Strategies to improve photodynamic therapy efficacy by relieving the tumor hypoxia environment

Zijun Shen¹, Qingming Ma¹, Xinyu Zhou¹, Guimin Zhang², Guizhou Hao², Yong Sun¹ and Jie Cao¹

Abstract
Photodynamic therapy (PDT) is an emerging technology for tumor treatment in which photosensitizer (PS)-mediated light irradiation reduces oxygen, producing high levels of reactive oxygen species (ROS) that can cause vascular injury and effectively kill tumor cells. However, the naturally hypoxic tumor microenvironment is the main obstacle that hinders the photodynamic response in vivo and prevents its extensive application to tumor treatment. Moreover, PDT-mediated oxygen consumption further increases tumor hypoxia, potentially causing a variety of adverse consequences, such as angiogenesis, tumor invasion, and metastasis. To overcome these limitations caused by hypoxia, multiple strategies have been investigated, including the use of oxygen carriers and reactive oxygen supply materials, the regulation of tumor microenvironments, and multimodal therapy including PDT. In this review, we summarize the latest progress in the development of strategies to relieve tumor hypoxia for improved PDT efficacy and better therapeutic effects.

Introduction
Photodynamic therapy (PDT) has become a major strategy for solid cancer treatment due to its inherent advantages, such as high selectivity, noninvasiveness, and low systemic toxicity. Effective PDT typically involves the use of photosensitizers (PSs), appropriate laser irradiation, and a sufficient oxygen supply¹. Specifically, the electrons of PS are elevated from the ground state (S₀) to the excited state (S₁) upon light irradiation and then pass through the excited triplet state (T₁) through intersystem crossing, forming free radicals through a type I reaction or transferring energy to the surrounding molecular oxygen (O₂) to produce highly active singlet oxygen (¹O₂), as illustrated schematically in Fig. 1 (ref. ²). The generated ¹O₂ and adjacent biological macromolecules undergo oxidative reactions that can further lead to cytotoxicity, cell damage, and even death. While it has numerous advantages, the application of PDT for cancer treatment is limited due to several intrinsic drawbacks. For instance, when subjected to light irradiation, PS will convert oxygen to reactive oxygen species (ROS) with high cytotoxicity, which further aggravates the hypoxia of tumors. Therefore, in addition to pre-existing tumor hypoxia, the effectiveness of PDT will be further deteriorated by the oxygen consumption involved in the generation of ROS³. Moreover, the deterioration of tumor hypoxia will further promote cancer progression and metastasis, increasing the risk of PDT resistance⁴. Therefore, proposing new and effective strategies to reduce tumor hypoxia has become a primary research focus for improving PDT efficacy.

Recently, many studies on improving the hypoxic status of tumors to enhance PDT efficacy have been carried out, and significant progress has been made⁵–⁸. For instance, novel nonreactive oxygen carriers, such as liposome-encapsulated hemoglobin (HB) and perfluorocarbon carbide, have been designed and used⁹. Moreover, reactive
oxygen supply materials, such as metal oxides, hydrogen peroxide (H$_2$O$_2$) enzymes, active nanoparticles that can react with acid and H$_2$O$_2$ in vivo to produce oxygen, and materials that can produce oxygen under PDT conditions, such as PT(IV) nanocomposites, have also been studied. In addition, other strategies that can alleviate or take advantage of hypoxic environments have also been reported, such as administering hypoxia-inducible factor inhibitors, targeting organelles, increasing blood perfusion, and performing combined therapy with hypoxia-response drugs.

Therefore, a comprehensive and in-depth depiction of the whole scene of the recent development of tumor hypoxia-improving strategies to enhance PDT efficacy, from fundamentals to applications, is desirable. In this review, we summarize the main research strategies in recent years, from the design of novel nonreactive oxygen carriers to reactive materials and other strategies, including the regulation of tumor microenvironments and PDT-involved multimodal therapy, to improve the hypoxic microenvironment to enhance PDT efficacy (Fig. 2).

**Nonreactive oxygen carriers**

**Hemoglobin**

HB is one of the major components in red blood cells with inherent reversible oxygen-binding capability and can transport oxygen molecules to tissues. However, as an oxygen donor, cell-free HB presents several problems, including poor stability, short circulation time, and potential side effects.$^{10}$ Therefore, the incorporation of HB into hybrid oxygen carriers, such as glutaraldehyde-polymerized HB and poly(ethylene glycol)-conjugated HB (PEG-HB), to form HB-based oxygen carriers (HBOCs) to facilitate PDT has been widely investigated.$^{11-14}$ However, most HBOCs cause vascular contraction due to their nitric oxide (NO) scavenging capacity, leading to an unfavorable sharp increase in blood pressure.$^{15}$ Compared with HBOCs, oxygen carriers with sizes in the nanometer range can perfuse tumor tissues more efficiently and provide a higher oxygen supply in hypoxic tumors. Many studies on the development of HB-based nano-oxygen carriers have been carried out, and significant progress has been achieved.$^{16,17}$

