

Oxygenation: Nanotechnological Strategies for Conquering Tumor Hypoxia in Photodynamic Therapy

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Abstract: Photodynamic therapy (PDT) is a clinically established treatment with high selectivity and minimal invasiveness. However, its efficacy against solid tumors is severely compromised by hypoxia, a hallmark of the tumor microenvironment (TME). Although conventional approaches, such as oxygen delivery and in situ oxygen generation, offer certain benefits, their passive and uncontrolled nature poses substantial challenges. This review explores alternative strategies to actively overcome tumor hypoxia, highlighting recent advances in nanotechnology that go beyond traditional oxygen replenishment methods. We focus on three main avenues for enhanced PDT: remodeling the hypoxic TME, circumventing intratumoral hypoxia, and harnessing hypoxia. Furthermore, we offer a forward-looking perspective on nanotechnology-mediated hypoxia modulation and discuss potential pathways for oxygen-optimized PDT in next-generation cancer therapy. This review provides valuable and clinically significant insights into the development of PDT.

Keywords: photodynamic therapy, hypoxia, nanotechnology, tumor microenvironment

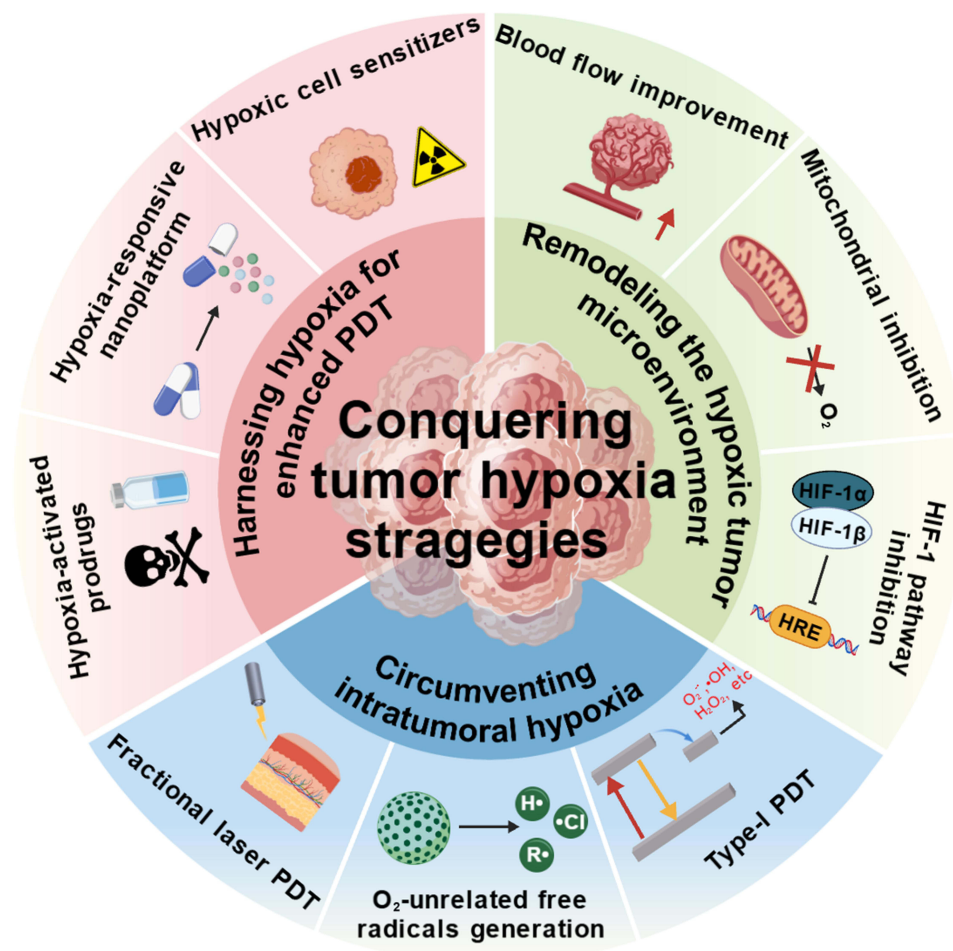
Introduction

Malignant tumor seriously threatens human health now.¹ Up to now, surgery, radiotherapy and chemotherapy remain the most common clinical treatments for cancer.^{2–7} Surgical resection is the most effective method for non-metastatic solid tumors.⁸ However, this is an inappropriate approach for patients with high-risk tumors (eg, near critical organs or metastatic tumors).^{9,10} Radiotherapy and chemotherapy induce severe adverse effects that significantly impair patients' quality of life.^{11,12} Therefore, scientists are dedicated to seeking alternative treatment strategies that maximize efficacy and minimize side effects.¹³

Photodynamic therapy (PDT) has emerged as a potential antitumor therapy, which exhibits the beneficial advantages including minimal invasion, high tumor selectivity, low systemic toxicity, and lack of drug resistance.^{14,15} The PDT process involves three essential components: a specific wavelength of light, a photosensitizer (PS), and oxygen.¹⁶ Under laser irradiation, the PS in its ground singlet state (S_0) absorbs photons to become excited to the singlet state (S_1), and then undergoes intersystem crossing (ISC) to reach the triplet state (T_1), which is crucial for therapeutic efficacy.^{17–20} In Type I PDT, the triplet-state PS transfers electrons to biomolecules, generating radicals (such as H_2O_2 and $\cdot OH$) that cause oxidative damage.^{17–20} In Type II PDT, T_1 -stated PS energy transfers to the surrounding triplet oxygen, producing highly cytotoxic singlet oxygen (1O_2) to kill tumor cells.^{17–20} Currently, the most widely used PDT agents operate via the Type II mechanism, which is highly dependent on the local oxygen concentration.

The uncontrolled proliferation of tumor cells leads to hypoxia, a well-established hallmark of solid tumors.^{21–24} Notably, tumor hypoxia promotes tumor progression and metastasis, thereby increasing treatment difficulty.^{25–27} Several studies have

Graphical Abstract



reported that hypoxia activates key regulatory proteins, including hypoxia-inducible factor 1 (HIF-1) and vascular endothelial growth factor (VEGF), which subsequently stimulate tumor angiogenesis.^{28–30} However, the newly formed vasculature is often aberrant, disorganized, and inefficient, ultimately failing to alleviate hypoxia.³¹ Consequently, hypoxia remains a critical barrier that limits the efficacy of oxygen-dependent PDT. Therefore, it is essential to develop advanced nanotechnology-based strategies to overcome tumor hypoxia and enhance the effectiveness of PDT.

