International Journal of Nanomedicine

Dovepress
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REVIEW

# Emerging Nanoplatforms are Effective Against Tumor Hypoxia

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**Abstract:** Hypoxia is a characteristic feature of the solid tumor microenvironment and serves as a pivotal factor in tumor progression, metastasis, and therapeutic resistance. It has long been recognized as a significant barrier to advancing cancer therapy. Although traditional oxygen supplementation strategies can partially enhance local oxygen levels, their effectiveness is limited by the spatiotemporal heterogeneity of tumor tissues, low delivery efficiency, and biosafety concerns, making them inadequate for the precise oxygen regulation required by the complex tumor microenvironment. In recent years, nanotechnology-based platforms designed to alleviate hypoxia have emerged as innovative approaches for remodeling the tumor microenvironment and enhancing multimodal synergistic therapies. These platforms operate through three primary strategies: exogenous oxygen delivery, endogenous oxygen generation, and metabolic oxygen conservation. This review systematically elucidates the underlying mechanisms of tumor hypoxia, summarizes the design principles and recent advancements of related nanomedicines, and discusses the potential and challenges of these platforms in multimodal combination therapies. The study aims to furnish a comprehensive reference for the design of hypoxia-alleviating nanoplatforms and the optimization of synergistic therapeutic strategies, with the objective of providing novel insights and prospects for the development of nanomaterials in this domain.

**Keywords:** tumor hypoxia, tumor microenvironment remodeling, oxygen delivery and generation, nanomedicine, multimodal synergistic therapy

## Introduction

Cancer represents a significant global public health challenge, with approximately 20 million new cases and nearly 10 million deaths occurring annually worldwide.[1] Currently, conventional therapeutic modalities, including surgery, radiotherapy (RT), and chemotherapy, alongside emerging strategies such as targeted therapy, immunotherapy, cellular therapy, and gene therapy,[2] have demonstrated favorable prognostic outcomes for certain patients to some extent. However, their therapeutic efficacy is constrained by various factors, including tumor drug resistance, pronounced heterogeneity, adverse toxic and side effects during treatment, and the regulation of the tumor proliferative microenvironment.[3–5] Among these factors, the pervasive hypoxic condition within the tumor microenvironment (TME) is widely acknowledged as a significant barrier, contributing to therapeutic resistance, malignant progression, and poor clinical prognosis.

Under typical physiological conditions, the average partial pressure of oxygen ($pO_2$) is approximately 40 mmHg. A hypoxic environment is established when the $pO_2$ falls below this threshold.[6] Tumor hypoxia is a common characteristic of most solid tumors, primarily resulting from excessive oxygen consumption due to rapid tumor cell proliferation, in conjunction with impaired oxygen delivery caused by abnormal neovascular structures and inadequate blood perfusion. As a result, the $pO_2$ in tumor tissues remains chronically low, creating a persistent hypoxic microenvironment.[7] This pronounced imbalance between oxygen supply and demand leads to the continuous activation of hypoxia-associated molecular signaling pathways. Among these pathways, hypoxia-inducible factor-1α (HIF-1α) serves as a central regulatory factor, being stably expressed under hypoxic conditions. HIF-1α initiates the transcription of various downstream

https://doi.org/10.2147/IJN.S615263
Received: 8 April 2026
Accepted: 4 June 2026
Published: 15 June 2026

genes involved in tumor adaptation and progression, including vascular endothelial growth factor (VEGF), glucose transporter-1 (GLUT1), and carbonic anhydrase IX (CAIX), among others. These genes play a critical role in angiogenesis, the enhancement of glycolytic pathways, cell proliferation, and immune evasion, among other processes, thereby facilitating tumor invasion and metastasis, therapeutic resistance, and poor prognosis. Hypoxia also significantly alters the immune and stromal composition of the TME, leading to immunosuppression, extracellular matrix remodeling, and further enhancement of therapeutic resistance.[8,9] Additionally, the structurally abnormal and poorly perfused tumor vasculature under hypoxic conditions severely restricts the intratumoral penetration and uniform distribution of therapeutic agents. Elevated interstitial fluid pressure and dense extracellular matrix deposition further impede nanoparticle extravasation and cellular uptake,[7] while the pronounced spatial heterogeneity of hypoxic regions may also compromise the targeting accuracy of ligand-modified nanoplatforms.[10] Consequently, the efficacy of cancer treatment is further limited by inefficient drug delivery and insufficient targeting specificity.[11–13]

In recent years, the application of nanotechnology in clinical therapeutics has expanded significantly, with nanoplatform-based delivery systems offering innovative insights and strategies for modulating the hypoxic TME. Due to their distinctive physicochemical properties, nanomaterials demonstrate exceptional tumor-targeting capabilities, biocompatibility, and responsiveness to the microenvironment. These attributes facilitate not only the nanoscale delivery of small-molecule therapeutics but also the co-encapsulation of multiple therapeutic agents to achieve synergistic treatment effects.[14,15] In addressing tumor hypoxia, a range of nanoplatform-based strategies have been developed. Nevertheless, comprehensive reviews of these emerging technologies are relatively scarce, with limited studies concentrating specifically on nanodelivery as the central enabling technology.

This review adopts a systematic approach to summarize key advancements in the design of nanoplatforms aimed at mitigating the hypoxic TME, with a particular emphasis on research published over the past five years. Additionally, it incorporates several seminal earlier studies to provide a comprehensive developmental context for this field. The review specifically concentrates on three principal strategies: (1) Oxygen-carrying nanoplatforms, which facilitate the delivery of exogenous oxygen to tumor sites using carriers such as perfluorocarbons (PFCs), hemoglobin (Hb), biomimetic materials, or oxygen micro/nanobubbles (MNBs); (2) In situ oxygen-generating nanoplatforms, which continuously produce oxygen within tumors through processes such as hydrogen peroxide catalysis, photocatalysis, water-splitting reactions, microbial catalysis, or biomimetic photosynthesis; and (3) Oxygen-economization nanoplatforms, which aim to decrease oxygen consumption and enhance local oxygen tension by inhibiting mitochondrial respiration, modulating tumor metabolic pathways, or promoting oxygen retention and preferential utilization. Figure 1 illustrates the construction strategies for relevant nanoplatforms aimed at alleviating tumor hypoxia. These strategies have shown considerable potential across various antitumor modalities. This review aspires to offer theoretical insights and practical references concerning structural design, synergistic mechanisms, biological metabolic behaviors, and clinical translation, thereby contributing to the advancement of more effective cancer treatment strategies.

## Pathophysiological Features and Therapeutic Challenges of Tumor Hypoxia

Research into tumor hypoxia can be traced back to the 1950s. In 1953, Gray et al conducted a systematic investigation into the influence of dissolved oxygen concentration in tissues on the efficacy of radiotherapy. They were the first to report that tumor cells exposed to X-rays under well-oxygenated conditions exhibited approximately three times greater radiosensitivity compared to hypoxic cells. This study highlighted the critical role of oxygen in the radiobiological oxygen effect and established the pivotal importance of tissue $pO_2$ in radiobiology.[16] In 1955, Thomlinson and Gray, while examining tumor sections from lung cancer patients, observed necrotic centers within large tumor masses, surrounded by viable tumor cells in close proximity to blood vessels. Based on these observations, they proposed the concept of extensive hypoxic regions within solid tumors. This morphological finding is considered a significant historical milestone in the study of tumor hypoxia.[17] These early studies illuminated the biological importance of hypoxia by examining its impact on radiosensitivity and histological structure, thereby directly catalyzing further investigations into the mechanisms underlying tumor hypoxia.

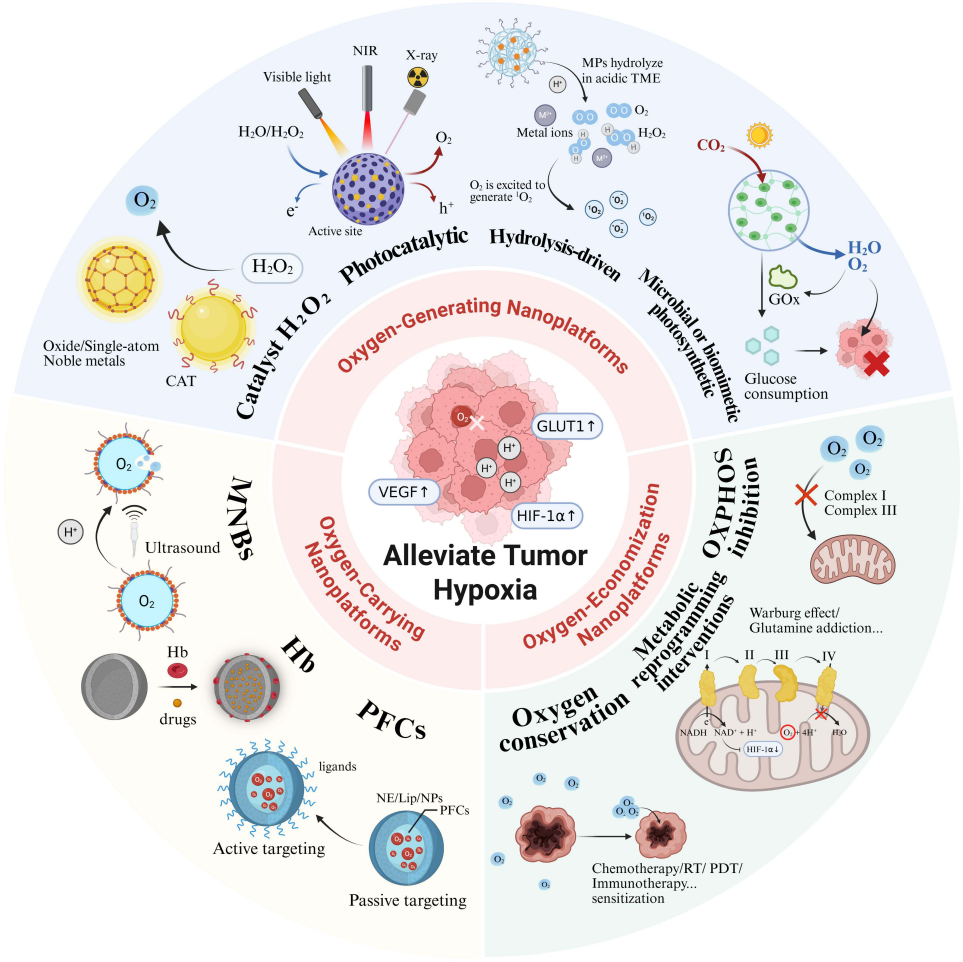


**Figure 1** Schematic diagram of construction strategies for different nanoplatforms to alleviate tumor hypoxia. In this schematic, upward arrows (↑) indicate upregulation of the corresponding biological indicators; downward arrows (↓) indicate downregulation of relevant factors; blunt-ended inhibitory lines represent pathway inhibition; cross symbols denote pathway blockade or suppression of the corresponding factors; the red circle highlights the intracellular oxygen preserved by reduced mitochondrial oxygen consumption following electron transport chain inhibition (Created in BioRender. Yu, (Z) (2026) https://BioRender.com/tzlz2c6).

