conducted to identify and optimize specific ligands or antibodies that have high affinity and selectivity for cancer cell receptors, 3) Combination therapies, 4) Personalized medicine approaches: Tailoring the passive and active targeting strategies to individual patients' specific tumor characteristics can improve treatment outcomes. 5) To overcome biological barriers, research efforts may target obstacles like the extracellular matrix or the blood-brain barrier, which could impede the efficient delivery of photosensitizers. 6) Combination of multiple targeting strategies: Combining passive and active targeting approaches can potentially enhance the overall delivery efficiency and specificity of PSs, 7) Combination of multiple targeting strategies: Combining passive and active targeting approaches can potentially enhance the overall delivery efficiency and specificity of PSs, 8) Long-term stability and safety: Ensuring the long-term stability and safety of the nanocarriers and PSs is crucial for their clinical application, 9) Stimuli-responsive nanocarriers: Designing nanocarriers that respond to specific stimuli in the tumor microenvironment, such as pH, temperature, or enzyme activity, can improve the targeted release of PSs, 10) Combination of physical and chemical targeting: Combining physical targeting strategies, such as passive accumulation through the EPR effect, with active targeting using ligands or antibodies can enhance the overall delivery efficiency and specificity of PSs, 11) Nanoscale drug delivery systems: Investigating the use of nanoscale drug delivery systems, such as liposomes, polymeric NPs, or exosomes, can improve the stability and pharmacokinetics of PSs. These systems can also be engineered to enhance cellular uptake and intracellular release of PSs.

6 Conclusion

In conclusion, both passive and active targeting of PSs have shown potential in improving PDT efficiency. Passive targeting takes advantage of the EPR effect to accumulate PSs in tumor tissues, while active targeting uses ligands or antibodies to specifically target cancer cells. Additionally, there are some key points regarding the role of stimuli-responsive changes in PS delivery and controlled release of drugs.

In the future, it will be important to continue developing and optimizing targeted delivery systems for PSs. This includes exploring new ligands or antibodies that can specifically recognize different types of cancer cells and developing multifunctional delivery systems that can carry both PSs and imaging agents for real-time monitoring. Furthermore, the integration of other emerging technologies, such as nanotechnology and immunotherapy, could further improve the PDT outcomes. NPs can be used as carriers for PSs, allowing the controlled release and improved delivery to tumors. Immunotherapy approaches, such as immune checkpoint inhibitors, can be combined with PDT to enhance the immune response against cancer cells. It seems, the future of targeted delivery of PSs in PDT looks promising. Continued research and development in this field will undoubtedly lead to improved therapeutic outcomes and better patient care. Additionally, the stimuli-responsive changes in PS delivery have the potential to significantly enhance the effectiveness of PDT. By designing systems that can release or activate PSs in response to specific stimuli, researchers can achieve controlled release, improve selectivity, overcome biological barriers, and combine therapies for synergistic therapeutic outcomes.

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Disclosures

The authors declare that they have no conflict of interest.

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