Liposomes have attractive prospects in clinical applications due to their inherent advantages, such as good biocompatibility, targeting ability and drug protection. Recently, liposome-encapsulated HB has been proposed and studied as an oxygen carrier and was found to reduce side effects and enhance the half-life of the HB cycle. For example, as illustrated in Fig. 3, Yang et al.$^{18}$ developed a multifunctional liposome with enhanced chemotherapeutic effects by simultaneously incorporating HB as the oxygen carrier and doxorubicin (DOX) as the antitumor drug. First, HB can be cross-bonded in the phospholipid membrane by hydrophobic forces. Then, DOX and HB are loaded into the aqueous phase of the liposome, while part of the HB is connected to the surface of the liposome membrane through hydrophobic interactions to form DOX–HB–liposomes (DHL). The prepared DHL can offer sufficiently high oxygen loading and can perform site-specific delivery of oxygen to tumors, which can improve tumor hypoxia. MTT results indicated that even at a concentration of 150 μg/mL, the cytotoxicity to the test cells was very low; hematoxylin and eosin (H&E) staining results showed that there was no obvious histological damage to normal organs, which further proved the safety and biocompatibility of liposomes.
Studies have shown that excessive iron can promote the occurrence and growth of tumors, and many types of cancer cells (such as breast cancer, liver cancer, and colon cancer) upregulate proteins related to iron uptake. Therefore, cancer cells may absorb iron-containing HB more easily, allowing such HB-liposomes to be specifically internalized into cancer cells. Consistently, the results of an in vivo distribution experiment with HBL revealed that compared with liposomes without HB, HBL showed stronger fluorescence at the tumor site, indicating that the HB-mediated drug combination could improve specific uptake into tumor cells. Moreover, under the effect of O₂ interference, hypoxic cancer cells showed an increased capacity to take up the delivered drugs, resulting in significant cancer cell apoptosis. In addition, DHL can markedly increase ROS production in hypoxic tumors and thereby increase the cytotoxicity of DOX, which is typically mediated by ROS. Due to the resultant higher drug and oxygen concentrations in tumor regions, DHL shows great promise in reversing hypoxia-induced chemoresistance and exhibits improved antitumor effects.

In addition, Cai et al. developed biomimetic lipid-polymer nanoparticles (I-ARCs) that can load a special compound assembled from indocyanine green (ICG) as a PS and HB as an oxygen carrier (Fig. 4). The prepared I-ARCs can act as nanosized artificial red blood cells with the ability to generate oxygen and provide real-time monitoring of the PDT process simultaneously. Specifically, I-ARCs consist of biocompatible lipid shells, which were designed to mimic the cell membrane, and poly(ε, l-lactic acid-co-glycolic acid) (PLGA) nuclei, in which HB was assembled with ICG to form HB/ICG complexes. Upon 808 nm light irradiation, I-ARCs can produce 9.5 times more ROS than deoxidized ICG nanoparticles. Moreover, since ICG shows fluorescence signals and a photoacoustic response, the biodistribution and metabolism of HB/ICG complex-loaded I-ARCs can be easily monitored during PDT.

**Perfluorocarbon**

Considering that HB may be susceptible to conformational changes during the chemical modifications involved in the fabrication process of HB-based nanomaterials, other candidates, such as solutions or materials with considerable oxygen storage capacity, would be suitable alternatives. For example, compared with HB, perfluorocarbons (PFCs) can exhibit a higher oxygen solubility (40–56 ml O₂ per 100 ml PFC at 760 Torr and 25 °C) and can donate molecular oxygen in the tumor tissue, thereby improving PDT efficiency in the hypoxic region. Recently, many efforts have been made to improve PDT efficacy by adding PFCs in preclinical or clinical research, as summarized in Table 1. For instance, Cheng et al. explored oxygen self-enrichment PDT (Oxy-PDT) by loading the PS IR780 into PFC nanodroplets to enhance the PDT effect (Fig. 5). In this system, a continuous oxygen supply facilitates the prolongation of PDT and fully utilizes the efficacy of IR780. The results demonstrated that compared with traditional PDT methods, the tumor growth of mice can be significantly inhibited by intravenously injecting a single dose of Oxy-PDT.

Although PFCs have a high oxygen capacity, the oxygen release efficiency is purely based on oxygen concentration gradient-dependent passive diffusion and is lower than that of HB. To overcome this obstacle, Song et al. developed an ultrasound-triggered tumor oxygenation strategy by using nano-PFC as the oxygen carrier, as shown by the schematics in Fig. 6. A human serum albumin-stabilized PFC nanodroplet system was proposed to regulate tumor-specific oxygen delivery and readily trigger oxygen release by external synchronous ultrasound.
therapy. The nanodroplets were intravenously injected into tumor-bearing 4T1 mice, and then the mice were treated with pure oxygen breathing for 30 min and ultrasonication for 30 min. In this process, nanodroplets adsorbed oxygen in the lungs, carried it into tumors through blood circulation, and then released oxygen effectively in the tumors. The level of O$_2$ in the tumors increased rapidly from 17 to 49%, improving the anti-tumor effect of the PDT regimen.

Oxygen-containing microbubbles/nanobubbles

In addition to HB and PFCs as oxygen carriers, oxygen-loaded microbubbles/nanobubbles have recently been used as a novel potential reagent to provide supplemental
oxygen in the hypoxic microenvironment of solid tumors. These bubbles have excellent biocompatibility and effective and high oxygen-carrying capacity (>70% v/v). The combination of microbubbles/nanobubbles and PSs has been demonstrated to have great potential to enhance therapeutic efficacy in hypoxic tumor models. In general, nanobubbles bound to PS can accumulate in the cytoplasm, and then the PS inside is released by destroying the shell of the bubbles. When the oxygen diffuses out from the shell, the bubble shrinks to a point where the external Laplace pressure breaks the bubble, thereby releasing the PS. Then, the PS generates singlet oxygen under laser irradiation and exerts an efficient PDT effect in a high oxygen environment.