Subsequent studies progressively unveiled that hypoxia is not merely an incidental occurrence but rather a pervasive characteristic of the TME. At the level of pathological mechanisms, the primary cause of hypoxia is an imbalance between oxygen supply and consumption. On one hand, the rapid proliferation of tumor cells significantly elevates oxygen consumption, surpassing the limited oxygen supply and resulting in the formation of a hypoxic TME in tissue regions. On the other hand, although angiogenesis is highly active in tumors, the newly formed blood vessels often exhibit structural and functional deficiencies, such as vascular tortuosity and dilation, irregular diameters, disorganized branching, collateral circulation, insufficient pericyte coverage, and pronounced vascular leakage. These structural defects collectively diminish the efficiency of blood perfusion and result in a heterogeneous spatiotemporal distribution of oxygen, ultimately causing localized oxygen deprivation.[18–20] As the tumor volume increases, the diffusion distance for oxygen within the tissue extends, leading to persistent hypoxia (ie, $pO_2 < 10$ mmHg) in certain regions of the tumor, particularly those distant from blood vessels.[21] Concurrently, the metabolic reprogramming of tumor cells further aggravates the consequences of hypoxia. Even in conditions where oxygen is sufficiently available, tumor cells preferentially utilize glycolysis for energy production, resulting in the accumulation of lactate and protons, which causes local acidification. This acidic microenvironment impairs the function of vascular endothelial cells, exacerbates perfusion disorders, and enhances the metabolic adaptation, survival, invasion, metastasis, immune evasion, and drug resistance of tumor cells.[22,23] Importantly, hypoxia within tumors is not a static condition but rather exhibits a cyclic and fluctuating nature. This unstable oxygen supply further intensifies tumor heterogeneity and resistance to therapy.[21]


https://doi.org/10.2147/IJN.S615263

Persistent or cyclic hypoxic TMEs initiate a series of molecular and cellular adaptive mechanisms that support the survival and proliferation of tumor cells under hypoxic conditions. Numerous studies have demonstrated that HIF-1α plays a central role in facilitating tumor progression. In hypoxic conditions, HIF-1α evades hydroxylation and ubiquitination, resulting in its stable accumulation in the cytoplasm. Subsequently, it translocates into the nucleus, where it dimerizes with HIF-1β and binds to hypoxia response elements (HREs). This binding activates a wide array of target genes associated with angiogenesis (eg, VEGF), glycolytic metabolic reprogramming (eg, GLUT1), cell survival and invasion (eg, C-X-C chemokine receptor type 4, CXCR4), and immune evasion (eg, cluster of differentiation 47, CD47), among others. Collectively, these mechanisms enable cancer cells to maintain proliferation and advance malignancy under hypoxic conditions.[24–26]

In addition to its direct impact on tumor cells, hypoxia significantly alters the immune and stromal composition of the TME. Hypoxic stress inhibits the infiltration and cytotoxic functions of $CD8^+$ T cells and natural killer (NK) cells, while facilitating the polarization of tumor-associated macrophages (TAMs) towards an immunosuppressive M2-like phenotype.[27,28] Concurrently, hypoxia orchestrates the recruitment of regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), actions that collectively establish a niche conducive to tumor immune evasion.[29,30] Furthermore, stromal elements such as cancer-associated fibroblasts (CAFs) become activated under hypoxic conditions, contributing to extracellular matrix remodeling and desmoplasia, which exacerbate intratumoral transport barriers and resistance to therapy.[31,32] Hypoxia also compromises DNA damage repair pathways, increases genomic instability and mutation frequency, and significantly enhances resistance to RT, chemotherapy, and photodynamic therapy (PDT).[33] The key characteristics of the hypoxic TME and the associated therapeutic challenges are illustrated in Figure 2.

Within the hypoxic TME, tumor cells progressively develop increased plasticity and resistance to stress, establishing hypoxic regions as prevalent "niches" for tumor invasion, metastasis, and recurrence. Studies suggest that tumor metastasis accounts for approximately 90% of cancer-related mortalities. The hypoxic microenvironment facilitates the

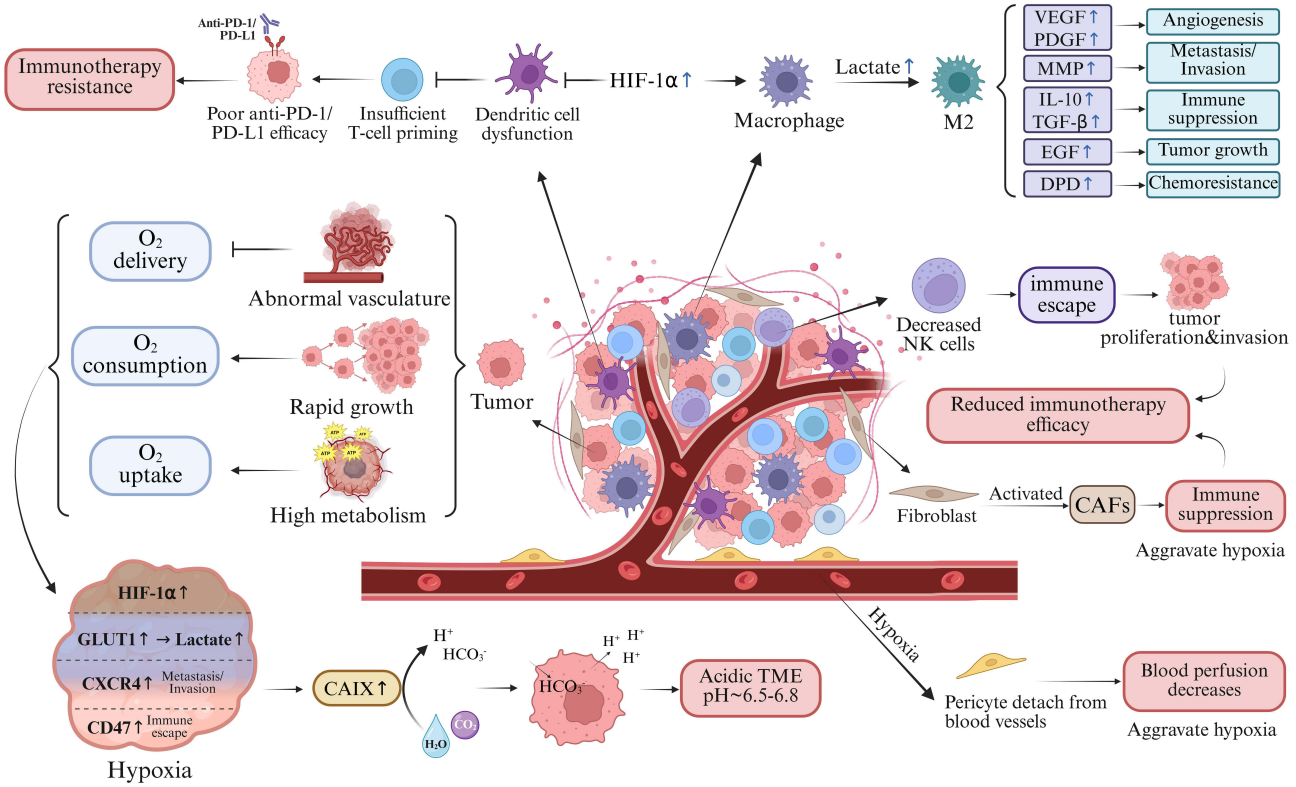


**Figure 2** Schematic illustration of core characteristics and therapeutic challenges of the tumor hypoxic microenvironment. In this schematic, solid arrows indicate activation, promotion, directional regulation, and cascading progression of biological processes; blunt-ended inhibitory lines represent blockade, suppression, or impairment of cellular activities and signaling pathways; upward arrows (↑) indicate elevated levels or upregulation of key molecules, cytokines, and pathological factors (Created in BioRender. Yu, (Z) (2026) https://BioRender.com/dy66oz5).

transition of non-cancerous cells from an epithelial to a migratory phenotype by activating the hepatocyte growth factor (HGF)/c-MET signaling pathway. This process reduces tumor cell adhesiveness and significantly enhances tumor invasion and metastasis. Elevated levels of HIF-1α under hypoxic conditions promote c-MET transcription, augment stromal HGF signal transduction, increase tumor cell sensitivity to HGF, and enhance their capacity to detach from the primary tumor and enter the circulatory system. Concurrently, this signaling pathway contributes to the degradation of the extracellular matrix and the epithelial-to-mesenchymal transition, further intensifying tumor cell migration.[34–36]

Tumor hypoxia significantly compromises the therapeutic efficacy of RT, PDT, chemotherapy, immunotherapy, and other treatment modalities, presenting a fundamental challenge in contemporary cancer management. Hypoxia is not only an intrinsic characteristic of the TME but also a dynamically evolving obstacle throughout the treatment process. Under hypoxic conditions, the production of reactive oxygen species (ROS), which is essential for the mechanism of radiotherapy, is inhibited. Consequently, hypoxic tumors exhibit inherent radioresistance, leading to substantially diminished radiosensitivity.[37] PDT is a minimally invasive treatment strategy that utilizes a photosensitizer (PS) activated by light of specific wavelengths to transfer energy or electrons to molecular oxygen, thereby producing cytotoxic ROS, particularly singlet oxygen ($^1O_2$). These ROS cause oxidative damage to cellular components, ultimately resulting in tumor cell death. Given that molecular oxygen is a critical substrate for ROS generation, the therapeutic efficacy of PDT is highly contingent upon the availability of local oxygen.[38] During PDT, hypoxia poses a dual challenge. Initially, the low $pO_2$ limits the efficiency with which photosensitizers are converted into ROS. Furthermore, the PDT process itself rapidly depletes local oxygen levels, while photodynamically induced microvascular embolism and occlusion further impede the supply of exogenous oxygen, exacerbating the condition into a more severe state of "secondary hypoxia". This locally induced hypoxia not only directly restricts the sustained production of ROS but also activates HIF-1α-mediated autophagy as a cytoprotective mechanism. Consequently, this promotes multidrug resistance in tumors and significantly reduces the overall therapeutic efficacy of PDT.[39] In the context of chemotherapy, low $pO_2$ decreases the likelihood of oxidative stress, thereby impairing drug uptake and cellular response. Additionally, the structural abnormalities of tumor neovasculature under hypoxic conditions compromise drug bioavailability, collectively diminishing therapeutic effectiveness.[40] Hypoxia also induces tumor cells to secrete immunosuppressive factors, which inhibit T cell activation and facilitate immune evasion by cancer cells, thereby increasing the risk of immunotherapy failure.[41] Consequently, effectively mitigating the hypoxic TME constitutes a significant advancement in overcoming the complex challenges induced by hypoxia. Additionally, it offers a crucial opportunity for the development of combination therapies.

## Oxygen-Carrying Nanoplatforms for Tumor Hypoxia Alleviation

The development of efficient oxygen carriers for the direct delivery of oxygen to hypoxic TMEs constitutes a highly effective and straightforward strategy with profound implications for the enhancement of cancer therapy. The central approach involves the engineering of materials with high oxygen solubility or oxygen-carrying capacity, which are incorporated into nanoplatforms. These platforms can be delivered to tumor sites with efficiency and safety, where they gradually release oxygen to increase local $pO_2$ and alleviate hypoxia. Hyperbaric oxygen therapy (HBOT), a commonly used clinical approach at present, can temporarily increase the $pO_2$ in blood and tissues. However, due to the abnormalities in tumor blood vessels and insufficient perfusion, it fails to penetrate the core regions of tumors effectively.[42] Consequently, researchers have concentrated on artificial oxygen carriers to develop more efficient targeted nanoformulations. These nanoplatforms typically employ PFCs, Hb, or MNBs to encapsulate oxygen molecules within the carrier via physical dissolution or non-covalent binding. Through ongoing modification and optimization of these structures, researchers have devised various direct oxygen-carrying nanoplatforms with diverse targeting capabilities. These platforms present distinct advantages and challenges in terms of oxygen loading efficiency, release mechanisms, and synergistic therapeutic potential. The subsequent sections will provide a detailed elaboration and comparison of these platforms.