Numerous nanotechnology-based strategies have been developed to overcome tumor hypoxia and enhance PDT treatment. Most existing reviews primarily focus on oxygen-supplying approaches, such as the delivery of exogenous oxygen or in situ oxygen generation.^{14,32–34} However, the delivery of exogenous O₂ is constrained by limited loading capacity and uncontrolled release, which may inadvertently promote tumor progression. Similarly, in situ oxygen generation is often hampered by the scarcity of endogenous substrates (eg, H₂O₂), resulting in an insufficient oxygen supply. Furthermore, many published reviews have overemphasized Type-I PDT while neglecting other promising strategies designed to circumvent intratumoral hypoxia.^{14,33} With the rapid evolution of this field, a growing number of innovative strategies for PDT in hypoxic tumors have recently been reported. In this review, we highly focus on active hypoxia conquest strategies and conclude recent advances in nanotechnology-based approaches for overcoming hypoxia to improve PDT efficacy. These strategies are categorized into three main themes: 1) remodeling the hypoxic tumor microenvironment, 2) circumventing intratumoral hypoxia, and 3) harnessing hypoxia for enhanced PDT. By viewing

hypoxia not just as an obstacle, but as a targetable and exploitable component of tumor, we provide a comprehensive perspective that could transform PDT into a more effective and adaptable treatment for tumor hypoxia.

Remodeling the Hypoxic Tumor Microenvironment

Tumor hypoxia is a major challenge in PDT because most nanotechnology-based strategies heavily consume oxygen. In addition, the strategy of passively increasing the oxygen content faces problems, such as limited carrying capacity and oxygen leakage. Therefore, the development of active methods to overcome hypoxic tumor is crucial for enhancing PDT efficacy. Remodeling the hypoxic tumor microenvironment strategies mainly include (I) improving blood flow in tumor, (II) inhibiting mitochondrial respiration, and (III) inhibiting HIF-1 signaling pathway (Table 1).

Improving Blood Flow in Tumor

Compared to normal vasculature, tumor blood vessels exhibit distinct structural abnormalities, including dilation, tortuosity, and disarray.^{41–43} These aberrant vessels, along with dysfunctional lymphatic vessels, exacerbate tumor hypoxia, further promoting cancer progression, metastasis, and drug resistance.^{44–46} Therefore, improving tumor blood flow represents a promising strategy to alleviate hypoxia for enhancing PDT treatment.

Mild hyperthermia (40–42°C) can locally raise tumor temperature, thereby enhancing blood flow and perfusion to lighten tumor hypoxia.^{47,48} Coincidentally, photothermal therapy (PTT), a revolutionary phototherapy technique, absorbs specific light wavelengths and converts them into thermal energy, inducing tumor cell death through cellular protein denaturation and membrane disruption.^{20,48–52} Hence, the synergistic therapy of PTT and PDT not only reduces tumor hypoxia by boosting blood flow efficiently but also helps to precisely eliminate malignant tumors.²⁰

Li et al constructed pH-responsive gold nanosystem (AuNS@ZrTCPP-GA@LP) for enhanced therapy of breast cancer by improving blood perfusion, which consisted of gold nanostars (AuNS), Zr⁴⁺, tetrakis(4-carboxyphenyl) porphyrin (TCPP), and gambogic acid (GA) (Figure 1A).³⁵ After NIR light irradiation, the mild temperature increase caused by AuNS boosted blood flow to alleviate tumor hypoxia, and thereby efficiently enhancing the therapeutic efficacy of TCPP-mediated PDT.

Furthermore, several agents can also normalize abnormal tumor vasculature to improve blood perfusion to ease tumor hypoxia, including antiangiogenic drugs (eg, sunitinib,⁵³ dexamethasone⁵⁴ and lenvatinib⁵⁵) and therapeutic gases (eg, NO^{56,57}). Recently, Zhu et al fabricated an NIR-excitable nitric oxide (NO) nanotractor to improve intratumoral penetration and overcome hypoxic resistance (Figure 1B).³⁶ SiO₂ shell loaded with NO, fuel molecules (RBS), and PDT photosensitizers (ZnPc). UCNP functioned as a light transducer under 980 nm light irradiation, converting NIR light to visible light, which excites the RBS and releases NO. NO not only strengthens intratumoral penetration but also suppresses cellular respiration to reduce hypoxia.

Improving blood flow to increase O₂ levels is a potential strategy to enhance nanotechnology-based PDT treatment. However, the precise targeting and penetration of nanodrugs into hypoxic solid tumors remains a major challenge in oncology drug delivery.

Inhibiting Mitochondrial Respiration

Delivering exogenous and generating O₂ are typical strategies to ease hypoxia. However, due to the increased tumor proliferation and lack of endogenous H₂O₂, the above methods can only temporarily improve hypoxia.^{33,58} The primary functions of O₂ consumption include tumor cell respiration and proliferation. Recently, several studies have shown that utilizing the O₂ consumption inhibitors to inhibit mitochondrial respiration can reduce O₂ consumption rate.^{59–63}

Lin et al constructed a novel 2D nano-photosensitizer (BrP@MOL) that could significantly reduce endogenous O₂ consumption by tumor cells to enhance PDT efficacy (Figure 2A).³⁷ The nano-photosensitizer was fabricated by 3-Bromopyruvate (BrP) and metal-organic layer (MOL). By suppressing both mitochondrial respiration and glycolysis, BrP@MOL induced tumor oxygenation and reduced lactate production. This, in turn, effectively enhanced PDT efficacy and activated the immune response. The significant inhibition of mitochondrial respiration by BrP@MOL improved the antitumor effects of PDT, thereby preventing lung metastasis in breast cancer.

Table 1 Representative Paradigms for Improving Blood Flow in Tumor, Inhibiting Mitochondrial Respiration and Inhibiting HIF-1 Signaling Pathway to Relieve Tumor Hypoxia

Strategy	Nanoplatforms	Tumor Type	Mode of Cancer Therapies	Molecular Mechanism	Dose of Administration	Therapeutic Efficacy	Ref.
Improving Blood Flow in Tumor	AZGL	4T1	PDT/PTT	• TCPP-mediated PDT • AuNS-mediated PTT • Lower the thermal resistance	i.v. injected (1 mg mL ⁻¹ of AZGL)	Strongly inhibit tumor growth within 14 days	[35]
	UCNP	Hela	PDT	• NO gas generation under blue light • ROS production under red light	i.m. injected	Significant antitumor effect within 14 days	[36]
Inhibiting Mitochondrial Respiration	BrP@MOL	4T1/ CT26	PDT/ Immunotherapy	• Inhibition of mitochondrial respiration and glycolysis • Enhanced ROS generation	i.v. injected (0.2 μmol of BrP@MOL)	Over 90% of tumor growth inhibition within 23 days	[37]
	LonCe	4T1	PDT	• Lon inhibits mitochondrial respiration • More ¹O₂ generation to	i.v. injected (5.34 mg kg ⁻¹ of LonCe)	Effective tumor suppression within 21 days	[38]
Inhibiting HIF-1 Signaling Pathway	CI@HSA	I43B/ HOS	PDT	• The combination of CAP and PDT synergistically promote ferroptosis • CAP downregulates HIF-1α to alleviate hypoxia	s.q. injected (200μL of Poly-porphyrin)	Tumor growth was inhibited effectively within 15 days	[39]
	ISDN	Panc02	PDT/ Immunotherapy	• I7-DMAG inhibits the HSP90/HIF-1α axis • Enhanced PDT efficacy promotes stronger immunogenic cell death	i.v. injected (5 mg kg ⁻¹ of ICG and 4.3 mg kg ⁻¹ of I7-DMAG)	Significant tumor growth inhibition within 12 days	[40]