For example, Song et al. designed bilaminar oxygen nanobubbles with chlorin e6 (Ce6) connected to a polymer shell as a new oxygen supply material. The developed oxygen-loaded nanobubbles can provide a large amount of oxygen to improve the therapeutic effect of oxygen-consuming PDT (Fig. 7). The lipid-polymer bilaminar oxygen nanobubbles were prepared using a combination of emulsion solvent evaporation and internal phase separation. Compared with the phospholipids or surfactants used in other oxygen delivery systems, the lipid molecules around the polymer shell selected by the researchers show good biocompatibility. The combination of the hydrophilic polymer PEG and lipid provides an invisible layer of nanocapsules, thereby inhibiting the phagocytosis of mononuclear macrophages and improving the stability of nanocapsules and system circulation life. Moreover, the synthesized nanobubbles have good stability that can inhibit premature oxygen release and can be stored in the form of freeze-dried powders to enable simple pre-use reconstruction, thus solving the storage problems troubled by PFC oxygen delivery systems. Both in vitro and in vivo results showed that PDT treatment with oxygen-containing nanobubbles can greatly enhance the production of singlet oxygen and achieve excellent therapeutic effects.

Reactive oxygen supplementation materials

PDT-dependent materials

In recent years, researchers have prepared PDT-dependent materials for oxygen generation, which can effectively supplement oxygen in PDT by decomposing nanoparticles under laser irradiation. Pt(IV) is a Pt-based light-activated precursor drug that can be decomposed into oxygen and Pt(II) with anticancer activity under long-wavelength light irradiation. The Pt can therefore be assembled with Pt(IV) to form a nanocomplex for photodynamic-chemotherapy combined treatment. For example, Xu et al. designed self-generated multifunctional nanocomposites containing oxygen and Pt(II) to reverse the PDT resistance induced by hypoxia, as illustrated in Fig. 8. The nanocomposites consist of Pt(IV) and Ce6, by which upconversion nanoparticles (UCNP) are loaded to convert near-infrared (NIR) light at 980 nm to light emission at 365 and 660 nm, respectively, further inducing the decomposition of Pt(IV)
and the production of oxygen and thereby properly driving PDT with UCNP-embedded nanoparticles (denoted UCPP). When laser irradiation at 980 nm is used to trigger the decomposition of UCPP, oxygen can be generated through chemical reactions to compensate for oxygen consumption in the PDT process, and active Pt(II) can be released for synergistic photochemistry.

PDT-independent materials
In addition to PDT-dependent materials, PDT-independent materials could generate oxygen through chemical reactions not involved in the PDT process. Various reactive oxygen-generating materials, including metal oxides, catalase-active materials, and water-splitting materials, have been used to overcome hypoxia.

Metal oxide materials
In recent years, metal oxides have been demonstrated to produce oxygen through chemical reactions with acids or H$_2$O$_2$ and can effectively alleviate the oxygen consumption in the PDT process$^{38-41}$. Therefore, metal oxides show promise for use along with PSs to improve the efficiency of PDT.

MnO$_2$ nanomaterials. Manganese oxide (MnO$_2$) has attracted increasing attention due to its ability to generate excessive oxygen with the aid of acid and H$_2$O$_2$ in the tumor microenvironment.

The following reactions illustrate how acid-induced H$_2$O$_2$ promotes the degradation of MnO$_2$ and the resultant generation of oxygen:

\[
\text{MnO}_2 + 2\text{H}^+ \rightarrow \text{Mn}^{2+} + \text{H}_2\text{O} + 1/2\text{O}_2; \quad (1)
\]

\[
\text{MnO}_2 + \text{H}_2\text{O}_2 + 2\text{H}^+ \rightarrow \text{Mn}^{2+} + 2\text{H}_2\text{O} + \text{O}_2; \quad (2)
\]

MnO$_2$ shows high reactivity and specificity to acidic environments and the presence of H$_2$O$_2$, where it can produce oxygen continuously to overcome hypoxia in tumors$^{42-45}$. After reacting with excessive H$_2$O$_2$ in an acidic tumor microenvironment, MnO$_2$ nanosheets can be degraded to produce a large amount of oxygen, thus greatly improving the efficiency of PDT. In addition to increasing the oxygen content, MnO$_2$ can also be used as a glutathione (GSH) inhibitor in vivo to increase PDT efficacy. Moreover, it can be used to make upconversion nanocomposites to stimulate PSs at various wavelengths to enhance the selectivity of PDT. In addition, Mn$^{2+}$ produced by MnO$_2$ is a strong T1 magnetic resonance (MR) contrast agent for tumor detection, which can also be used for in site tumor imaging$^{46,47}$. At the same time, it is worth mentioning that, as an essential trace element in the human body, Mn can be adjusted by metabolism, so it has good biocompatibility.

MnO$_2$ as a GSH inhibitor to replenish oxygen and increase PDT efficacy In addition to low oxygen, the effectiveness of PDT is also limited by the hypoxia-induced...
overexpression of GSH, which consumes ROS before they reach their target and hence greatly reduces the efficiency of PDT. Numerous studies have attempted to develop a more stable and effective PDT system by the incorporation of GSH depletors\(^4\). \(\text{MnO}_2\) can be used as an efficient glutathione dehydrogenase inhibitor to reduce GSH levels; therefore, a \(\text{MnO}_2\)-containing PDT system is expected to overcome the drawbacks caused by hypoxia and GSH overexpression at the tumor site\(^4\).