### Perfluorocarbon-Based Oxygen-Carrying Nanoplatforms

PFCs constitute a category of inert organic compounds characterized by the substitution of all hydrogen atoms in the hydrocarbon backbone with fluorine atoms. This substitution results in the formation of carbon-fluorine bonds, which

possess exceptionally high bond energies. Consequently, PFCs exhibit remarkable chemical stability, excellent biocompatibility, and extremely low surface energy.[43] In their liquid state, PFCs display weak intermolecular cohesion and substantial free volumes between molecules, facilitating the accommodation of significant quantities of gas molecules. The solubility of gases in PFCs is considerably higher than in water or plasma, with oxygen solubility being approximately 20 times greater than that in water. These properties render PFCs highly suitable as artificial oxygen carriers.[44] The potential of PFCs to support mammalian survival was first demonstrated in a liquid breathing experiment conducted by Leland C. Clark and Frank Gollan in 1966, which pioneered the research trajectory of employing PFCs as artificial oxygen carriers.[45] During the mid-to-late 1960s, PFCs were progressively investigated as potential blood substitutes and imaging contrast agents, undergoing numerous rounds of clinical validation in the ensuing decades. Despite initial clinical applications being constrained by dosage limitations, inadequate stability, and suboptimal oxygen release efficiency, these early endeavors undeniably established the groundwork for subsequent advancements in the use of PFCs for oxygen delivery.[46] With the emergence of nanotechnology, researchers have employed strategies such as emulsification and surface modification to encapsulate PFCs within stable nanocarriers. These innovations confer upon PFCs an extended in vivo circulation time, improved tumor-targeting accumulation capacity, and regulated oxygen release performance. Consequently, this evolution has broadened the application of PFCs beyond their initial roles as blood substitutes and imaging agents to include the mitigation of tumor hypoxia and enhancement of therapeutic sensitization, particularly in oxygen-dependent treatment modalities such as RT, PDT, and immunotherapy.[47]

In the domain of nanomedicine, research concerning PFCs is predominantly concentrated on three key areas: (1) augmenting the aqueous solubility and stability of PFCs to facilitate prolonged systemic circulation and effective tumor accumulation in vivo; (2) advancing the controllability and precision of oxygen release via surface modification or external stimuli; and (3) integrating PFCs with functional modules, such as pharmaceuticals, photosensitizers, or immunomodulators, to develop multifunctional synergistic therapeutic platforms.[48–50] Recent studies on PFC-based nanoplatforms have demonstrated significant advancements in tumor oxygenation within animal models, thereby substantially enhancing therapeutic efficacy and potentially overcoming hypoxia-induced drug resistance.

## Passive Tumor-Targeting PFC-Based Nanoplatforms

The fundamental mechanism underpinning passively targeted PFC-based nanoplatforms is their exceptional oxygen solubility. The porous molecular architecture of PFCs facilitates the ingress of oxygen molecules into the liquid PFC core through the process of physical dissolution. These nanoplatforms preferentially accumulate at tumor sites via the enhanced permeability and retention (EPR) effect. Subsequently, driven by the $pO_2$ gradient, the dissolved oxygen is gradually released at the tumor site. This release elevates the local $pO_2$, mitigates hypoxia, and downregulates hypoxic signaling pathways, such as HIF-1α. Consequently, this process augments the efficacy of therapies that are dependent on oxygen.[49]

Nanoemulsions are recognized as one of the most traditional and extensively utilized carrier systems for PFCs. Concurrently with the development of PFCs, emulsification technology has transitioned from its origins in the food industry to applications within the pharmaceutical sector. In 1996, the term nanoemulsion (NE) was first introduced in the scientific literature to characterize droplets with diameters in the nanometer range, gradually supplanting earlier terminology such as “miniemulsion” and establishing a standardized definition for dispersed systems of nanoscale droplets.[51] Nanoemulsions are kinetically stable colloidal dispersions comprising two immiscible liquids. Research has indicated that PFC-based nanoemulsions are typically formulated through high-energy emulsification techniques, such as microfluidization or ultrasonic emulsification, and are stabilized using emulsifiers like phospholipids, polymers, or proteins, with droplet sizes generally below 500 nm. The small droplet size and capacity to solubilize highly hydrophobic drugs render nanoemulsions an effective drug delivery system, offering enhanced bioavailability.[48,52]

Katarina et al designed an oxygen-carrying perfluorocarbon nanoemulsion (PFC-NE) composed of 60% (w/v) perfluorooctyl bromide (PFOB) and perfluorododecyl bromide (PFDB), stabilized by egg yolk phospholipids (EYPs), with a particle size below 200 nm. Upon intravenous administration, the PFC-NE accumulates in tumor tissues through the EPR effect. When combined with 60% oxygen inhalation, it significantly increases intratumoral $pO_2$ and downregulated HIF-1α expression. Moreover, PFC-NE reduces adenosine accumulation and subsequently inhibits the

immunosuppressive A2AR→cAMP→PKA signaling pathway, thereby enhancing the infiltration and activity of anti-tumor $CD8^+$ T cells and NK cells, ultimately leading to the suppression of tumor growth.[53] Similarly, Yun et al engineered nanodroplets consisting of a perfluorooctyl bromide (PFOB) core, which was encapsulated by a composite of lecithin and DPPE-PEG, resulting in an average particle size of approximately 250 nm. These nanodroplets demonstrated preferential accumulation in tumor tissues via the EPR effect within 24 hours following administration, leading to a significant increase in local $pO_2$ levels. Quantification of hypoxia using $^{18}$F-FAZA PET imaging indicated that the reoxygenation efficacy of the PFOB nanodroplets was comparable to that achieved through conventional carbogen breathing. This finding substantiates that passive PFC-based nanoplatforms are capable of independently facilitating effective tumor reoxygenation, even in the absence of supplemental exogenous oxygen.[47] Moreover, the utilization of low-dose PFC nanoemulsions has been increasingly expanded, demonstrating significant potential in imaging and diagnostic applications. Shin et al employed $^{19}$F-MRI to track the intratumoral distribution of PFC nanoemulsions (PFCNE) and applied them to guide high intensity focused ultrasound (HIFU) tumor ablation. This approach allowed for the quantitative assessment of the correlation between the accumulated concentration of PFCNE in the tumor and the resulting therapeutic outcomes.[54] High-concentration PFC nanoemulsions (M2F8H18/PFCE NE, approximately 200 nm) have been applied for $^{19}$F-MRI imaging, demonstrating long-term stability and the ability for passive tumor targeting.[55]

Liposomes, among the earliest nanodelivery systems to achieve clinical translation, are spherical entities characterized by a hydrophilic core surrounded by a bilayer membrane composed of amphiphilic lipid materials, predominantly phospholipids.[56] These structures demonstrate high biocompatibility, adjustable particle size and surface characteristics, and the capacity to encapsulate both hydrophilic and hydrophobic substances, rendering them highly suitable for applications in drug delivery, imaging, and tissue-targeted therapies. In contrast to normal capillary structures, the endothelial cells within the tumor microvasculature possess unique pore sizes. Consequently, by optimizing the dimensions of liposomes to facilitate extravasation into tumor tissues while preventing their escape from normal tissue capillaries, passive tumor targeting can be achieved. Liposomes offer a stable and low-toxicity encapsulation environment, which can significantly extend the plasma residence time of liquid PFCs and inhibit their droplet aggregation or rapid clearance in vivo. This positions them as one of the most promising strategies for PFC delivery in passive targeting oxygen supply applications.

Xu et al encapsulated perfluorohexane (PFH), a PFC with high oxygen solubility, into liposomes (Lip(PFH)) with an average particle size of approximately 200 nm. In vivo study results showed that Lip(PFH) could passively accumulate in tumors after intravenous injection, and significantly enhance the tumor suppressive effect of X-ray RT without the need for additional oxygen inhalation, while inducing no obvious toxicity in major organs. Compared with the previously reported perfluorocarbon emulsions for radiosensitization, Lip(PFH) exhibited a markedly improved therapeutic efficacy.[57]

Liang et al devised a technique to encapsulate liquid perfluorooctyl bromide (PFOB) within porphyrin-grafted lipid (PGL) matrices using ultrasonic dispersion, thereby creating self-oxygenating PDT nanoparticles ($O_2$@PFOB@PGL NPs) that integrate both a photosensitizer and oxygen. Due to the robust hydrophobic interactions between PFOB and PGL molecules, this system achieved an exceptionally high PFOB core loading efficiency of 98.15% and a substantial porphyrin loading efficiency of 38.5%. Transmission electron microscopy (TEM) analysis demonstrated that the PFOB@PGL NPs exhibited a highly uniform spherical morphology, with an average particle size ranging from 10 to 30 nm. Such small nanoparticles with a narrow size distribution facilitated their passive accumulation in tumor tissues through the EPR effect. Furthermore, $O_2$@PFOB@PGL NPs formed after oxygen capture could passively accumulate in hypoxic tumors and release oxygen sustainably without external stimulation, thus significantly alleviating tumor hypoxia. Interestingly, the ordered arrangement of porphyrins and alkyl chains in PGL NPs not only ensured the high efficiency of $^1O_2$ generation but also reduced the fluorescence quenching of porphyrins, endowing PGL NPs with strong fluorescence. This structural configuration enhanced the efficiency of $^1O_2$ production, thereby augmenting the therapeutic efficacy of PDT in inhibiting tumor growth and metastasis in the HT-29 colorectal cancer liver metastasis model. Furthermore, the nanoparticles served as a fluorescent and CT bimodal contrast agent for visualizing nanoparticle accumulation, guiding the timing of light irradiation to achieve precise irradiation and reduce damage to surrounding tissues. This study exemplifies the direct delivery of PFCs to proximal sites, utilizing them as an in vivo oxygen reservoir to overcome the

hypoxic limitations of PDT, thereby providing a significant theranostic strategy for the treatment of colorectal cancer and other malignancies.[58]

In terms of clinical visualization and long-term tracking, Liu et al reported a silica-lipid-based PFC nanocomposite (SSNP). This platform co-encapsulated perfluorohexane (PFH) and superparamagnetic iron oxide (SPIO) nanoparticles in a silane-lipid hybrid shell, forming a nanotheranostic platform for MRI-guided high-intensity focused ultrasound (HIFU) tumor therapy. The nanocomplex exhibits both the liquid-phase oxygen storage capability of PFH and the MRI contrast enhancement properties of SPIOs, facilitating real-time MRI monitoring of nanoparticle distribution within tumors, both pre- and post-treatment. The findings of the study further revealed that SSNPs could augment HIFU-induced tumor ablation. Moreover, the integrated imaging and therapy functionality allowed more precise control over both drug administration and irradiation timing, as image-guided optimization improved therapeutic accuracy and reproducibility.[59]

Additionally, Ren et al synthesized perfluorocarbon-modified Pluronic F127 (PFC-F127) as a carrier for the co-delivery of the photosensitizer chlorin e6 (Ce6) and the ferroptosis inducer sorafenib (Sor), resulting in a self-oxygenating nanomicelle platform (Ce6-Sor@PFC-F127). Benefiting from the high oxygen solubility of PFC groups on the micellar surface, this nanoplatform achieved self-oxygenation and increased surface hydrophobicity, thus promoting cellular uptake by cancer cells. In vivo tumor models demonstrated that the PFC-F127 formulation effectively enabled the synergistic delivery of Ce6 and Sor, markedly augmenting the combined efficacy of PDT and ferroptosis through ROS generation. This integrated strategy ultimately resulted in cancer cell death upon laser irradiation. The oxygen-loading strategy elucidated in this study holds significant promise for integrated anticancer therapies.[60]

In addition to directly leveraging the physical oxygen-carrying capacity of PFCs, several studies have extended and intensified reoxygenation effects by modulating tumor hemodynamics. Zhou et al reported an albumin-coated PFC nanoparticle system (PFTBA@HSA) and proposed a representative "two-stage oxygen delivery" mechanism. Following intravenous administration, the system first enabled a rapid initial increase in local tumor oxygen levels through passive release of highly dissolved oxygen from the PFC core. Subsequently, the PFC nanoparticles enhanced tumor blood flow and promote the infiltration of red blood cells (RBCs) into tumor tissues, facilitating a second stage of oxygen delivery. Interestingly, PFTBA@HSA exhibited no significant impact on hemoglobin content or RBC infiltration in normal tissues, including the heart, liver, spleen, lungs, and kidneys. Benefiting from this synergistic process, PFTBA@HSA significantly alleviated tumor hypoxia and markedly enhanced RT efficacy across multiple tumor models without the need for exogenous hyperoxia or carbogen breathing. This study demonstrates that PFTBA@HSA can function not only as short-term oxygen reservoirs for direct oxygen supplementation but also as modulators that cooperate with physiological oxygen delivery systems to achieve more sustained and stable tumor reoxygenation, providing important insights for the functional expansion and clinical translation of passive oxygen-delivering nanoplatforms.[61]

## Active Tumor-Targeting PFC-Based Nanoplatforms

While the EPR effect has traditionally been considered the primary mechanism for nanocarrier accumulation in tumors, increasing evidence indicates significant heterogeneity in clinical tumor presentations.[62–64] This heterogeneity is particularly pronounced in solid tumors characterized by inadequate angiogenesis, dense stromal components, or extensive necrotic areas, thereby challenging the efficacy of passive targeting strategies. Numerous reviews have highlighted that to address the constraints imposed by tumor vascular architecture, stromal barriers, and elevated interstitial fluid pressure on the distribution and penetration of nanoparticles, active targeting has emerged as a pivotal strategy in the development of next-generation nanomedicine carriers.[65–68]