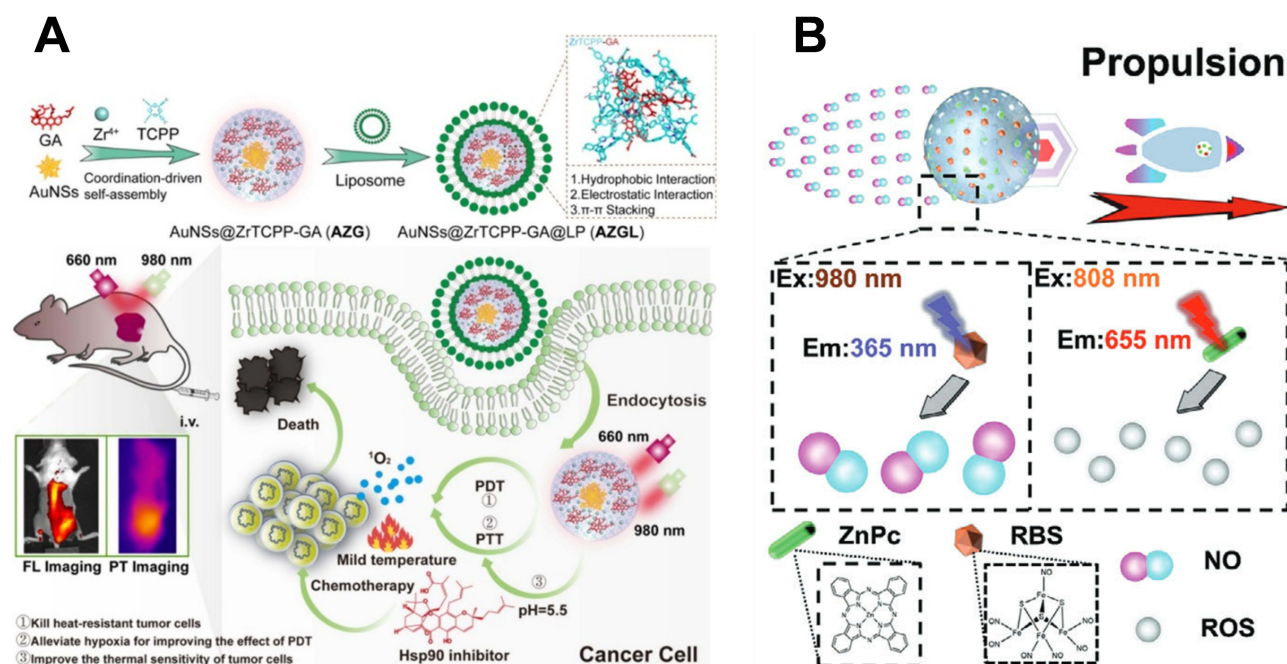


Figure 1 (A) Schematic illustration of the mechanism of AZGL killed tumor cells by synergy therapy of PTT and PDT. Reproduced with permission.³⁵ (B) Schematic illustration of self-released NO nanotractor to generate ROS under 980 and 808nm light laser. Reproduced with permission.³⁶ Copyright 2024, John Wiley and Sons.

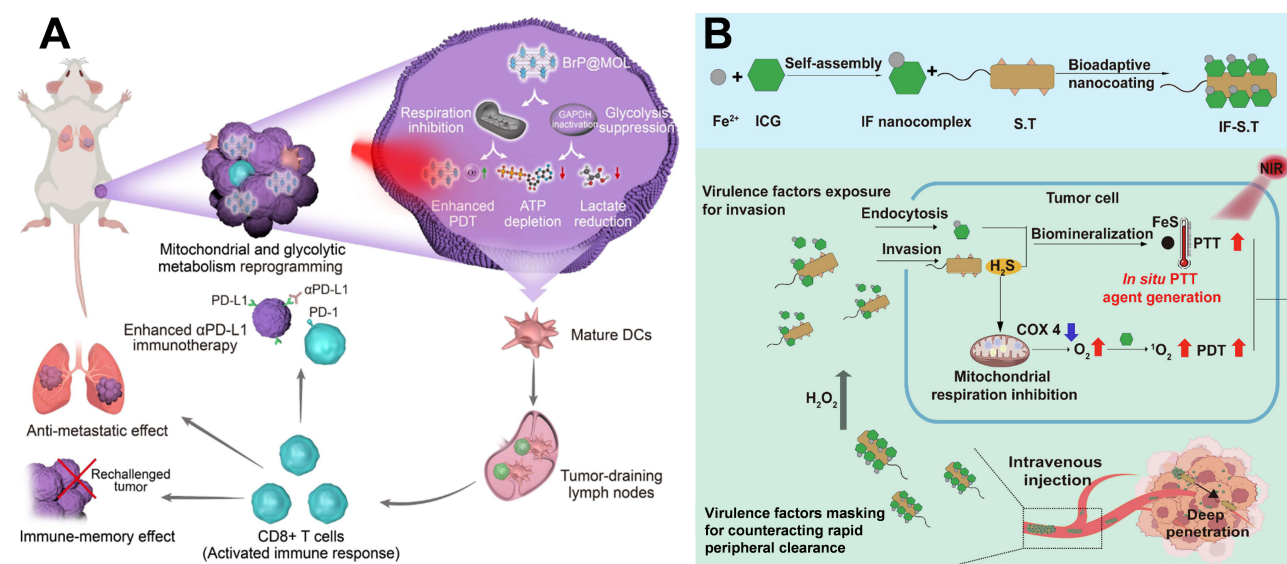


Figure 2 (A) Schematic representation of the designed nano-photosensitizer (BrP@MOL) for enhancing PDT by inhibiting mitochondrial respiration. Reproduced with permission.³⁷ Copyright 2024, Wiley-VCH GmbH. (B) Schematic illustration of the mechanism of LonCe for enhancing PDT by inhibiting mitochondrial respiration. Reproduced with permission.³⁸ Copyright 2022, Wiley-VCH GmbH.

For instance, Cheng et al created a carrier-free O₂-economizer (LonCe) that exhibited reduced systemic toxicity and immunogenicity in vivo (Figure 2B).³⁸ The antitumor drug Lonidamine (Lon) and the photosensitizer chlorin e6 (Ce6) were used to build the nanoparticle through intermolecular interactions. When LonCe entered tumor cells, a large number of toxic ¹O₂ was produced to kill tumor cells under irradiation. Subsequently, the releasing Lon could interrupt cell respiration by inhibiting mitochondria complex II s to reduce O₂ consumption for enhanced PDT therapy.

The inhibition of mitochondrial respiration can reduce O_2 consumption at the source, thus enhancing PDT antitumor efficacy. Nevertheless, the oxygen-sparing effect of this approach is temporally limited (only during active intervention) and is quantitatively insufficient to meet the therapeutic requirements of PDT.