Sun et al.\(^5\) proposed a simple and convenient method for achieving the controllable growth of ultrathin manganese dioxide nanosheets by introducing a redox reaction on polydopamine nanoparticles (Fig. 9). The prepared multifunctional polydopamine@ultrathin manganese dioxide/methylene blue (MB) nanoflowers (termed PDA@ut-MnO\(_2\)/MB NFs) are suitable platforms for synergistic tumor therapy and can efficiently modulate the tumor microenvironment by generating \(\text{O}_2\) and depleting GSH. In addition, they can support ultrasensitive reduction-responsive MR imaging (MRI). The morphology and composition of PDA@ut-MnO\(_2\) were identified and characterized by scanning electron microscopy (SEM),...
transmission electron microscopy (TEM), high-resolution transmission electron microscopy (HR-TEM) and high-angle annular dark field scanning transmission electron microscopy (HAADF-STEM), and their therapeutic effects were evaluated in mice bearing HCT116 colorectal tumors as models. Tumors were collected 15 days after injection, and PDA@MnO₂/MB showed nearly complete tumor growth inhibition under MRI-guided PDT/PTT cotreatment. The H&E staining results of tumor sections also confirmed serious pathological damage, such as severe nuclear pyknosis and nuclear necrosis. Moreover, MRI of tumor-bearing mice found that the T1-weighted MR signal of the kidney was significantly enhanced 2 h after the injection, and the total manganese content in urine was measured by inductively coupled plasma mass spectrometry (ICP-MS). Approximately 65% of the manganese content was detected, suggesting that Mn²⁺ was eliminated from the body through the kidneys, and the in vivo toxicity was minimal. These results demonstrated that PDA@MnO₂/MB NFs can achieve a high degree of tumor growth suppression under MRI-assisted treatment. Furthermore, Fan’s group51 developed an intelligent PS-MnO₂ nanosystem, which exhibited high intracellular drug delivery capacity and enhanced PDT efficacy by reducing GSH levels and increasing oxygen content in cancer cells. Specifically, MnO₂ nanosheets act as oxygen supplements and oxidants to reduce intracellular GSH levels. In addition, they have been shown to effectively induce the fluorescence quenching of Ce6 to offer an on–off fluorescence signal for real-time monitoring. In the Ce₆-MnO₂ nanosystem, Ce6 can be well protected from light-induced self-destruction and can be effectively transported to the cytoplasm. After endocytosis, MnO₂ nanosheets were reduced by intracellular GSH. The results show that the nanosystem can be disintegrated, generate oxygen, and reduce the GSH level, subsequently inducing 95% cell death when combined with Ce6. Moreover, the fluorescence recovery, accompanied by the dissolution of MnO₂ nanosheets, can be used as a reporting signal for monitoring the transmission capacity.

Upconversion nanocompounds loaded with MnO₂ to replenish oxygen and increase PDT selectivity Under the effect of upconversion nanocompounds loaded with MnO₂, NIR light can be turned to ultraviolet (UV)/visible light with a broad emission spectrum; therefore, MnO₂-loaded upconversion nanocompounds can also be applied as powerful tools to activate various PSs. Meanwhile, MnO₂ can be decomposed in vivo to produce oxygen and further enhance PDT. As a result, NIR light-mediated upconversion nanocompounds, especially lanthanum-doped upconversion nanocrystals (UCNs) combined with MnO₂, have been systematically investigated to effectively induce cell extirpation.

Xing’s group52 demonstrated the successful establishment of PS-loaded UCN nanoconjugates (PUNs) that can enhance the effectiveness of PDT by reducing the population of tumor-associated macrophages (TAMs) and hypoxia. PUNs can be prepared by combining MnO₂ nanosheets with hyaluronic acid (HA) biopolymers (Fig. 10). When subjected to the acidic tumor microenvironment with excessive H₂O₂, MnO₂ nanosheets can be degraded and produce a large amount of oxygen, which can greatly improve the efficiency of oxygen-dependent PDT. Moreover, by transitioning NIR light to UV/visible light, PUNs can also offer a high degree of tissue penetration and help solve the safety problems involved in conventional PDT techniques. In addition, due to the existence of biologically stimulated HA, PUNs can drastically decrease the tumor recurrence rate by reprogramming the propagation of tumor-promoting M2 TAMs into tumor-unfavorable M1 macrophages. This strategy provides an excellent opportunity for enhanced cell ablation in NIR-mediated PDT therapy by weakening the hypoxic tumor microenvironment and therefore inspires new strategies for immunotherapy that can prevent tumor recurrence in the later stage of PDT.

In addition, mesoporous silica nanospheres incorporating fine CaF₂:Yb and Er upconversion nanocrystals were synthesized by the thermal decomposition method by Gu et al.53 Then, a new nano-PDT platform was obtained by coating the nanospheres with a thin layer of manganese dioxide and loading the PS Ce6. In the composite nanoparticles, Mn²⁺ ions doped in the CaF₂ crystal lattice effectively enhanced the red upconversion luminescence triggered by NIR light, which stimulated the adsorption of Ce6 by resonance energy transfer, thus improving the photodynamic phenomena. At the same time, the MnO₂ coating regulated the hypoxic microenvironment of tumors by the in situ generation of O₂ through reacting with endogenous H₂O₂ of tumors. These two mechanisms play important roles in the treatment of NIR-triggered photodynamic tumors. After Ce6 loading, the nanoparticles showed good stability in physiological solutions (including ultrapure water, phosphate-buffered saline, fetal bovine serum, and cell culture medium (RPMI-1640) containing 10% serum) without any agglomeration. More importantly, the results of in vitro experiments showed that the tumor shrank significantly under NIR light irradiation and remained small for 14 days without recurrence.