Active targeting PFC-based nanoplatforms achieve selective recognition of tumor-associated epitopes or receptors either by introducing ligands (eg, antibodies, peptides, glyco/polysaccharide receptor ligands, oligonucleotide aptamers, etc.) onto the PFC-based core or its encapsulating shell, or through surface chemical post-modification. These ligands exhibit specificity in binding to receptors or molecular markers that are overexpressed on tumor cells, stromal cells (including endothelial cells, tumor-associated macrophages (TAMs), and tumor-associated fibroblasts (TAFs)), as well as noncellular extracellular matrix components. This targeted approach significantly enhances the accumulation of nanocarriers within the TME, thereby improving oxygen transport efficiency and augmenting the sensitization effects of subsequent RT, PDT, or immunotherapy.[66,69–71]

In the realm of active targeting strategies, receptor-based ligand functionalization emerges as a particularly intuitive and extensively employed approach. An illustrative example of this is the nanoparticle system ($O_2$@FHA@PFC NPs) developed by Wang et al, which employs hyaluronic acid (HA) as a targeting ligand. In this system, the PFCs were pre-saturated with oxygen. By leveraging the specific interaction between HA and the overexpressed CD44 receptors, the accumulation of PFC nanocarriers at the tumor site is significantly enhanced, thereby markedly prolonging the duration of oxygen release. RT is a prevalent clinical treatment modality that eradicates tumor cells by inducing DNA damage through ionizing radiation, with its therapeutic efficacy being largely contingent upon the oxygen levels within tumor tissues.[72] Tumor hypoxia can significantly weaken the oxygen fixation effect of radiation-induced DNA damage, making the resulting lesions more susceptible to cellular repair and consequently leading to radioresistance.[73,74] In vivo studies have demonstrated that this system facilitates precise oxygen delivery to tumors through the active targeted binding of HA to CD44 receptors on the tumor surface, significantly mitigating the hypoxic condition. When combined with RT, the tumor growth inhibition effect was nearly threefold greater than that observed with RT treatment alone, with no significant systemic toxicity detected. These findings suggest that active targeting of oxygen delivery can effectively enhance the therapeutic efficacy of RT in the treatment of hypoxic tumors.[75]

Folate receptors (FR) exhibit a high affinity for binding with folic acid (FA) and facilitate its intracellular transport through receptor-mediated endocytosis.[76] Li et al designed FR-targeted nanoparticles (FRNPs) consisting of a liquid perfluorooctyl bromide (PFOB) lipid core and a targeted shell chemically conjugated with FA and polyethylene glycol (PEG), with an average particle size of approximately 300 nm. Due to PEG modification, FRNPs retained their targeting affinity for FR while exhibiting reduced uptake by reticuloendothelial system (RES) macrophages. Fluorescence imaging in xenograft tumor models demonstrated that FRNPs could accumulate in FR-overexpressing tumors and extravasate through the endothelial gaps of tumor vasculature, thus enabling targeted therapy for FR-positive malignancies.[77] Tseng et al combined FA as a targeting ligand with fluorinated polymeric micelles (PFFA) to develop PFFA-Ce6, a nanocarrier for delivering the hydrophobic photosensitizer Ce6. These fluorinated micelles exhibited a low critical micelle concentration, excellent stability and markedly enhanced oxygen-carrying capacity, which significantly promoted intracellular $^1O_2$/ROS generation and augmented PDT cytotoxicity. Furthermore, they enhanced PDT efficacy under hypoxic conditions through oxygen supplementation from the PFC phase, positioning them as a promising platform for oxygen delivery to cancer cells to mitigate hypoxic microenvironments.[78]

In recent years, cell membrane-coated nanocarriers have garnered significant attention in the realm of active targeted tumor delivery. This innovative approach imparts nanocarriers with the surface protein composition and biological recognition properties characteristic of natural cell membranes, thereby conferring immune evasion capabilities and homotypic targeting advantages within the complex in vivo microenvironment. Consequently, this strategy markedly enhances the efficiency of tumor accumulation. Building on this concept, Fang et al developed a cancer cell membrane-coated PFC nanoparticle (CCm-HSA-ICG-PFTBA) with a particle size of 131.3 ± 1.08 nm. In this construct, PFTBA functions as the oxygen-carrying core, while the membrane coating augments the homotypic targeting capability towards corresponding tumors. In this study, $^{18}$F-FMISO PET/CT imaging and immunohistochemical analysis demonstrated that the nanocarrier significantly increased the $pO_2$ in tumors at 24 hours post-injection. Following administration, near-infrared (NIR) irradiation markedly inhibited tumor growth in triple-negative breast cancer in vivo, with the treatment group exhibiting the lowest tumor volume and weight. The efficacy of PDT was further enhanced by oxygen delivery, without observable systemic toxicity. This example highlights an integrated strategy combining biomimetic membrane targeting, PFC-mediated oxygen delivery, and PDT, simultaneously addressing both oxygen supply and tumor specificity, representing a key advancement in actively targeted PFC nanocarriers.[79] Wang et al developed a PFC-based nanocarrier, CmPF, with a particle size of 150.17 ± 4.13 nm, capable of delivering oxygen to the TME and monitoring immunotherapy efficacy via PET imaging. In this work, a biomimetic oxygen-carrying platform CmPF was constructed by coating PFTBA nanoparticles with cancer cell membranes (CCm) derived from murine Lewis lung cancer (LLC) cells. This platform enhanced the accumulation of oxygen carriers within tumor tissues and enabled quantitative real-time in vivo imaging of TME improvements following oxygen delivery. Utilizing Granzyme B PET/CT imaging to assess alterations in immune-mediated cytotoxic activity, the findings revealed that the combination of CmPF with immunotherapy markedly suppressed tumor progression in mouse models compared to immunotherapy alone. The treatment elevated

the expression of effector immune cell markers, suggesting that oxygen delivery alleviated the hypoxia-induced immunosuppression. This strategy shows potential for overcoming resistance to immune checkpoint inhibitors (ICIs) and for precise stratification of tumor immune responses, paving the way for personalized cancer therapy.[80]

Sonodynamic therapy (SDT) is a noninvasive tumor treatment strategy that employs ultrasound to activate sonosensitizers, generating ROS to kill tumor cells and induce immunogenic cell death (ICD), thus releasing tumor-associated antigens and activating antitumor immunity.[81,82] To address the challenges posed by tumor hypoxia in SDT and immunotherapy, Zhang et al developed a targeted nanosystem, DPPM@HA, by encapsulating oxygen-carrying PFCs and the STING agonist DMXAA within PCN-222-Mn metal-organic frameworks (MOFs), followed by surface modification with HA. Within this system, PCN-222-Mn served as an effective sonosensitizer for ROS production during SDT. The high-valent manganese within the MOFs was reduced in the glutathione (GSH)-rich intracellular environment of tumor cells to release $Mn^{2+}$, which worked in synergy with DMXAA to activate the STING-TBK1-IRF3 signaling pathway. The STING pathway, a pivotal connection between innate and adaptive immunity, can substantially enhance antitumor immune responses upon activation.[83] Upon ultrasound stimulation, PFC enabled controlled oxygen release, effectively alleviating the hypoxic TME, thereby significantly enhancing sonodynamic ROS generation and promoting ICD of tumor cells. Both in vitro and in vivo experiments demonstrated that DPPM@HA efficiently accumulates within tumor tissues. When used in conjunction with ultrasound, it markedly downregulated intratumoral HIF-1α expression, promoted the infiltration of $CD8^+$ T cells, and reduced the presence of Tregs and M2-type macrophages, thus achieving a remodeling of the immune microenvironment. In models bearing 4T1 tumors and bilateral tumors, the combination of DPPM@HA and ultrasound significantly inhibited tumor growth and induced apoptosis. Further combination with a PD-1 inhibitor elicited a durable systemic antitumor immune response and enhanced immune memory, demonstrating excellent antimetastatic efficacy in lung metastasis models. By integrating active targeting, PFC-based oxygen delivery, SDT, and STING pathway activation, this study proposes a novel nanotherapeutic strategy to reverse tumor hypoxia and amplify the efficacy of sonodynamic immunotherapy.[84]

In summary, PFC-based nanoplatforms offer distinct advantages in augmenting oxygen delivery to tumor tissues, mitigating local hypoxia, and enhancing therapeutic efficacy in treatments associated with hypoxic conditions. These benefits are largely attributable to their high oxygen solubility and the potential for targeted delivery through ligand modification or biomimetic interfacial engineering. Nonetheless, despite the promising outcomes observed in experimental settings, the clinical translation of PFC-based nanoplatforms has been considerably delayed, encountering substantial challenges. These limitations are fundamentally rooted in the intrinsic biophysical properties of the nanoplatforms. Firstly, PFCs demonstrate pronounced hydrophobic and lipophobic characteristics, resulting in exceptionally high interfacial tension with aqueous phases and commonly utilized biological surfactants. This interfacial instability poses significant challenges in the fabrication of long-term stable PFC nanoemulsions. Particularly within the complex in vivo circulatory environment, high shear forces and competitive displacement by endogenous lipoproteins often lead to Ostwald ripening or demulsification of the formulation, consequently resulting in uncontrolled oxygen release kinetics. For example, Fluosol-DA, an early PFC emulsion tested in clinical settings, experienced poor long-term storage stability and performance degradation due to inadequate interfacial stability and flocculation during storage, which was considered a major factor contributing to its clinical failure.[85,86] Second, in the complex biological environment in vivo, PFC nanoplatforms readily undergo adsorption of plasma proteins, leading to the formation of a protein corona. This phenomenon modifies their surface physicochemical properties and influences cellular uptake pathways, thereby facilitating recognition and clearance by the mononuclear phagocyte system (MPS). As a result, there is a decrease in targeting efficiency and a potential increase in immunological risks.[87]

While ligand functionalization or multifunctional surface modifications can enhance targeted recognition, they often alter the interfacial stability between the PFC core and its shell. This compromise can negatively impact the oxygen loading capacity and release kinetics, potentially undermining the high-efficiency oxygen-carrying characteristics that are fundamentally dependent on physical dissolution mechanisms.[46] Furthermore, PFC-based systems rely on a "physical dissolution-diffusion" mechanism for oxygen loading and release, and their oxygen delivery behavior inherently lacks active regulatory capability. Within the highly heterogeneous and dynamically evolving TME, this passive mode of oxygen delivery is unable to achieve precise spatiotemporal oxygen distribution aligned with therapeutic requirements,

thus constraining its sustained sensitization efficacy in RT, PDT, and SDT. These challenges have been consistently emphasized in recent systematic and critical reviews that address the translational bottlenecks of PFC-based artificial oxygen carriers (AOCs). The relevant literature indicates that current mainstream PFC formulations continue to exhibit significant limitations regarding compositional complexity, biological stability, and scalable manufacturing, which are the primary factors impeding their clinical advancement.[88] Therefore, future research on PFC-based oxygen-carrying nanoplatforms urgently needs to further simplify formulation compositions, optimize interfacial stability, and establish quantifiable in vivo oxygen supply evaluation systems while maintaining high-efficiency oxygen-carrying and release performance. These efforts are essential to narrow the gap between experimental success and clinical application.