Inhibiting HIF-1 Signaling Pathway

Hypoxia-inducible factor 1 α (HIF-1 α) is the key regulator of hypoxia.⁶⁴ HIF-1 α can be rapidly degraded under normoxia, whereas under hypoxic conditions, HIF-1 α is activated in tumor cells, driving tumor metastasis and progression in a HIF-dependent hypoxia manner.^{65–67} Therefore, inhibiting HIF-1 signaling pathway to alleviate tumor hypoxia displays a potential strategy for enhancing PDT efficacy.⁶⁸ Several studies have shown that some natural or artificial agents can selectively inhibit HIF-1 α , such as acriflavine, topotecan and capsaicin.^{39,69} Lv et al created a multifunctional nanomedicine (CAP@IR780@HSA) for increasing PDT efficacy, which was consisted of capsaicin (CAP), photosensitizer IR780 and serum albumin (HSA) (Figure 3A).³⁹ Under NIR irradiation, PSs IR780 could generate ROS to eliminate tumor. Moreover, CAP not only could induce ferroptosis but also suppress the HIF-1 α to mitigate tumor hypoxia, thereby mitigating tumor hypoxia and enhancing the antitumor efficiency of PDT.

The most representative molecular chaperone is the heat shock protein (HSP).⁷⁰ Several studies have shown that HSP90 can bind to HIF-1, thereby enhancing its stability.^{58,71–73} Therefore, to successfully combat hypoxia, it is crucial to focus on HIF itself, as well as the associated proteins. For instance, Deng et al fabricated a self-assembled nanoparticle (ISDN) to downregulate HIF-1 α , which contained indocyanine green (ICG) and 17-dimethylaminoethylamino-17-demethoxygeldanamycin (17-DMAG).⁴⁰ Owing to the hydrophobic interactions between ICG and 17-DMAG, ICG could generate more ROS for the treatment of pancreatic cancer. In addition, 17-DMAG was capable of restraining HSP90/HIF-1 α axis to ease tumor hypoxia, thereby improving PDT efficacy (Figure 3B).

HIF-independent hypoxia response is another signaling pathway that tumor cells sense to hypoxia. When HIF is restrained, tumor cells survive in a number of signaling pathways: they sense hypoxia directly and adapt rapidly to changing conditions.^{74–77} Lately, studies on HIF-independent hypoxia have centered chiefly on domains such as ferroptosis, while it has scarcely been investigated in relation to PDT.^{78,79} In brief, HIF-dependent and HIF-independent hypoxia together form the “hypoxic adaptation network” of tumors. Therefore, the design of novel PDT nanomedicines should aim to simultaneously target both HIF-dependent pathways and HIF-independent mechanisms, thereby more comprehensively overcoming tumor hypoxia and improving therapeutic outcomes.

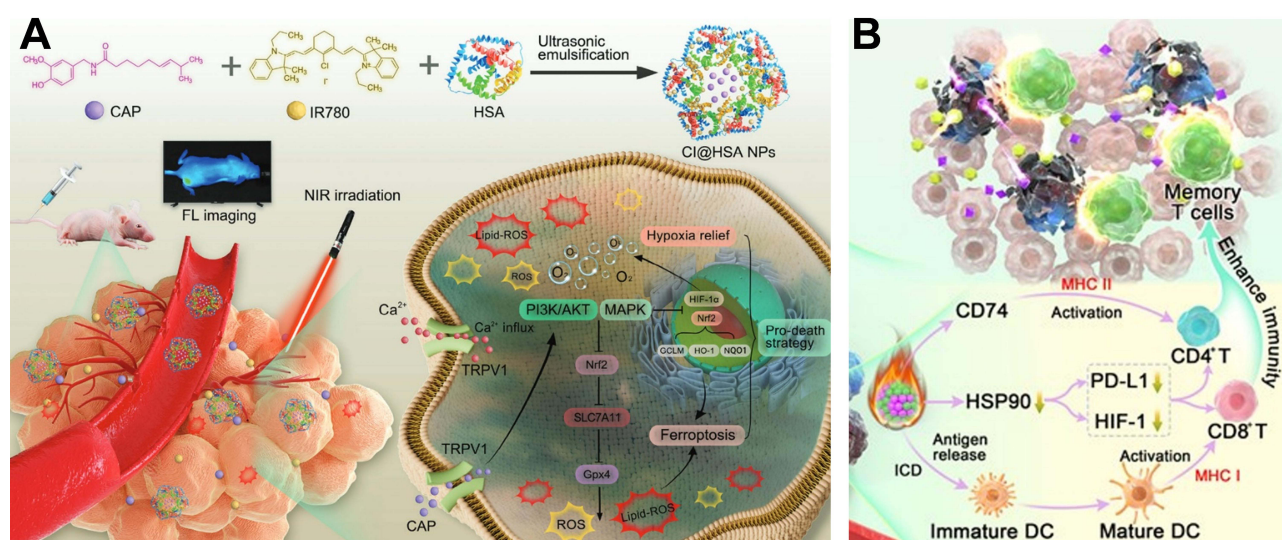


Figure 3 (A) The preparation of CAP@HSA NPs and its mechanism for enhanced PDT efficacy. Reproduced with permission.³⁹ Copyright 2024, John Wiley and Sons. (B) The synthesis procedure preparation process of ISDN and its mechanism for improved PDT. Reproduced with permission.⁴⁰ Copyright 2024, John Wiley and Sons.

Circumventing Intratumoral Hypoxia

Currently, O₂-independent therapeutic strategies represent a promising approach to conquer tumor hypoxia by generating cytotoxic ROS without extra O₂ to eliminate the tumor cells.^{19,80–82} Therefore, strategies to circumvent hypoxia may be effective solutions for cancer treatment. Hypoxia circumvention strategies mainly include (I) Type-I PDT, (II) generating O₂-unrelated free radicals, and (III) fractional laser PDT (Table 2).

Type-I PDT

The aforementioned strategies to overcome hypoxia are mostly focused on increasing O₂ concentration via various methods. However, traditional Type-II PDT has limited therapeutic efficacy because of inherent tumor hypoxia and constant consumption of oxygen.^{90,91} Conversely, Type-I PDT has attracted a lot of interest in recent years and has shown great superiority in hypoxic tumors, as it is far less or no dependent on O₂.^{92,93}

The primary significance of the Type I mechanism is its relative oxygen independence, since the initial reaction does not strictly require the involvement of O₂ (Figure 4A).^{93–96} In addition, Type-I PDT can utilize superoxide dismutase (SOD) to drive the disproportionation reaction (Equation (1)), Haber-Weiss reaction (Equation (2)) or Fenton reaction (Equation (3)) to create O₂, which further decreases the dependence on O₂.^{96–99}



Recently, Huang et al constructed an applicable pyroptosis nanoinducer (HB NPs) composed of uniform carbon nanodots (HNCs) and bovine serum albumin (BSA) (Figure 4B).⁸³ HNCs could convert the Type II PDT process to Type I to disregard hypoxia. The result of the experiment proved that HB NPs could generate excessive O₂^{•−} to kill tumor cells even under an extremely hypoxic environment (2% O₂).