UCNPs loaded with MnO₂ based on this unique material design strategy not only have the anticancer prospects shown above but also offer guiding significance for the development of other types of functional nanostructures.

Other metal oxide nanomaterials Lan et al.54 developed novel nano metal–organic framework-based metal oxide nanoparticles by using 5,10,15,20-tetra(p-benzoic acid)
porphyrin (TBP) ligands and Fe$_3$O clusters to form Fe-TBP, as illustrated schematically in Fig. 11. O$_2$ was generated by the Fenton-like reaction of Fe$_3$O clusters and then converted into cytotoxic singlet oxygen ($^{1}$O$_2$) by photostimulated porphyrin. PDT mediated by Fe-TBP can trigger a systemic antitumor response to improve alpha-PD-L1 ICB (immune checkpoint blocker), resulting in the disappearance of microscopic effects in treating primary and untreated distant tumors. Treatment with Fe-TBP plus alpha-PD-L1 can induce the proliferation of CD4$^+$ and CD8$^+$ T cells, which infiltrate distant tumors to induce exfoliation. In a mouse model of colorectal cancer, Fe-TBP-mediated PDT significantly improved the therapeutic effect of alpha-PD-L1. A sustained abscopal effect was induced, both the primary tumor under the treatment and the untreated distant tumor regressed >90%. Moreover, ICP-MS analysis showed that Fe-TBP mostly gathered at the tumor site after 4 h of incubation and was cleared within 10 days, and no dark regions indicating toxicity of Fe-TBP were observed. This study proposes a new strategy combining enhanced PDT with immune therapy to induce systemic antitumor therapy.

Moreover, due to the spontaneous cycling of cerium dioxide (CeO$_2$) between Ce$^{3+}$ and Ce$^{4+}$ in redox reactions, CeO$_2$ can react with high levels of endogenous H$_2$O$_2$ in tumor cells and simultaneously generate H$_2$O and O$_2$. Therefore, CeO$_2$ can be used as an optional O$_2$-evolving agent to enhance the efficacy of PDT. Zeng et al. developed a core–shell Bi$_2$S$_3$@Ce$_6$–CeO$_2$ nano-composite. Bi$_2$S$_3$ showed good photothermal, photoacoustic, and computed X-ray tomography (CT) imaging performance, and the PS Ce6, which has good photodynamic effects, was adsorbed on the surface of Bi$_2$S$_3$. Finally, CeO$_2$, an O$_2$-evolving agent, was coated on the Bi$_2$S$_3$@Ce6 surface to provide an in situ oxygen supply. The biocompatibility of Bi$_2$S$_3$@Ce$_6$–CeO$_2$ was evaluated by the MTT method, and the results showed that at concentrations of 12.5–200 $\mu$g/mL, 4T1 cells had a survival rate of more than 95% within 24 h, even at the maximum concentration of 200 $\mu$g/mL. The survival rate at 48 h also exceeded 90%. Similarly, Bi$_2$S$_3$@Ce6–CeO$_2$ showed consistently low toxicity in mouse embryonic fibroblast NIH 3T3 cells. Moreover, the results of in vivo treatment showed that the tumor volume of the mice in
the Bi$_2$S$_3$@Ce$_6$–CeO$_2$ group was close to zero, and the CD31 and Ki67 immunohistochemical results also showed significant damage to the microvessels of CD31-positive tumors and inhibited proliferation of positive cells. Multifunctional nanomaterials that combine photodynamic/photothermal/oxygen supply properties have shown improved tumor therapy efficacy both in vitro and in vivo.

**Catalase-active material**

Catalases capable of triggering the decomposition of H$_2$O$_2$ into water and oxygen are enriched in malignant tumor cells, with concentrations higher than those in healthy cells, and are closely related to the progression and proliferation of tumors. Such materials can also be used as an oxygen source to trigger PDT$^{56-59}$. Based on this understanding, the concept that catalase-combined PS can enhance PDT efficiency by the synergistic promotion of in situ oxygen production in tumor tissues has been proposed and demonstrated.

For example, gold nanoclusters (AuNCs) have been widely used as materials with catalase activity in recent years$^{60,61}$. Nanomaterial-based enzymes can be used as artificial catalases with controllable release to use catalase-like activities to catalyze the transformation of intratumoral H$_2$O$_2$ into O$_2$ to alleviate tumor hypoxia. Dan et al.$^{61}$ reported the use of ultrasmall AuNCs-ICG as nanozymes with theranostic features, efficient renal clearance, and superior catalase-like activity to modulate tumor hypoxia and enhance PDT and radioisotope tracer (RT) (Fig. 12). AuNCS effectively decompose a large

![Fig. 11 Design and characterization of metal oxide nanoparticles (Fe-TBP).](image-url)
amount of H$_2$O$_2$ in the tumor to produce oxygen, thus improving the naturally hypoxic tumor microenvironment and enhancing conventional PDT and RT efficacy.