## Hemoglobin-Based Biomimetic Nanoplatforms for Oxygen Delivery

In addition to PFC-based nanoplatforms that rely on the physical dissolution of oxygen, hemoglobin-based oxygen carriers (HBOCs) represent another important category of oxygen-supply strategies. Hb is a natural oxygen-transport protein in the body, consisting of a stable tetramer composed of two α-chains and two β-chains, and each subunit contains a heme prosthetic group. The central ferrous ion ($Fe^{2+}$) can form reversible coordinate bonds with oxygen molecules, enabling a single hemoglobin molecule to bind up to four oxygen molecules and thus endowing it with an extremely high oxygen-carrying capacity per molecule.[89] Hb demonstrates a pronounced cooperative binding effect, wherein the attachment of oxygen to one heme group triggers a conformational shift of the entire tetramer from a low-affinity T-state (Tense) to a high-affinity R-state (Relaxed). This conformational transition subsequently increases the oxygen-binding affinity of the remaining heme sites.[90,91] The oxygen affinity of Hb is further modulated by local environmental factors, including pH and carbon dioxide ($CO_2$) concentration, a mechanism referred to as the Bohr effect. An increase in $CO_2$ levels or a decrease in pH within tissues results in a reduced oxygen affinity of Hb, thereby promoting the release of oxygen into metabolically active, hypoxic regions. Conversely, the elevated $pO_2$ in the alveolar environment enhances oxygen binding. This physiologically adaptive regulation of oxygen loading and unloading optimizes the efficiency and flexibility of Hb-mediated oxygen transport in vivo.[92]

Based on these natural advantages, HBOCs have been proposed as a class of semi-synthetic oxygen delivery systems. These systems are centered on natural Hb and formed through molecular modification or structural reconstruction, initially intended primarily for oxygen-supply support in ischemic diseases and as alternatives to allogeneic blood transfusion. In comparison to PFC-based oxygen carriers, HBOCs closely mimic endogenous Hb with respect to oxygen binding, transport, and release mechanisms. Theoretically, this enables them to facilitate more efficient and regulated oxygen delivery.[93] However, early research has indicated that unmodified free Hb tends to dissociate into αβ dimers in plasma, leading to a markedly reduced circulation time. Additionally, this dissociation induces adverse effects such as vasoconstriction, systemic hypertension, and nephrotoxicity through the scavenging of nitric oxide (NO), thereby significantly limiting its clinical utility. To address these challenges, researchers have devised various molecular engineering strategies focused on enhancing the structural stability and biosafety of Hb. These strategies include polymerization, cross-linking, conjugation modification, and antioxidant functionalization. The primary objectives of these approaches are to stabilize the tetrameric structure of Hb, extend its in vivo circulation time, and mitigate systemic toxicity.[94]

### Hemoglobin-Encapsulated Nanocarriers

Nanostructural engineering constitutes a pivotal approach in the advancement of Hb-based oxygen delivery systems. A prevalent methodology entails the encapsulation of Hb within nanocarriers, including liposomes, polymeric nanoparticles, and protein-based nanostructures. These carriers substantially mitigate the deleterious effects associated with cell-free Hb in vivo, such as dissociation, rapid clearance, and nitric oxide scavenging. Concurrently, they enhance the circulation dynamics and tumor accumulation potential of Hb.

Liposome-encapsulated Hb represents one of the earliest and most widely investigated forms of Hb encapsulation. Murayama et al demonstrated that liposome-encapsulated Hb (h-LEH) significantly enhanced oxygen delivery to tumor tissues. Their results showed that a single intravenous infusion under normobaric breathing conditions could sustain a tumor oxygenation effect for up to 72 hours and reduce the accumulation of the hypoxia marker HIF-1α. In mouse

tumor models, h-LEH enhanced the antitumor efficacy of RT, likely due to the ability of the liposomal carrier to facilitate Hb accumulation in tumors via the EPR effect, thus improving local $pO_2$ and oxygenation status.[95]

To further improve the alleviation of tumor hypoxia and enhance antitumor efficacy, researchers have co-encapsulated Hb with chemotherapeutic agents within a single liposomal carrier. Yang et al constructed a nanosystem co-loading Hb and doxorubicin (DOX) (DOX-Hb-lipo, DHL), with a particle size of 151 ± 10.4 nm, exhibiting good stability and sustained oxygen release capacity. This nanosystem not only facilitated efficient oxygen delivery and promoted ROS generation to enhance ROS-mediated cytotoxicity of DOX but also significantly increased the uptake and accumulation of DOX in hypoxic cancer cells. Consequently, it reversed hypoxia-associated chemoresistance and exhibited enhanced antitumor efficacy in mouse tumor models. This study indicated that the presence of Hb on the carrier surface could facilitate the internalization and accumulation of nanoparticles at tumor sites, improving the synergistic effect of oxygen delivery and chemotherapy.[96] Hb-encapsulated liposomal carriers have also been employed to enhance the efficacy of oxygen-dependent therapies, such as PDT. Guo et al developed liposomes (Lipo-ICG-Hb, LIH) co-loading Hb and the photosensitizer indocyanine green (ICG). The ICG served as a near-infrared photosensitizer, which was modified with octadecanamide (ODA) and incorporated into the lipid membrane, while Hb was encapsulated within the inner aqueous phase, thereby greatly enhancing ROS generation and the antitumor efficacy of PDT.[97]

Platinum (Pt)-based chemotherapeutic agents are extensively utilized in clinical oncology. Nevertheless, their therapeutic efficacy is frequently compromised by tumor hypoxia. Structurally, hypoxia impedes drug delivery due to disorganized tumor vasculature and elevated interstitial fluid pressure, which significantly obstructs the convective transport and deep penetration of therapeutic agents.[98] Additionally, hypoxia fosters an immunosuppressive microenvironment by augmenting regulatory T cell activity, inhibiting the maturation of dendritic cells, and diminishing the infiltration of cytotoxic T cells.[99] Moreover, hypoxia-induced metabolic reprogramming and the upregulation of HIF-1α contribute to intrinsic resistance to Pt-based drugs. This resistance is facilitated by mechanisms such as active drug efflux, a reduction in intracellular ROS, and the enhancement of DNA damage repair pathways, thereby circumventing apoptosis.[100–102] To circumvent these limitations, Sun et al developed a biotin receptor (BR)-targeted Pt(IV) prodrug lipid nanoparticle (Hb@BTOPt$^{IV}$), which co-encapsulates Hb as an oxygen carrier with a Pt(IV) prodrug to simultaneously enable oxygen delivery and targeted chemotherapy. Hb@BTOPt$^{IV}$ was covalently linked to hydrophilic biotin via hydrophobic long-chain lipids and self-assembled into a targeted structure in aqueous solution, achieving effective targeting to tumors. In vitro studies showed that BTOPt$^{IV}$ led to a 4.71-fold increase in Pt accumulation in 4T1 cells compared with traditional oxaliplatin-treated cells, confirming the efficacy of BR targeting. Moreover, the treatment did not induce significant weight loss and extended the overall survival of mice. Additionally, Hb@BTOPt$^{IV}$ provided a localized oxygen supply through the release of Hb, which alleviated tumor microenvironment hypoxia and enhanced chemosensitivity. In vivo investigations demonstrated that intravenously administered Hb@BTOPt$^{IV}$ selectively accumulated within tumor sites, where it dissociated to release platinum-based drugs and oxygen. This dual-function strategy not only enhanced the efficacy of chemotherapy but also modulated the immune microenvironment by promoting the maturation of dendritic cells, increasing the infiltration of effector T cells, and reducing regulatory T cells, thereby ultimately leading to immune activation. The preparation of Hb@BTOPt$^{IV}$ and its mechanism for overcoming hypoxia-induced suppression of immunochemotherapy are depicted in Figure 3. Overall, the design strategy of Hb@BTOPt$^{IV}$ underscores the potential of hemoglobin-encapsulated nanocarriers in mitigating tumor hypoxia, improving drug delivery, and facilitating combined immunotherapy.[103]

In recent years, the encapsulation or functionalization of Hb within MOF nanocarriers to develop oxygen delivery platforms with integrated oxygen transport and synergistic therapeutic functions has emerged as a prominent area of research. These composite systems exploit the high porosity and structural stability of MOFs to safeguard Hb, while facilitating oxygen delivery to biological tissues through the oxygen-binding and release properties of Hb. This methodology is anticipated to substantially improve the effectiveness of therapeutic strategies in hypoxic microenvironments.[104] Zhao et al reported a MOF-based nanosensitizer, Hb@HP(Hf), with both radiosensitizing capability and tumor hypoxia alleviation for enhancing the synergistic efficacy of radiotherapy-radiodynamic therapy (RT-RDT). This platform was constructed using Hf clusters as metal nodes and the photosensitizing ligand tetrakis(4-carboxyphenyl)porphyrin (TCPP) as organic linkers, forming a highly ordered porous nanostructure that enabled efficient

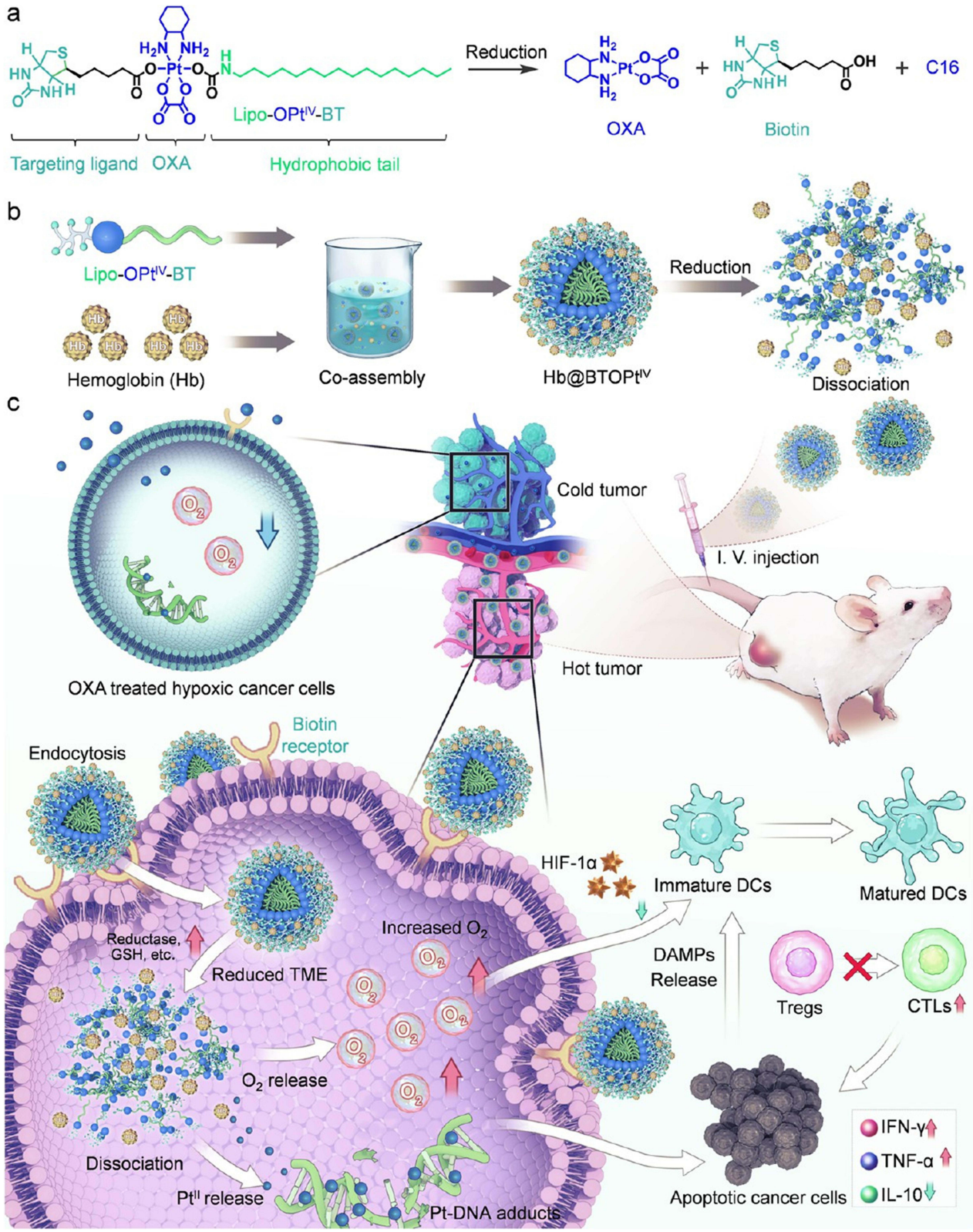


**Figure 3** Preparation and hypoxia-alleviating mechanism of BR-targeting oxygen-carrying prodrug nanoplatform. (**a**) Degradation pathway of Lipo-OPt$^{IV}$–BT. (**b**) Schematic preparation of Hb@BTOPt$^{IV}$ via electrostatic encapsulation of Hb within Lipo-OPt$^{IV}$–BT. (**c**) BR-targeting Hb@BTOPt$^{IV}$ enhances Pt$^{IV}$ drug delivery, improves tumor oxygenation, and alleviates hypoxia-induced immunosuppression during chemotherapy. In this schematic, upward arrows (↑) indicate elevated levels or upregulation of corresponding biological indicators; downward arrows (↓) indicate decreased levels or downregulation of corresponding biological indicators; the cross symbol indicates blockade of inhibitory pathways. Reproduced with permission.[103] 