Liu's group synthesized on-demand switchable nanoparticles (TPFN-AzoCF₃ NPs) to achieve precision treatment and reduce side effects (Figure 4C).⁸⁴ TPFN-AzoCF₃ NPs were composed of hypoxia-normoxia cycling-responsive group (AzoCF₃), Type I PS (TPFN), and carrier liposomes (DSPE-PEG-2000). In hypoxic tumors, TPFN-AzoCF₃ NPs could be activated to produce ROS to suppress tumor growth, whereas in normal tissues, they remained completely non-toxic, which not only reduces potential side effects but also overcomes tumor hypoxia.

Dong et al developed a mitochondrion-targeted nanoagonist (HABH) composed of Type I photosensitizer (BDP) and Au nanoparticles for achieving light-controlled PDT therapy (Figure 4D).⁸⁵ HABH nanoagonist could effectively target the tumor site, while the released BDP triggered Type I PDT under laser irradiation to generate vast •OH to kill tumor cells. Therefore, HABH nanoagonist showed excellent phototoxicity under normoxic conditions owing to its high potential to surmount the hypoxic constraints of traditional PDT.

Type-I PDT nanotechnology-based methods can inhibit tumors, while neglecting tumor hypoxia to a certain extent. However, stable quantitative methods for evaluating the generation of Type-I ROS are lacking, leading to difficulties in developing novel Type-I PDT agents.⁹³

Generating O₂-Unrelated Free Radicals

The strategy for generating O₂-unrelated free radicals refers to the generation of other cellular toxic free radicals (eg, H•, •Cl, and R•) to inhibit tumor cells without relying on O₂. Beyond Type-I PDT, this approach circumvents the limitations of tumor hypoxia.

Feng's group constructed a light-responsive organic photosensitizer (TAF) for enhanced PDT (Figure 5A).⁸⁶ In this work, TAF could efficiently generate vast H• because of its photocatalytic activity. H• exhibited dual phototherapeutic properties, enabling both photooxidative and reductive therapy. It could react with O₂ to facilitate ROS generation in the

Table 2 Representative Paradigms of Type-I PDT, O₂-Unrelated Free Radicals Generation and Fractional Laser PDT to Circumvent Hypoxia

Strategy	Nanoplatfoms	Tumor Type	Mode of Cancer Therapies	Molecular Mechanism	Dose of Administration	Therapeutic Efficacy	Ref.
Type-I PDT	HB NPs	4T1	PDT/ Immunotherapy	- Type II PDT converts to Type I - O₂^{•−} generation efficiently in hypoxia - HB induces pyroptosis	i.v. injected	Complete inhibition of tumor growth with minimal tumor volume	[83]
	TPFN-AzoCF3 NPs	Hela	PDT	Triggering only in hypoxia to generate type I ROS	i.v. injected (5 mg mL ^{−1} of TPFN-AzoCF3 NPs)	Significant Hela tumor inhibition within 21 days	[84]
	HABH	4T1	PDT/ Immunotherapy	- BDP achieves type I PDT in mitochondria for releasing mtDNA - cGAS-STING immune pathway is activated	i.v. injected	Dramatically suppressed 4T1 tumor growth within 14 days	[85]
Generating O ₂ -unrelated free radicals	TAF	Hela	PDT	- TAF produces H• with GSH consumption - H• causes apoptosis of tumor cells in hypoxia	/	/	[86]
	Ru-Chlos @ABTS	4T1	PDT/ Immunotherapy	- Forming toxic oxABTS without O₂ - Ru triggers ICD effects	i.v. injected	Remarkably suppressed 4T1 tumor growth within 16 days	[87]
	P2@IR1061-RGD	4T1	PTT/PDT	- Generating heat to break the azo bonds - R• production even in a hypoxic TME	i.v. injected	97.8% of tumor inhibitory rates	[88]
Fractional laser PDT	FSNC	Hela	PDT	- Generating endoperoxide for ¹O₂ storage with NIR - Producing ¹O₂ without NIR	/	/	[89]