Moreover, taking advantage of Pt's catalase activity to change H$_2$O$_2$ into oxygen, Wei et al.\textsuperscript{62} designed novel two-dimensional PdS-based nanomaterials with good biocompatibility, good near-infrared absorption characteristics, and high tumor enrichment ability, which show great promise in the diagnosis and treatment of tumors. In particular, Pd@Pt-PEG-Ce6 nanocomposites were designed by using Pd–Pt two-dimensional palladium nanocomposites as carriers of PSs, as shown in Fig. 13. Pd@Pt-PEG-Ce6 can effectively deliver PS to tumor cells and decompose endogenous H$_2$O$_2$ to facilitate oxygen generation, thus significantly enhancing the efficacy of PDT. Moreover, the PDT efficacy of Pd@Pt-PEG-Ce6 can also be improved by the mild photothermal effect of Pd:Pt nanoplates.

In addition, the combination of catalase and a PS to achieve a better PDT effect has been investigated. Hu's group\textsuperscript{58} developed a new type of oxygen self-sufficient PDT platform by coloading with catalase and MB to construct zeolite-catalase-MB nanocapsules (ZCM nanocapsules), as illustrated by the SEM, TEM, and HRTEM images in Fig. 14. The prepared ZCM nanocapsules showed 90% relative activity compared to equivalent free catalase. Under real-time ultrasound imaging guidance, ZCM nanocapsules can be precisely implanted into the tumor area. Since they can decompose endogenous H$_2$O$_2$ in a sustained manner and provide in situ O$_2$ generation,
the ZCM nanocapsules can effectively improve hypoxia and enhance intratumoral ultrasound contrast. Moreover, the incorporated MB can prevent the rapid leaching of the PS and contribute to its sustained release of PS at tumor site. In vitro results demonstrated that local PC cells can be completely killed upon near-infrared laser irradiation, and no therapy-induced side effects or tumor recurrence were observed. As described above, the use of catalase-active materials in combination with PSs and the formation of new processing systems through reasonable design strategies will help overcome the challenges in PDT and improve its efficacy.

**Water-splitting materials**

Current strategies for oxygen supplementation typically involve the use of biological oxygen-producing materials such as MnO2 and catalase-like materials, but their O2 yield may be limited by intracellular restricted H2O2 concentrations. In nature, plants produce oxygen efficiently from abundant H2O through photosynthesis. Inspired by this phenomenon, water-splitting materials, such as nanocomposites based on inorganic, organic, macromolecular, or hybrid materials, have been developed to produce H2 and O2\(^6\)–\(^8\). As the most abundant compound in organisms, water can provide almost unlimited O2 production compared with other oxygen-producing materials. At present, the main water-splitting materials used to alleviate PDT hypoxia therapy are calcium peroxide (CaO2) nanoparticles, carbon nitride (C3N4) nanocomposites, and TiO2 nanotubes.

**Calcium peroxide (CaO2) nanoparticles** CaO2, a safe water-splitting material with high biocompatibility, rapid cell metabolism, and efficient O2 production, is considered to be a promising material to regulate solid tumor hypoxia and improve PDT efficiency\(^6\)–\(^8\). It can generate a large amount of O2 upon coming into contact with water to improve PDT efficacy. Typical CaO2-based oxygen-producing biomaterials are mainly fabricated by combining CaO2 with hydrophobic polymers.

For instance, Liu et al.\(^5\) synthesized the liposome-based nanoparticle LipoMB/CaO2 with oxygen self-enrichment properties (Fig. 15). Under laser irradiation, the singlet oxygen produced by the PS MB can induce lipid peroxidation and destroy the liposome structure, further exposing CaO2, expanding the contact area between CaO2 and H2O and producing a large amount of oxygen to alleviate hypoxia. In vivo and in vitro experiments have demonstrated that LipoMB/CaO2 shows superior oxygen production capability with an enhanced PDT effect that can effectively alleviate hypoxia in tumors.

**Carbon nitride (C3N4) nanocomposites** Among water-decomposing materials, C3N4 has attracted much attention due to its relatively narrow band gap (2.7 eV) and strong reduction ability. Water splitting by C3N4 can be triggered under high-penetration red light (>600 nm), making it suitable for in vivo therapy. Moreover, since C3N4 is not doped with metal elements, it has high biocompatibility, good stability, and nontoxicity, and can be used in the biomedical field\(^6\)–\(^8\).

For example, Zhang’s group\(^7\) designed an intelligent nanoreactor R-NCNP with a combined water-splitting effect and multimodal imaging function (Fig. 16). This nanocomposite has a mesoporous C3N4 layer coated on the core–shell structure of nitrogen-doped graphene quantum dot (N-GQD)@hollow mesoporous silica nanosphere and then bound P-PEG-RGD amphiphilic polymers to achieve targeted delivery, resulting in the nanoreactor designated R-NCNP. Upon 630 nm laser irradiation, the PSs are activated to produce singlet oxygen, while H2O molecules are transformed into O2 to increase the tumor oxygen content through C3N4-mediated water-splitting. In addition, N-GQDs endow
R-NCNP with both PTT/PDT and imaging capabilities. Experimental results show that R-NCNP can enhance the efficacy of PDT by alleviating hypoxia and assist with multimodal imaging for a good combination of diagnosis and treatment. Moreover, the distribution in the body showed only a weak fluorescent signal in the liver, possibly caused by phagocytosis of the nanoparticles by mononuclear phagocytes. In addition, a moderate accumulation of fluorescence was detected in the kidney tissue, indicating that the nanoparticles were excreted and eliminated from the kidney.