**Abbreviation**: BR, biotin receptor.


https://doi.org/10.2147/IJN.S615263

immobilization of Hb within the MOF pores, achieving a remarkably high Hb loading of up to 48.9 wt%. The high hemoglobin content endowed the system with substantial oxygen-carrying and sustained oxygen-release capacity, thus effectively alleviating tumor hypoxia and enhancing oxygen-dependent therapeutic responses. In vitro experiments have demonstrated that Oxy-Hb@HP(Hf) substantially increases ROS generation under X-ray irradiation, particularly $^1O_2$, which leads to significant DNA double-strand breaks and apoptosis in tumor cells. In CT26 tumor-bearing mouse models, this system not only significantly inhibited tumor growth, with some instances of tumor regression, but also notably downregulated HIF-1α expression, indicating effective alleviation of tumor hypoxia.[105]

Despite the excellent performance of MOF-Hb composite systems in oxygen delivery and radiosensitization, their microporous structures and low physiological stability still limit their further biological applications. In response to these limitations, Jin et al introduced an innovative inside-out engineering approach to develop a stable Hb nanocarrier. This was achieved by covalently PEGylating hierarchical porous UiO-66 nanoparticles (HP-UiO-66 NPs) using diphenylcyclooctyne-azide click chemistry on the particle surface. This strategy significantly enhanced Hb loading efficiency through the introduction of mesoporous structures while preserving micropores to facilitate oxygen diffusion. When the input Hb concentration was 10 $mg \cdot mL^{-1}$, the loading efficiency reached approximately 24%. The biorthogonal PEGylation was conducted without interfering with the conformation or oxygen-carrying function of Hb, substantially increasing the colloidal and physiological stability of the particles. The PEGylated nanoparticles had a size of 140.8 ± 8.3 nm with a PDI of 0.167 and remained stable in biological media for more than one week. Their stability was much higher than that of unmodified nanoparticles, avoiding phosphate-induced degradation and enabling selective accumulation in specific organs. This work provides a reliable strategy for constructing highly efficient and stable oxygen delivery platforms.[106]

## Self-Assembled Hemoglobin Nanocarriers

Compared with encapsulating Hb in exogenous nanocarriers, self-assembled Hb nanosystems form stable nanostructures by modulating intermolecular interactions with minimal or no carrier assistance. This provides a more concise and biocompatible oxygen delivery strategy for alleviating tumor hypoxia. These systems typically exploit hydrophobic, electrostatic, or coordination interactions among Hb molecules to facilitate nanoscale aggregation. Consequently, they prevent the rapid dissociation and clearance of free Hb while maintaining its inherent oxygen-binding and release capabilities.[107]

Hb-polymer conjugate self-assembly systems represent a typical class of self-assembled Hb nanocarriers. Wang et al constructed an Hb-PCL conjugate-coupled self-assembled biomimetic nano-erythrocyte system (V(Hb)), which can simultaneously carry the chemotherapeutic drug DOX and oxygen to achieve tumor hypoxia alleviation and immune microenvironment reprogramming. Empirical evidence demonstrated that V(Hb)@DOX effectively mitigated tumor hypoxia in both in vitro and in vivo experimental models. Compared with free Hb or unmodified carriers, V(Hb) exhibited oxygen-binding and release behavior more closely resembling that of natural red blood cells, indicating a higher oxygen release capacity under hypoxic conditions. In hypoxic cells, V(Hb) significantly decreased the expression of hypoxia-associated markers, including HIF-1α and PD-L1, suggesting an inhibition of hypoxia signaling pathways. Continuous monitoring of oxygen saturation in 4T1 tumor-bearing mouse models demonstrated that V(Hb) administration substantially increased tumor oxygenation levels compared to the control group. This increase was accompanied by the downregulation of hypoxia-inducible factors, thereby effectively mitigating the characteristic hypoxic TME.[108]

Analogous strategies have been employed in models of drug-resistant tumors. Wang et al introduced a Hb nanocluster composite carrier, designated as HPRG@SF, which co-encapsulates indocyanine green (ICG) and sorafenib (SF). This innovative system markedly enhanced oxygenation within tumor tissues and suppressed the expression of KPNA4, thereby augmenting the efficacy of PDT in drug-resistant hepatocellular carcinoma (HCC). Mechanistic investigations indicated that hypoxic conditions upregulate KPNA4, thereby altering mitochondrial function and contributing to SF resistance in HCC cells. The HPRG@SF formulation ameliorated the hypoxic TME through the delivery of oxygen via Hb, consequently increasing SF sensitivity. When combined with enhanced PDT, it further inhibited the proliferation of

drug-resistant HCC cells, illustrating the dual benefits of self-assembled Hb nanosystems in mitigating hypoxia and counteracting drug resistance.[109]

## Oxygen Micro/Nanobubble-Based Delivery Systems

Oxygen MNBs constitute a category of micro-nanocarrier systems distinguished by their gaseous core and a shell that may be composed of lipids, polymers, proteins, surfactants, or other materials. Unlike physical oxygen carriers, MNBs can deliver oxygen in gaseous form directly to hypoxic tumor regions and release it under certain conditions. They are anticipated to overcome the limitations associated with the blood's oxygen-carrying capacity, thereby increasing $pO_2$ in the hypoxic TME and augmenting the effectiveness of oxygen-dependent therapies. Contemporary systematic reviews on MNBs suggest that these carriers not only exhibit excellent oxygen-carrying capabilities but also facilitate the co-delivery of drugs and enable multimodal therapy through shell engineering and functional modifications. When compared to traditional liquid-phase oxygen carriers, MNBs offer higher gas payloads, greater flexibility in size tunability, and superior interfacial mass transfer properties. These attributes confer unique advantages to MNBs, including enhanced penetration of the abnormal tumor vasculature, improved retention within the microenvironment, and the capability for on-demand oxygen release under hypoxic conditions.[110]

Within the TME, MNBs facilitate the release of oxygen from their gaseous core to adjacent tissues through mechanisms of gas diffusion and mechanical rupture. This process leads to an increase in regional $pO_2$, thereby mitigating hypoxia-associated signaling pathways, such as HIF-1α, and enhancing the efficacy of oxygen-dependent therapies. Related studies highlight the critical role of MNB design and functionalization. For example, the modulation of polymeric or liposomal shells can extend circulation half-life, enhance tumor targeting, and enable concurrent drug delivery.[111] Furthermore, under hypoxic conditions, the direct oxygen delivery by MNBs can significantly impact essential cellular functions, including mitochondrial respiration and redox homeostasis. The restoration of oxygen levels aids in the recovery of mitochondrial oxidative phosphorylation and reduces dependence on anaerobic glycolysis, thereby decreasing lactic acid accumulation and the exacerbation of an acidic microenvironment, while also attenuating hypoxia-related inflammatory and immunosuppressive characteristics.[112] Building upon the comprehension of these molecular mechanisms, recent research has evolved MNBs from simple oxygen delivery systems into sophisticated multimodal platforms. These nanoplatforms feature adjustable oxygen-release kinetics, responsiveness to external stimuli, and functionalized designs. This advancement provides the biological basis for the further development of diverse MNB configurations and integrated therapeutic strategies.

### pH-Responsive Oxygen Micro/Nanobubbles

Due to the mildly acidic nature of the TME (pH ~6.5–6.8), researchers have leveraged the pH disparity between tumor and normal tissues to engineer pH-responsive oxygen MNBs that facilitate targeted oxygen release at tumor sites. These MNBs are typically designed with acid-sensitive components within their shell structure, ensuring stability under neutral pH conditions. In the slightly acidic TME, these structural components undergo changes that trigger the release of oxygen, thereby more effectively mitigating local hypoxia. This design concept has led to the development of various pH-responsive MNBs in recent years, aimed at enhancing the therapeutic efficacy of RT, PDT, and combined treatment strategies.[113,114]

Song et al engineered a nanobubble carrier capable of spontaneous oxygen delivery in mildly acidic TME by utilizing a pH-sensitive acetalated dextran polymer as the inner layer and biocompatible lipids as the outer shell. This nanobubble system was designed to overcome limitations of conventional oxygen carriers, such as premature gas release during circulation and dependence on external triggers. In a CNE2 tumor-bearing mouse model, treatment with these pH-responsive oxygen nanobubbles significantly increased intratumoral $pO_2$ by approximately 6-fold, demonstrating a direct effect on improving tumor hypoxia. The autonomous oxygen release mechanism operates without the need for external stimuli, with the nanobubble shell effectively sequestering oxygen during circulation and facilitating rapid release upon reaching the tumor site. This approach effectively reverses hypoxia-induced drug resistance and cell survival pathways, offering a potent strategy for hypoxia intervention without external excitation.[115]

Wang et al coupled ethylenediamine-modified dextran oxygen-carrying nanobubbles with PD-1 antibodies to design a nanobubble carrier (αPD1-$O_2$-NB) capable of accelerated oxygen release in acidic regions. αPD1-$O_2$-NB selectively inhibits PD-1 protein in $CD8^+$ T cells within tumor tissues, thereby enhancing the sensitivity of esophageal squamous cell carcinoma (ESCC) to $^{125}I$ radionuclide therapy. These nanobubbles, encapsulated in an acetylated dextran (Ac-DEX) polymer shell, act as a robust barrier preventing gas dissolution in the bloodstream and preserving most of the oxygen payload. The abundant acetal bonds in the Ac-DEX backbone exhibit significant pH sensitivity and undergo rapid hydrolysis in acidic environments (pH 5.0–6.5), accelerating shell degradation and enabling prompt oxygen release from the nanobubbles. In vitro oxygen release studies showed that αPD1-$O_2$-NB exhibited a faster release rate and higher sustained oxygen levels under acidic conditions. In contrast, the nitrogen bubble ($N_2$-NB) group showed no obvious increase in oxygen concentration under either pH condition, confirming the pH-responsive behavior. In $^{125}I$ RT mouse models, $^{125}I$ treatment alone increased $CD8^+$ T cell activity and cytokine (eg, IFN-γ, GZMB) secretion, whereas the combination of αPD1-$O_2$-NB and $^{125}I$ significantly enhanced these effects, resulting in higher $CD8^+$ T cell survival rates and cytokine levels. This enhancement not only attenuated the immunosuppressive effects of PD-1 signaling but also improved TME oxygenation, indirectly boosting the antitumor activity of immune cells.[116]

### Ultrasound-Triggered Oxygen Micro/Nanobubbles

Ultrasound-responsive MNBs represent a distinct category of acoustic carriers that react to the physical energy imparted by ultrasound waves. These carriers typically consist of a gaseous core encapsulated by a biocompatible shell, which may be composed of lipids, polymers, or biomimetic cell membranes. Upon activation by ultrasound, MNBs can undergo controlled oscillation, cavitation, and rupture. The cavitation effects significantly increase the permeability of vascular and cellular membranes, facilitating spatiotemporally controlled drug release, enhanced tumor penetration, and augmented ICD. Consequently, MNBs offer unique advantages in tumor therapy, diagnostic imaging, and drug delivery applications.[117,118]

Tian et al developed a multifunctional nanobubble system (Ce6-$O_2$NB) designed to induce necroptosis. This innovative system utilized lipid nanobubbles to co-encapsulate Ce6 and oxygen, with the nanobubbles serving as agents for ultrasound-targeted nanobubble destruction (UTND) and Ce6 facilitating SDT. In vitro analyses demonstrated that these nanobubbles exhibited excellent biocompatibility and a uniform size distribution, which allowed for efficient accumulation at tumor sites. Upon activation through UTND, the Ce6-$O_2$NBs underwent cavitation and rupture, releasing substantial concentrations of oxygen at the targeted locations. This significantly elevated oxygen levels within the TME and mitigated hypoxia. The "in situ oxygen supply" approach significantly enhanced the effectiveness of SDT and triggered a substantial increase in ROS generation. In 4T1 breast cancer mouse models, the combination of Ce6-$O_2$NBs and ultrasound markedly inhibited tumor growth and effectively stimulated antitumor immune responses. This was achieved through the dual mechanisms of ameliorating hypoxia and inducing necroptosis, thus offering a novel strategy for sonodynamic immunotherapy targeting hypoxic tumors.[119]

### Therapeutic Agent-Co-Loaded Oxygen Micro/Nanobubbles

In the field of tumor hypoxia research and the development of clinical treatment strategies, merely augmenting oxygen concentration often proves inadequate in completely mitigating hypoxia-induced therapeutic resistance. As a result, a growing body of research has focused on the integration of oxygen MNBs with antitumor drugs or functional molecules to create bifunctional or multifunctional nanosystems. These advanced systems are designed to concurrently alleviate hypoxia and enhance the synergistic efficacy of tumor therapies.