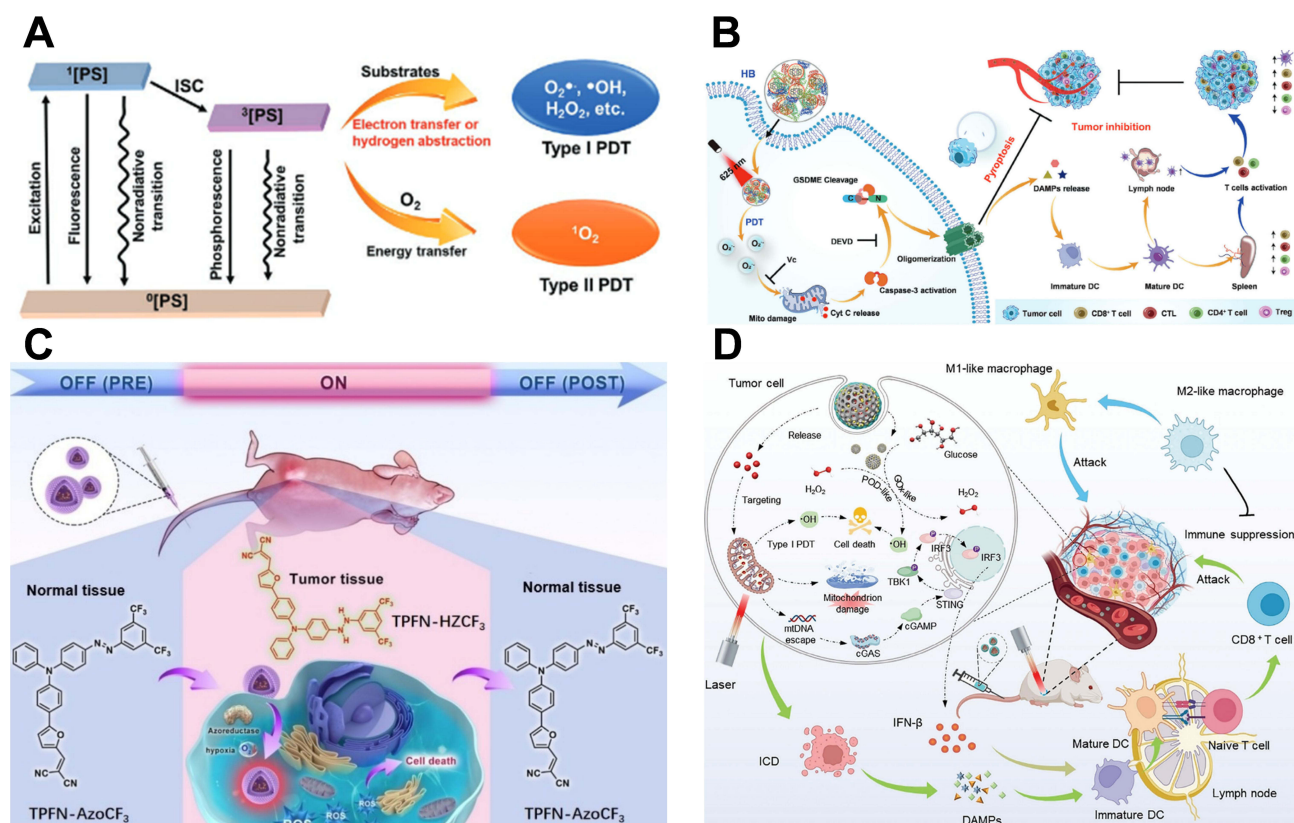


Figure 4 (A) Illustration showing how the Type-I and Type-II PDTs work. Reproduced with permission.⁹⁶ Copyright 2021, Wiley-VCH. (B) Schematic illustration of the tumor inhibition of HB NPs for efficient Type I PDT.⁸³ Reproduced with permission. Copyright 2025, Wiley-VCH GmbH. (C) Schematic illustration of antitumor mechanism of TPFN-AzoCF₃ NPs for overcoming hypoxia. Reproduced with permission.⁸⁴ Copyright 2023, Wiley-VCH GmbH. (D) Schematic depiction of HABH nanoagonist for mitochondrion-targeted Type I PDT. Reproduced with permission.⁸⁵ Copyright 2025, Wiley-VCH GmbH.

normoxic environment while triggering biological reductions in hypoxic environments for tumor cells apoptosis, which had the potential to conquer hypoxia in the future.

Recently, Sun et al designed a chlorosome-mimetic nanoreactor (Ru-Chlos@ABTS) consisting of ruthenium (Ru), chlorosomes, and the prodrug ABTS for efficient cancer photoimmunotherapy (Figure 5B).⁸⁷ Upon red light irradiation, Ru-Chlos could catalyze ABTS to produce cytotoxic free radicals (oxABTS) to achieve phototherapy without consuming any O₂ and H₂O₂. Ru-Chlos@ABTS showed significant tumor inhibition and elimination in vivo, indicating that these biomimetic chlorosomes possessed outstanding O₂-independent advantages.

Carbon radicals are not only highly reactive but also can be produced without O₂.¹⁰⁰ Liu et al fabricated a highly tumor targeting nanoplateform (P2@IR1061-RGD), loading with azo-containing polymer (P2), photothermal dye IR1061 and arginine-glycine-aspartic acid tripeptide (RGD).⁸⁸ Under 1064 nm NIR II laser irradiation, P2@IR1061-RGD was able to degrade and produce photothermal effects to accelerate cytotoxic carbon radical (R•) generation, which disrupted RNA transcription for tumor cells death accurately (Figure 5C).

Generating O₂-unrelated free radicals may not only ignore tumor hypoxia but may also display prominent therapeutic efficacy; however, the low heat transfer efficiency and limited availability of photothermal agents restrict their treatment.

Fractional Laser PDT

Fractional laser PDT possesses the ability to continuously release ¹O₂ compared to traditional PDT and can largely circumvent hypoxia to a certain extent compared to Type I PDT.

For instance, Song et al developed a functional silica nanocarrier (FSNC) composed of protoporphyrin IX derivative, 2-Pyridone derivative, cyanine derivative, and nano-silica carriers for fractional PDT (Figure 5D).⁸⁹ After entering tumor

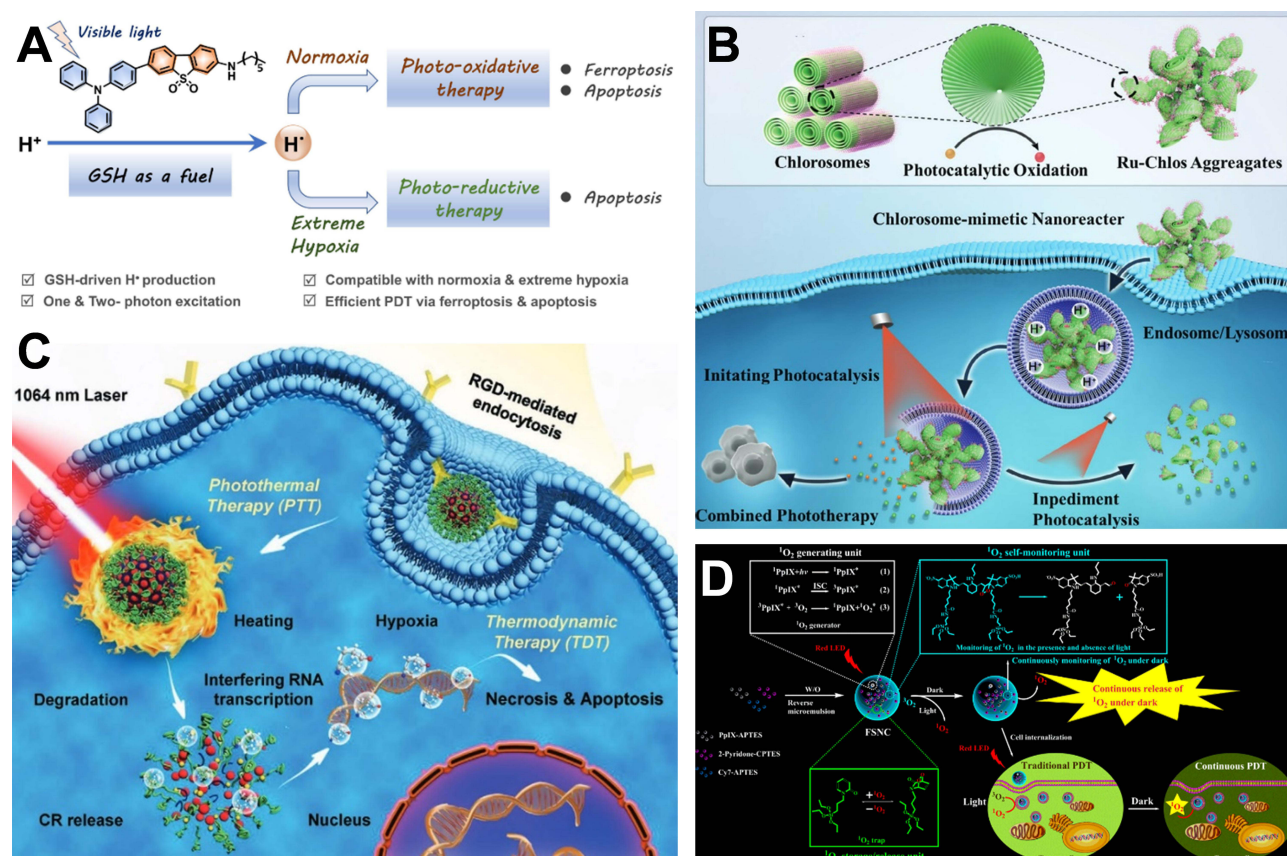


Figure 5 (A) Schematic illustration of the mechanism of H⁺ photogeneration and its function in normoxia and hypoxia environment. Reproduced with permission.⁸⁶ Copyright 2022, Wiley-VCH. (B) Schematic illustration of the mechanism of Ru-Chlos nanoreactors for efficient photoimmunotherapy. Reproduced with permission.⁸⁷ Copyright 2024, Wiley-VCH GmbH. (C) The synthesis of P2@IR1061-RGD nanosystem and the generation of H⁺ under 1064 nm laser to enhance PDT. Reproduced with permission.⁸⁸ Copyright 2021, John Wiley and Sons. (D) Schematic illustration of the mechanism of generation and storage for fractional PDT. Reproduced with permission.⁸⁹ Copyright 2019, American Chemical Society.

cells, protoporphyrin IX derivative produced ¹O₂ to kill tumor cells and formed an endoperoxide to enable ¹O₂ storage upon light irradiation. The stored ¹O₂ could then be released in the absence of light, enabling highly continuous PDT treatment.