**TiO<sub>2</sub> nanotubes** TiO<sub>2</sub> materials have attracted extensive attention in the field of water-splitting materials due to their adjustable band gap, excellent photostability, high catalytic activity, low toxicity, and low cost<sup>75,76</sup>. They can...
provide large internal and external surface areas to improve the light absorption intensity and facilitate further modification. They can be used in combination with carbon nanodots (CDots) for PDT treatment via water-splitting processes:

\[
2\text{H}_2\text{O} \rightarrow \text{H}_2\text{O}_2 + \text{H}_2; \\
2\text{H}_2\text{O}_2 \rightarrow 2\text{H}_2\text{O} + \text{O}_2. 
\]

Yang et al.\textsuperscript{77} designed carbon nanodot-modified TiO\textsubscript{2} nanotubes (CDots/TiO\textsubscript{2} NTS) to release oxygen and reactive oxygen species simultaneously in an anoxic environment. Under laser irradiation, the CDots/TiO\textsubscript{2} PS will produce a large amount of singlet oxygen through an upconversion process to induce apoptosis or necrosis and supply a large amount of oxygen through continuous water splitting to improve the efficacy of PDT. Experimental results in vivo and in vitro show that CDots/TiO\textsubscript{2} NTS have good PDT effects, which makes them an excellent photosensitive material with great potential for application in the biomedical field.

Other strategies involving regulating tumor microenvironments and multimodal therapy including PDT

Improving blood perfusion in tumors

With the rapid growth of solid tumors, the formation of a neovascular network lags behind cell proliferation, and the construction of a new microvascular network is irregular. The abnormal vascular network has temporary closure or “blind ends”, which a decrease of tumor blood perfusion and oxygen partial pressure (pO\textsubscript{2}) in the microenvironment, making it difficult for the tumor to obtain an adequate O\textsubscript{2} supply to meet its metabolic needs, resulting in tumor hypoxia and reducing the therapeutic effect of PDT\textsuperscript{78–81}. Therefore, improving blood flow perfusion by improving vascular conditions in tumors is a good approach to increasing oxygen content. It is mainly achieved by improving tumor hemodynamics via photothermal therapy (PTT) and regulating tumor microvessel structure using chemotherapeutic drugs.

Improving tumor hemodynamics

Tumor hypoxia is largely related to disordered and chaotic tumor blood flow, so improving blood flow has become an effective way to increase tumor O\textsubscript{2} concentration. Many studies have shown that increasing local temperature by mild heating can effectively increase tumor blood flow and increase oxygen content in solid tumors\textsuperscript{82,83}. Therefore, the combination of PDT and PTT is often used to treat cancer cells, as PTT can not only convert light energy into heat energy under the irradiation of an external light source to kill cancer cells but also be administered as a mild photothermal pretreatment to improve blood flow in solid tumors.

Our group\textsuperscript{84} designed a dual oxygenated nanoparticle MnO\textsubscript{2}@chitosan-CyI (MCC) for enhanced phototherapy, in which the PS CyI is a near-infrared dye with both PDT and PTT effects. When exposed to near-infrared radiation, the increase in tissue temperature caused by the photothermal effect accelerates blood flow and effectively alleviates tumor hypoxia. Moreover, MnO\textsubscript{2} can not only reduce the level of GSH but also act as an efficient in situ oxygen generator, thus further increasing the production of ROS. This MCC nanosystem shows great promise as an intelligent and versatile nanotherapy platform that can improve the tumor microenvironment under hypoxia to obtain better therapeutic effects of PDT/PTT.

Regulation of tumor microvessel structure

In addition to using photothermal effects to increase blood flow velocity within solid tumors, chemotherapeutic drugs have recently been used to regulate the disordered microvascular structure of tumors (e.g., gemcitabine, cyclophosphamide, and cisplatin) to restore the physiological perfusion and oxygenation of tumor vessels more efficiently\textsuperscript{83–87}. For example, Shen et al.\textsuperscript{88} found that thalidomide (Thal) can correct the imbalance between proangiogenic factors and antiangiogenic factors, resulting in decreased leakage of tumor vessels and increased thickness of blood vessels as well as tumor perfusion (Fig. 17). Finally, the tumor vascular system was normalized and tumor oxygenation was increased. Thal, as a new candidate drug, can maximize the efficacy of PDT for solid tumors if combined with a PS.

Targeting mitochondria in tumors

A lack of sustained alleviation of hypoxia in solid tumors is one of the major problems for in situ oxygen-producing nanomaterials, since the uninterrupted high respiration in tumors consumes oxygen through mitochondria. As an indispensable organelle responsible for cell respiration, mitochondria may aggravate tumor hypoxia and limit the efficacy of PDT\textsuperscript{89,90}. Hence, it is feasible to design nanocomposites that can selectively inhibit mitochondrial activity and produce O\textsubscript{2} sustainably in hypoxic tumors.

For example, Yang et al.\textsuperscript{91} constructed photodynamic Mn\textsubscript{3}O\textsubscript{4}@MSNs@IR780 nanoparticles with sustainable hypoxia mitigation capabilities (Fig. 18). The alleviation of hypoxia is achieved through intratumor H\textsubscript{2}O\textsubscript{2} catalysis and targeting mitochondria to inhibit respiration. These Mn\textsubscript{3}O\textsubscript{4} nanoparticles responded to the H\textsubscript{2}O\textsubscript{2}-enriched tumor microenvironment by decomposing and catalyzing H\textsubscript{2}O\textsubscript{2} to produce O\textsubscript{2}. Subsequently, IR780 was released and activated and spontaneously targeted mitochondria due to its natural mitochondrial affinity. Under laser
irradiation, Mn$_3$O$_4$@esoporous silica nanomaterials (MSNs)@IR780 can destroy mitochondria and inhibit cell respiration, which can alleviate the persistent hypoxia of tumor tissue, thus improving the therapeutic effect of PDT. In vitro experiments showed that Mn$_3$O$_4$@MSNs@IR780 can continuously alleviate tumor hypoxia and provide a new way to overcome sustainable hypoxia.