A notable approach within this paradigm is the utilization of nanobubble systems that co-load chemotherapeutic agents and oxygen. Khan et al developed doxorubicin-conjugated oxygen nanobubbles (Dox/ONBs) and conducted a systematic evaluation of their therapeutic efficacy in hypoxic models of MDA-MB-231 breast cancer cells and HeLa cells. The findings revealed that post-oxygen release, this system effectively alleviated the hypoxia-induced upregulation of HIF-1α, thereby attenuating hypoxia-associated drug resistance pathways. Concurrently, enhanced oxygenation significantly increased intracellular ROS generation, substantially amplifying the cytotoxic effects mediated by Dox. In comparison to Dox delivery systems lacking oxygen loading, Dox/ONBs demonstrated superior tumor cell-killing

efficacy under hypoxic conditions, underscoring the critical role of oxygen supplementation in restoring chemosensitivity. This study validated at the cellular level that the co-delivery of oxygen and chemotherapeutic agents transcends a mere physical combination, instead augmenting the overall efficacy of chemotherapy by modulating hypoxia signaling and oxidative stress dynamics.[120] Agent-co-loaded oxygen nanobubbles represent an advanced strategy that deeply integrates oxygen supply with pharmacotherapy. They can not only alleviate hypoxia and enhance therapeutic response but also significantly improve the efficacy of oxygen-dependent therapies, providing a reliable pathway for the future development of more efficient and targeted tumor treatment platforms.

### Gas Vesicle-Based Oxygen Delivery Systems

Gas vesicles (GVs) are hollow protein nanostructures that are naturally synthesized by specific bacteria and archaea. A defining characteristic of GVs is their rigid shell, which is formed through the highly ordered assembly of gas vesicle proteins, primarily GvpA and GvpC, in the absence of a lipid membrane. This structural feature facilitates the stable encapsulation of gas molecules.[121] Typically, GVs exhibit spindle-shaped or cylindrical morphologies, with dimensions ranging from 100 to 250 nm. They possess a hydrophobic gas core, which permits the free diffusion of small gas molecules, such as oxygen, while effectively repelling water molecules.[122] In recent years, biogenic gas vesicles have garnered significant attention as promising carriers for oxygen delivery and the regulation of tumor hypoxia. Compared to conventional synthetic nanobubbles, biogenic gas vesicles offer distinct advantages, including enhanced stability, improved systemic circulation, and targeted oxygen release, owing to their naturally protein-based gas cavity structures.[123,124]

Building on the inherent structure of natural GVs, researchers have successfully engineered these entities into stable oxygen-carrying nanobubbles aimed at mitigating tumor hypoxia and enhancing therapies reliant on oxygen. For instance, Song et al demonstrated the lipid coating of natural GVs, thereby creating a stable oxygen delivery system termed lipid-GVs($O_2$). In vitro experiments revealed that this nanoplatform substantially increased oxygen concentrations in both the surrounding solution and cells under hypoxic conditions. Furthermore, it was effective in elevating local tumor $pO_2$ in subcutaneous mouse tumor models. Quantitative analyses indicated that tumor regions in the treatment group exhibited significantly higher $pO_2$ levels compared to the control group, which was associated with the downregulation of HIF-1α expression and an increased proportion of apoptotic cells. Importantly, this oxygen delivery system demonstrated excellent biocompatibility in vivo, as evidenced by the absence of significant tissue damage or systemic toxicity following injection. These findings suggest that surface-modified natural GVs can be safely employed in research focused on tumor hypoxia intervention.[125]

In addition to facilitating oxygen delivery, GVs offer distinct advantages in the realm of integrated tumor theranostics. The pronounced disparity in acoustic impedance between their internal gas cavities and the surrounding medium endows GVs with the ability to enhance ultrasound contrast, making them a focal point of research in molecular imaging and ultrasound-based diagnostics. Shapiro et al have demonstrated that GVs can function as genetically encodable ultrasound contrast agents, with their acoustic signals being closely linked to their structural integrity. This characteristic enables the "visualized oxygen delivery" necessary for modulating tumor hypoxia, allowing for real-time monitoring of GV distribution, accumulation, and potential rupture behavior under ultrasound guidance. Consequently, this provides critical feedback for precision therapy.[126]

## Oxygen-Generating Nanoplatforms for Tumor Hypoxia Alleviation

Unlike passive strategies that deliver exogenous oxygen via the circulatory system, in situ oxygen-generating nanoplatforms adopt a more active and efficient approach. These platforms facilitate autonomous oxygen production within lesions by incorporating catalytically active agents (such as nanozymes or photo-/electrocatalysts) and leveraging the elevated levels of endogenous substrates (such as hydrogen peroxide or water) present in tumor tissues. Distinct from oxygen-carrying nanoplatforms, in situ oxygen-generating nanoplatforms can trigger catalytic, photocatalytic, or hydrolytic reactions in response to the TME. This strategy mitigates the risks of oxygen leakage and systemic oxygen toxicity associated with conventional oxygen carriers, while enabling precise spatial delivery of oxygen to hypoxic regions within tumors.[127,128] Table 1 provides a summary of representative nanoplatforms, detailing the tumor cells they target, their synergistic applications with other therapies, advantages, and mechanisms for tumor targeting.

https://doi.org/10.2147/IJN.S515263



**Table 1** Summary of the Construction Strategies, Therapeutic Advantages, and Tumor-Targeting Mechanisms of Oxygen-Generating Nanoplatforms

| Strategies | Therapeutic Agents | Tumor Cells | Therapy Methods | Advantages | Tumor-Targeting Mechanism | Refs. |
|---|---|---|---|---|---|---|
| Protein-based catalysis | $Ag_2S$@CAT-Ce6 @Oxa NPs | HT29 | PDT/PTT/ Chemotherapy | Imaging-guided therapy with controlled drug release. | TME-responsive disassembly triggered by acidic pH. | [129] |
| | CAT-ICG@CQD | Melanoma | PDT | High quantum yield for simultaneous cell imaging. | Enhanced cellular uptake via nanoplatform surface properties. | [130] |
| | SMONs-CAT-Ce6 | 143B | PDT | Deformable nanomotor architecture. Self-propelled tumor penetration and enhanced cellular uptake. | Catalase-driven self-propulsion-enhanced tumor penetration. | [131] |
| | LCC@Ce6-NPs | HepG2/ADR | Chemo-PDT | Reversal of hypoxia-induced multidrug resistance. Enhanced intracellular DOX retention and ROS amplification. | ASGPR receptor-mediated active targeting via LA modification. | [132] |
| Oxide-based catalysis | H-$MnO_2$@IR825 | PC3 | PTT/PDT/CDT | Enhanced tumor ablation under laser irradiation. Minimal systemic toxicity with effective antitumor efficacy. | TME-responsive acidic pH-triggered drug release. | [133] |
| | $MnO_2$-Dox@HFn | HeLa/4T1/ SKOV3 | Chemotherapy/MRI | Dual catalase/peroxidase nanozyme for enhanced $O_2$ production. MRI-guided theranostic capability. | TfR1 receptor-mediated active targeting. | [134] |
| | MH@CAT-Ce6 | MDA-MB -231/4T1 | PDT | GSH depletion to sensitize PDT and enhance ROS generation. Improved cellular uptake and tumor retention. | EPR-mediated passive tumor accumulation. | [135] |
| | $CeO_2$-$MnO_2$ NPs | HeLa | MRI-RT | MRI contrast enhancement via $Mn^{2+}$ release. Low toxicity with efficient radiosensitization | TME-triggered GSH/$H_2O_2$ responsiveness for local activation. | [136] |
| | CF@P nanozymes | U2OS | CDT/PTT | ROS cascade generation for enhanced CDT efficacy. Photothermal conversion boosting catalytic performance. GSH depletion disrupting redox homeostasis. | PEGylation-enhanced circulation and tumor delivery. | [137] |
| | $Mn_3O_4$&MLT@PDA-AS1411, MMPA | A549-HRE-LUC/LLC-HRE-LUC | Ferroptosis/PTT/ Immunotherapy | Melatonin inhibits HIF-1α, enhancing ferroptosis and immunogenic cell death. $Mn^{2+}$ activates cGAS-STING, promoting DC maturation and CTL infiltration. | AS1411 aptamer-mediated active targeting. | [138] |
| | HA-$CuMnO_x$@ICG | HeLa | PTT | Photothermal-amplified multienzyme catalysis and ROS generation. Glutathione depletion amplifying oxidative stress. | CD44 receptor-mediated active targeting via HA modification. | [139] |

| | | | | | | |
|---|---|---|---|---|---|---|
| Noble metal catalysis | Pt@Au nanozymes | HeLa | CT imaging/RT | Catalytic cascade for glucose depletion and $O_2$ supply.<br>CT imaging capability for precise radiotherapy guidance. | High-Z element–enhanced X-ray energy deposition. | [140] |
| | AuPtAg-GOx | 4T1 | PTT/ Immunotherapy/ Starvation therapy | Starvation therapy sensitizes mild PTT by reducing heat shock protein expression.<br>Combination with PD-L1 blockade boosts antitumor immune response. | Enhanced immune reprogramming of immunosuppressive TME. | [141] |
| | $IrO_2$@MSN@PDA-BSA(Ce6) | L929/HT29 | PDT/PTT | Strong catalase-like activity for $O_2$ generation. | EPR-mediated passive tumor accumulation. | [142] |
| | IrRu-GOx@PEG | 4T1 | Starvation therapy | Efficient glucose depletion and starvation induction. | TME (acidic pH and high $H_2O_2$) activation. | [143] |
| | SS-MSN-Au@BOM | 4T1 | Immunotherapy | Self-oxygen supply to support sustained catalytic therapy.<br>Excellent biocompatibility with prolonged circulation. | Biomimetic bacterial outer membrane coating for immune evasion and tumor accumulation. | [144] |
| | Pt-carbon-integrated nanozymes | CT26 | PDT/PTT | High tumor inhibition (>90% in CT26 model). | EPR-mediated passive tumor accumulation. | [145] |
| | Pd/H-$TiO_2$-PEG | C6 | SDT/CDT | High in vivo tumor inhibition (~90% with US).<br>Minimal systemic toxicity and favorable biosafety profile. | Acidic pH and high $H_2O_2$-triggered Fenton-like reaction and $O_2$ generation. | [146] |
| | RuCu NPs | MDA-MB -231 | RT | Dual enzyme-like activities (POD and CAT).<br>Good biocompatibility. | TME (acidic pH and high $H_2O_2$) activation.<br>High-Z Ru–enhanced X-ray energy deposition. | [147] |
| Visible light-responsive | CCFCA | CT26 | Chemotherapy/ Magnetic therapy/ PDT/CDT | Type-I PDT is oxygen independent, effective in hypoxia.<br>Enhanced cellular uptake and deep tumor penetration under static magnetic field and light.<br>Selective cytotoxicity to tumor over normal cells. | SMF magnetic targeting enhances accumulation and cellular uptake.<br>Ascorbic acid active targeting via interaction with overexpressed Gluts on cancer cells. | [148] |
| | PCCN | 4T1/MCF-7 | PDT | Enhanced tumor suppression under hypoxic conditions. | RGD motif-mediated active targeting. | [149] |