Harnessing Hypoxia for Enhanced PDT

Overcoming hypoxia is challenging due to the complex TME and disrupted vasculature. Although existing strategies have shown partial success, PDT consumes oxygen continuously to aggravate hypoxic tumors; thus, it is important to develop more effective strategies to enhance PDT efficacy. Recently, some studies have explored the use of hypoxia for PDT in hypoxic tumors. Hypoxia utilization strategies include (I) hypoxia-activated prodrugs, (II) hypoxia-responsive nanoplatforms, and (III) hypoxic cell sensitizers (Table 3).

Hypoxia-Activated Prodrugs

There is a significant difference in oxygen content between normal and tumor tissues, which can be exploited for tumor-targeted therapy. Hypoxia-activated prodrugs (HAPs) exhibit high cytotoxicity in hypoxic solid tumors but show completely low cytotoxicity in normal tissues.¹⁰⁵ Recently, hypoxia-activated prodrugs, such as banoxantrone, tirazamine (TPZ), and AQ4N, have become a hot topic of research.^{106–108}

Huang et al developed a multifunctional lipid-coated nanomedicine (T₁₀/TPZ@M/IR@L) to achieve synergetic therapy of PDT and hypoxia activated chemotherapy (Figure 6A).¹⁰¹ Under light irradiation, the released photosensitizer IR could produce ROS to further aggravate tumor hypoxia. Meanwhile, TPZ was activated by hypoxia and then possessed more cytotoxicity, leading to enhanced tumor-cell killing.

Table 3 Representative Paradigms of Hypoxia-Activated Prodrugs, Hypoxia-Responsive Nanoplatform and Hypoxic Cell Sensitizers to Utilize Hypoxia

Strategy	Nanoplatforms	Tumor Type	Mode of Cancer Therapies	Molecular Mechanism	Dose of Administration	Therapeutic Efficacy	Ref.
Hypoxia-activated prodrugs	T ₁₀ /TPZ@M/IR@L	4T1	PDT/ Chemotherapy	- Generating ROS to aggravate hypoxia - Activating TPZ in hypoxia	i.v. injected (2 mg kg ⁻¹ of TPZ and 1 mg kg ⁻¹ of IR)	Significant tumor growth inhibition within 15 days	[101]
	PCN-AQ@Z-FA	4T1	PDT/ Chemotherapy	- Releasing AQ4N in acid TME - Activating AQ4N to kill tumor cells in hypoxia	i.v. injected (100 µL, 20 mg kg ⁻¹ of PCN)	Remarkable tumor growth inhibition within 16 days	[102]
Hypoxia-responsive nanoplatform	SPN-TAPP-PCB ₄	Hela	PDT/ Chemotherapy	- Designing hypoxia-cleavable PEG derivative - Releasing toxic Ce6 under hypoxia	i.v. injected (5mg kg ⁻¹ of CB)	Strongly suppress tumor growth within 24 days	[103]
Hypoxic cell sensitizers	ZIF@IR780&GOx	4T1	PDT/PTT	- IR 780 dye generates ROS and hyperthermia - GOx catalyzes the decomposition of glucose to downregulate HSP90 - Amplifying heat-induced cytotoxicity	i.v. injected	Remarkable inhibition within 14 days	[104]