**Downregulating HIF-1 expression in tumors**

The high expression of hypoxia-inducible factor (HIF-1α) is one of the key barriers to PDT treatment. Although current in situ oxygen supply strategies can alleviate tumor hypoxia to some extent, the non-sustainable supply of O$_2$ offered by these strategies can induce only moderate HIF-1α degradation, and the residual HIF-1α will still adversely affect the PDT effect. Using effective HIF-1α inhibition in hypoxic tumors is a feasible way to achieve adequate tumor oxygenation to enhance PDT efficacy. Inspired by HIF-1 intracellular signaling pathways, researchers have been working on the precise blocking of HIF-1α by small molecular inhibitors in recent years.

Liu et al. utilized rapamycin (RAP) as an upstream activator of HIF-1 and mammalian rapamycin targeting gene (mTOR) inhibitor in cancer cells, whose inhibition of mTOR leads to HIF-1α expression and HIF-1 transcription-dependent blockade. As illustrated in Fig. 19, an efficient core–shell nanosystem was designed to alleviate hypoxia and improve PDT efficacy through simultaneous oxygenation and HIF-1α inhibition. The PSs Ce6 and RAP formed dual-drug nanopores through self-assembly and were then loaded with catalase. Catalase, as an oxygen provider, catalyzes H$_2$O$_2$ decomposition into O$_2$ and leads to the sustained release of RAP to downregulate HIF-1α expression, thus achieving in situ oxygen generation and HIF-1α inhibition in tumor tissues, together relieving PDT pressure on hypoxia.

**PDT-activated hypoxia-amplified bioreductive therapy**

In recent years, the application of hypoxia-reactive anticancer drugs combined with PDT under hypoxic conditions has aroused great interest. Unlike other strategies focused on alleviating hypoxia in tumors, this new approach takes advantage of the lack of oxygen in tumors. In addition, PDT-induced oxygen consumption can further enhance the role of hypoxia-activated drugs. Recent studies have demonstrated the feasibility and effectiveness of this strategy, in which the combined delivery of PS and produgs is achieved by nanoparticles, such as silica-shell nanoparticles or liposomes.

Hypoxic response drugs usually produce highly cytotoxic substances under hypoxic conditions, and their
cytotoxic activity can be triggered when combined with hypoxic induction therapy. The current combination of PDT with hypoxia-responsive drugs mainly involves telapamide (TPZ), TH-302, PR-104A, and benzoan-thraquinone (AQ4N), which produce sufficient hypoxia in tumors by cotransporting with PS molecules and show strong cytotoxicity in the hypoxic microenvironment. Although this approach is rarely used in the field of PDT, its anticancer potential is certainly worth further exploration and confirmation.

Liu et al.\textsuperscript{99} designed double-layer silica-shell UCNPs, which can transfer the PS and bioreductive precursor drug TPZ together to achieve synergistic cancer treatment. UC-PDT was used to induce the cytotoxicity of active TPZ and produced a large amount of ROS. Compared with UC-PDT, TPZ UC/PS can significantly inhibit the growth of tumors, suggesting that TPZ exhibits a significant increase in cytotoxicity during PDT-induced hypoxia and has a profound impact on the therapeutic effect. This NIR-induced intratumoral hypoxia is sufficient to enhance hypoxia-induced bioreduction therapy, demonstrating an efficient synergistic approach to cancer treatment.

Conclusions and outlooks

Because of its minimal invasiveness, high feasibility, and enhanced efficiency, PDT has made tremendous progress in anticancer therapy. The latest advances in oxygen supplementation nanoparticles have opened up promising perspectives to develop new PDT systems and provide multiple opportunities to circumvent the current PDT paradigm. On the one hand, exogenous molecular oxygen can be captured by biological, bionic, or physical mechanisms and then transported to solid tumors with the help of nanocarriers. On the other hand, through PDT-dependent materials, PDT-in-dependent materials or other methods, oxygen can be generated in vivo to provide a continuous local oxygen supply to improve PDT efficiency. Both strategies have demonstrated their potential in improving the oxygen content of PDT.

In this review, we present strategies to improve PDT efficiency by focusing on hypoxia, a key challenge in PDT-mediated cancer therapy. However, it is worth noting that although a large number of studies investigated improving PDT efficiency by relieving hypoxia in the tumor microenvironment, increasing the singlet oxygen yield of the PS itself is also an important means to enhance the efficiency of PDT. For example, we found that the heavy metal atom iodine can be modified in ICG PSs by the heavy atom effect and can significantly improve the singlet oxygen yield\textsuperscript{100}. If such PSs are combined with the oxygen supplements described above, better PDT effects are expected. In addition, for clinical applications, PDT needs to meet many specific requirements, including biocompatibility and biodegradability. For example, when manganese dioxide nanosheets are used to produce oxygen, their degradation needs to be carefully evaluated in vivo. With these challenges seriously considered and addressed, overcoming tumor hypoxia in the use of PDT will become a powerful and versatile strategy for complicated cancer therapy.

Conflict of interest

The authors declare no competing interests.

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