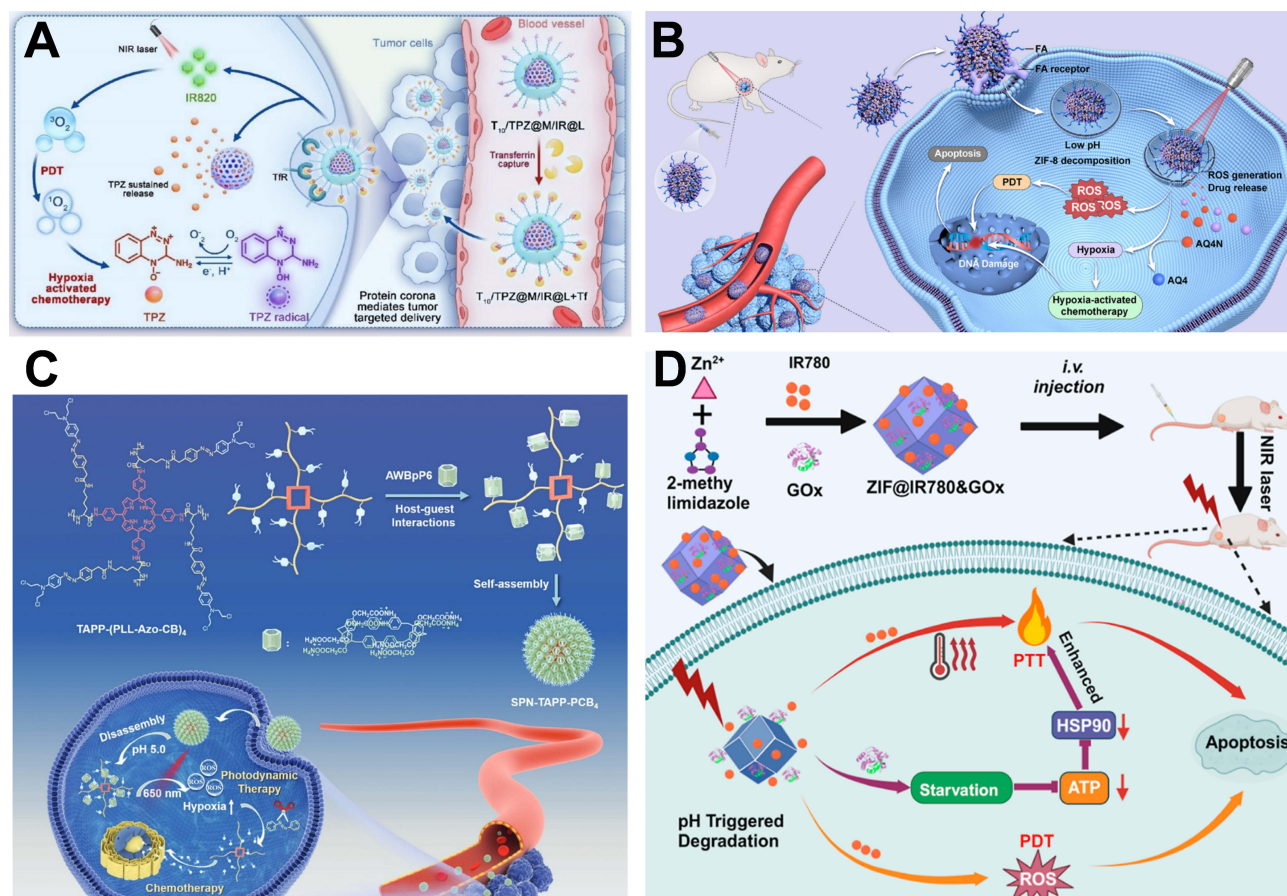


Figure 6 (A) Schematic illustration of the $T_{10}/TPZ@M/IR@L$ mechanism for synergy therapy of PDT and hypoxia activated chemotherapy. Reproduced with permission.¹⁰¹ Copyright 2025, American Chemical Society. (B) Schematic illustration of mechanism of PCN-AQ@Z-FA via a combination of PDT and hypoxia-activated chemotherapy. Reproduced with permission.¹⁰² (C) Schematic illustration showing how the nanomedicine triggered hypoxia-responsive for PDT and chemotherapy treatment. Reproduced with permission.¹⁰³ Copyright 2023, Wiley-VCH GmbH. (D) The preparation and schematic depiction of ZIF@IR780&GOx to suppress tumor for PDT. Reproduced with permission.¹⁰⁴ Copyright 2024, American Chemical Society.

For instance, Chu et al designed a novel hypoxia-activated nano-prodrug (PCN-AQ@Z-FA) to achieve synergy therapy of chemotherapy and PDT (Figure 6B).¹⁰² In this system, a zeolitic imidazolate frameworks (ZIF-8) and AQ4N were encapsulated in the mesopores of metal-organic framework (MOFs). The PCN core, as a photosensitizer, could generate ROS to induce DNA damage. In acid TME, ZIF-8 could decompose and release AQ4N in a controlled manner. Once AQ4N was activated to cytotoxic AQ4, it precisely would inhibit the tumor for chemotherapy.

Hypoxia-Responsive Nanoplatform

Except hypoxia-activated prodrugs, nanoplatforms involving hypoxia-sensitive structures can similarly increase the antitumor effect of nanomedicine. Hypoxia-responsive nanoplatforms are engineered with structures like nitroimidazole, azobenzene, or N-oxide that, upon reaching TME, undergo rapid cleavage to release the encapsulated antitumor drugs.^{103,109–112}

Yi et al fabricated a hypoxia-responsive tetrameric supramolecular polypeptide nanomedicine (SPN-TAPP-PCB₄) to achieve the combination therapy of PDT and chemotherapy.¹⁰³ Upon NIR light irradiation, the 5,10,5',20-tetrakis (4-aminophenyl)-porphine (TAPP) central would generate 1O_2 (Figure 6C). In acid TME condition, SPN-TAPP-PCB₄ was rapidly dissociated. Under hypoxic TME, the disassembly of azobenzene could lead to chlorambucil (CB) release to kill tumor cells, thus achieving a precise and strong antitumor effect.

Although hypoxia-activated prodrugs and hypoxia-responsive nanoplatforms can exploit the hypoxic microenvironment to overcome tumor hypoxia for enhanced PDT antitumor efficacy, their therapeutic impact on deep-seated tumors

remains unsatisfactory. Furthermore, the complexity and heterogeneity of the TME, along with non-uniform hypoxia levels, pose challenges in ensuring the consistent and effective activation of nanodrugs.

Hypoxic Cell Sensitizers

Hypoxic cell sensitizers may enhance lethality by increasing the sensitivity of tumor cells. Yan et al created an innovative nanoparticle (ZIF@IR780&GOx) loaded with IR780 dye and GOx, which led to the synergistic therapy of PDT and PTT (Figure 6D).¹⁰⁴ IR780 dye not only promoted ROS generation but also improved hyperthermia efficacy and accelerated tumor cell death. Meanwhile, GOx could downregulate the expression of heat shock protein 90 (HSP90), thereby sensitizing hypoxic cells.

Conclusion

PDT has emerged as a highly promising non-invasive antitumor modality with distinct advantages over conventional treatments, including high specificity, minimal systemic toxicity, and reduced risk of drug resistance. However, its therapeutic efficacy is severely constrained by tumor hypoxia, which is a core characteristic of TME. Although conventional approaches such as oxygen delivery and in situ oxygen generation provide certain benefits, their passive and uncontrolled nature restricts their therapeutic potential. Against this backdrop, this review emphasizes innovative nanotechnology-based strategies designed to proactively address tumor hypoxia, moving beyond the limitations of traditional oxygen replenishment techniques. Specifically, we explore three principal, mutually complementary avenues: (1) remodeling the hypoxic tumor micro-environment (eg, through increased blood flow, inhibition of mitochondrial respiration, and suppression of the HIF-1 α signaling pathway); (2) circumventing intratumoral hypoxia (eg, via Type-I PDT, oxygen-independent free radical generation, and fractional laser PDT); and (3) harnessing hypoxia as a trigger to enhance PDT efficacy (eg, with hypoxia-activated prodrugs, hypoxia-responsive nanoplateforms, and hypoxic cell sensitizers).

Although nanotechnology-driven strategies have significantly alleviated tumor hypoxia and enhanced PDT efficacy, several critical challenges that constrain their clinical translation remain unresolved. The first and foremost aspect is the long-term biosafety of nanomaterials. Given the complex composition of many nanoplateforms, their inherent toxicity and potential off-target side effects demand systematic and rigorous investigation prior to the initiation of clinical trials, particularly to clarify their long-term biological behaviors (eg, in vivo metabolism, tissue accumulation, and clearance). Thus, more and more scientists have acknowledged the critical importance of biosafety. To this end, they have established degradable green nanoparticle synthesis routes and developed a comprehensive risk assessment framework covering the entire product life cycle.^{113–116} Second, the scalable manufacturing of complex nanoplateforms presents a major hurdle. Addressing this issue requires the integration of advanced nanofabrication technologies, optimized processing protocols, and robust quality control systems, all of which are essential to ensure the consistent production of multifunctional nanostructures that meet clinical standards at an industrial scale.¹¹⁷ Finally, there is interpatient heterogeneity of tumor hypoxia. This variability often results in suboptimal treatment outcomes and may contribute to tumor recurrence and metastasis. To address this challenge, comprehensive and long-term investigations into the effects of hypoxic heterogeneity on treatment outcomes are imperative. Additionally, the formulation of personalized approaches that customize nanotechnology-based PDT according to individual hypoxic characteristics warrants further in-depth exploration.^{118,119}

In summary, this review challenges conventional passive oxygen supplementation strategies by proposing a beyond oxygenation framework that involves remodeling, circumventing and harnessing hypoxia. Based on this, we take a forward-looking perspective on the active hypoxia conquest by nanotechnology, outlining actionable pathways towards PDT enhancement for next-generation cancer treatment. Furthermore, it is widely recognized that addressing the aforementioned critical challenges will serve as a pivotal breakthrough. Such progress holds great promise for enabling precise hypoxia-resistant PDT against hypoxic tumors, thereby advancing the clinical utility of this noninvasive therapeutic modality.

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Disclosure

The authors declare no competing interests in this work.

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