(*Continued*)

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**Table 1** (Continued).

| Strategies | Therapeutic Agents | Tumor Cells | Therapy Methods | Advantages | Tumor-Targeting Mechanism | Refs. |
|---|---|---|---|---|---|---|
| NIR-I/II driven | CS-DA@Ru | 4T1/HeLa | PTT/PDT | NIR-II absorption enables deep tissue PTT with strong PA signal. | CS-CD44 receptor mediated active uptake. | [150] |
| | HIL@Z/P/H | B16F10 | PDT | Simultaneous inhibition of tumor recurrence and metastasis after surgery.<br>Local administration minimizes systemic toxicity.<br>PCC 7942-derived EVs further promote angiogenesis and tissue repair. | Active targeting via HA.<br>Local delivery by in-situ spraying to surgical wound. | [151] |
| | 3ACy-3ipr NPs-iRGD | 4T1 | PDT | Converts typical Cy7 dye into a type-I photosensitizer with enhanced radical generation for hypoxia-tolerant PDT.<br>Peptide-modified liposomes improve biocompatibility and tumor retention. | Tumor-targeting peptide functionalization on liposomes enhances tumor retention and cellular uptake through receptor-mediated recognition. | [152] |
| | FCs@PEG | HepG2 | PTT/PDT/CDT | High photothermal conversion efficiency (~50.5% at 1064 nm) facilitates deep-tissue therapeutic activation.<br>Biodegradable and eliminable via feces and urine within ~14 days. | EPR-mediated passive tumor accumulation. | [153] |
| | $Cu_{2-x}O$@$MnO_2$ @GOx@HA | HCT116 | CDT/PTT/ Immunotherapy | Self-replenishing $O_2$/$H_2O_2$ overcomes hypoxic limitations and boosts CDT and starvation therapy. | Active targeting via HA to CD44 receptors in TME. | [154] |
| X-ray activated | ITC-NPs | 4T1 | X-PDT | Purely organic phosphorescent nanoscintillator serves as both scintillator and photosensitizer without heavy metals. | Passive tumor accumulation of ITC-NPs after systemic administration. | [155] |
| | AuNC@DHLA | Hepa1-6 | RDT | Direct X-ray activation without additional scintillators or classical PSs.<br>Ultra-small size for rapid clearance and negligible systemic toxicity. | Passive tumor accumulation of ultra-small AuNC@DHLA via TME factors and enhanced retention in tumor sites. | [156] |
| | BPT-HOF@PEG | Hepa1-6 | X-PDT | Dual-function nanoscintillator acting as both scintillator and photosensitizer without heavy-metal components.<br>Significant tumor growth inhibition (~90.4%) in vivo. | Passive tumor accumulation and cellular uptake via enhanced retention and internalization of nanoscintillators. | [157] |


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|---|---|---|---|---|---|---|
| Hydrolysis-driven oxygen-releasing nanoplatforms | HSA-Ce6-$CuO_2$ | 4T1 | CDT/PDT | Provides continuous $H_2O_2$ depot for ROS amplification. | pH-responsive activation in acidic TME. | [158] |
| | DTCOP | MCF-7 | Chemotherapy/PDT | Self-supplied $O_2$ alleviates hypoxia and enhances PDT efficacy.<br>pH-responsive delivery ensures site-specific drug release. | pH-responsive activation in acidic TME. | [159] |
| | $CaO_2$@CUR@ZIF-Cu | B16-OVA | CDT | $H_2O_2$ self-supply overcomes the limitation of endogenous $H_2O_2$ in tumors.<br>Synergistic CDT and $Ca^{2+}$ overload enhance tumor cytotoxicity. | Passive accumulation via nanoparticle retention at tumor site. | [160] |
| | $ZnO_2$@PDA | HeLa | PTT | Combines photothermal and redox-metabolic regulation.<br>Uses mild hyperthermia to reduce damage to normal tissues. | EPR-mediated passive tumor accumulation. | [161] |
| | HSA-PFTBA | 4T1 | Contact-electro-dynamic therapy (CEDT) | Novel mechanism independent of traditional Fenton or enzymatic reactions.<br>No need for metal catalysts or photosensitizers.<br>Continuous radical generation at liquid–liquid interface. | Therapeutic selectivity arises from localized ROS production. | [162] |
| | H-$MnO_2$/GOX&CQ-iRGD | PANC-1 | CDT | Addresses three major barriers of pancreatic CDT: low $H_2O_2$, autophagy resistance, and stromal penetration.<br>iRGD enhances delivery/penetration through dense fibrotic stroma. | Tumor penetration peptide iRGD targets integrin $\alpha v\beta 3$ overexpressed on pancreatic cancer cells and vasculature. | [163] |
| | $Fe_3O_4$ @ZIF-8/GOx@$MnO_2$ | 4T1 | Starvation therapy/ CDT/PTT/ Immunotherapy | $O_2$ generation and GSH depletion alleviate resistance to oxidative therapy.<br>Favorable biosafety profile and tumor suppression in vivo. | Magnetic targeting by $Fe_3O_4$ core directs accumulation to tumor sites. | [164] |
| Microbial photosynthesis | ACG gel | 4T1 | Starvation therapy/ Immunotherapy | Sustainable in situ oxygen generation via photosynthesis.<br>Living system allows prolonged functional activity. | Local intratumoral injection with in situ hydrogel formation ensures retention at tumor site. | [165] |
| | PMCs | MCF-7/4T1 | Immunotherapy | Converts hypoxic TME into hyperoxic status, inhibiting proliferation and metastasis.<br>Reinvigorates antitumour immune responses. | Intratumoral injection ensures local delivery of PMCs. | [166] |
| | CV@CaP | 4T1 | RT/PDT | Sustainable biological oxygen generation.<br>Innovative integration of living photosynthetic system with inorganic coating. | CaP coating improves tumor-site retention. | [167] |
| Biomimetic photosynthesis | AIE@SDNV | 4T1 | PDT/ Immunotherapy | Plant-derived nanovesicles provide natural biocompatibility and delivery capability.<br>Effective against both primary and distant tumors in bilateral models. | Prolonged tumor retention observed in vivo, enabling precise AIEgen delivery. | [168] |
| | $La_2O_3$ NPs | 4T1/CT26/ LLC | RT/Immunotherapy | Enhances ROS generation and pyroptosis-mediated immunogenicity.<br>Integrates biological oxygenation with nanoparticle radiosensitization. | Cyanobacteria exhibit hypoxic-tissue preference, enhancing local $O_2$ supply. | [169] |

https://doi.org/10.2147/IJN.S615263

## $H_2O_2$-Catalytic Nanoplatforms for in situ Oxygen Generation

As a result of aberrant metabolic processes, tumor tissues tend to accumulate elevated concentrations of hydrogen peroxide ($H_2O_2$), often reaching levels of several hundred micromolar, thereby providing a substrate for localized oxygen generation.[170] Consequently, the utilization of nanocatalysts to efficiently decompose $H_2O_2$ into $O_2$ at tumor sites has emerged as a prominent area of research. This strategy not only elevates the local $pO_2$, thereby effectively alleviating hypoxia and enhancing the efficacy of oxygen-dependent therapies, but also reduces oxidative damage to cells caused by excessive $H_2O_2$. Thus, it achieves a dual improvement of the TME.[171]

### Enzyme-Inspired Protein Catalytic Nanoplatforms

Protein-based catalytic nanoplatforms utilize the decomposition of $H_2O_2$ by natural enzymes as their fundamental mechanism to produce oxygen. These platforms achieve in situ conversion of endogenous $H_2O_2$ into oxygen within tumors by either directly delivering catalase (CAT) or employing nanocatalysts that mimic its active sites. This conversion process significantly increases local oxygen concentrations, thereby mitigating tumor hypoxia and enhancing the efficacy of oxygen-dependent therapeutic interventions. Natural catalase-based delivery systems, which directly catalyze the decomposition of $H_2O_2$ into $O_2$, represent the earliest iteration of such platforms. However, their direct application is constrained by rapid inactivation in vivo and limited systemic circulation time.[172] In response, recent studies have focused on integrating CAT or CAT-like nanozymes into nanocarriers to improve accumulation at tumor sites and enhance catalytic stability,[129,130] thus facilitating sustained in situ oxygen generation.[173,174]

Tan et al developed a self-oxygen-generating soft nanomotor (SMONs-CAT-Ce6) composed of soft mesoporous organosilica nanoparticles and CAT. In the $H_2O_2$-rich TME, this system not only decomposes $H_2O_2$ to $O_2$ but also enables the autonomous propulsion of the nanomotors along $H_2O_2$ gradients, thereby enhancing targeted accumulation and deep tumor penetration. In vivo experiments demonstrated that SMONs-CAT-Ce6 significantly alleviated the hypoxic in 143B osteosarcoma models. Furthermore, it synergizes with the photosensitizer Ce6 to augment the efficacy of PDT, thereby inhibiting tumor growth and preventing lung metastasis. With a particle size of approximately 234 nm, SMONs-CAT-Ce6 demonstrates excellent biocompatibility and nanomotor propulsion capabilities, offering an innovative strategy for integrating in situ $H_2O_2$-catalyzed oxygenation with nanodelivery systems.[131]

Cheng et al developed a multifunctional nanozyme-prodrug system LCC@Ce6-NPs by self-assembling lactobionic acid (LA), acid-sensitive DOX prodrug (CAD), CAT, and the photosensitizer Ce6. This system facilitates the catalytic decomposition of $H_2O_2$ to produce $O_2$ within tumor cells, leading to a substantial downregulation of HIF-1α and P-glycoprotein (P-gp) expression, thereby enhancing the cytotoxic efficacy of chemotherapy and PDT. In vivo experiments revealed that this combinatorial nanoplatform achieved a tumor growth inhibition (TGI) rate exceeding 90%, accompanied by partial tumor regression. These results highlight the significant sensitizing potential of protein-based oxygen-generating catalytic platforms in combination therapeutic strategies.[132]

### Metal Oxide Catalytic Nanoplatforms

Metal oxide-based intelligent nanomaterials have emerged as significant nanoplatforms for the in situ catalytic decomposition of $H_2O_2$ and subsequent oxygenation, attributed to their capacity to emulate diverse oxidoreductase activities. In comparison to natural enzyme systems, oxide-based nanozymes offer notable advantages, including enhanced structural stability, increased in vivo durability, and superior catalytic efficiency. Given that metal oxides typically exhibit multiple catalytic activities, they have the potential not only to generate oxygen but also to synergize with therapeutic mechanisms such as reactive ROS production, GSH depletion, and imaging functionalities. This multifunctionality facilitates the integrated design of multimodal therapeutic strategies.[128]

$MnO_2$-based nanomaterials are among the earliest and most extensively investigated oxide-based smart platforms. $MnO_2$ demonstrates catalase-like activity, enabling the decomposition of excessive $H_2O_2$ in the TME into $O_2$ and $H_2O$. Additionally, under acidic conditions, $MnO_2$ can be reduced to generate active $Mn^{2+}$, thereby fulfilling dual roles in oxygen supply and microenvironment regulation.[133,175] For example, Veroniaina et al designed a nanoplatform $MnO_2$-Dox@HFn that exhibits pronounced catalase-like and peroxidase-like activities. In the presence of $H_2O_2$, this system efficiently generated $O_2$, while the released $Mn^{2+}$ enhanced magnetic resonance imaging signals. As a result, $MnO_2$-Dox

@HFn effectively alleviated tumor hypoxia and improved therapeutic responsiveness, enabling the integration of therapy with diagnostic and imaging functions.[134] Similarly, Jia et al covalently modified catalase onto the surface of $MnO_2$ nanoaggregates to construct MH@CAT-Ce6. In the tumor, this system can be triggered by $H_2O_2$ for sustained oxygen production, while $MnO_2$ is decomposed into $Mn^{2+}$ under high intracellular GSH conditions, achieving simultaneous oxygen supply and GSH depletion. This programmed regulation of oxygen delivery and oxidative stress significantly enhances the efficacy of PDT.[135]

The composite oxide system of $CeO_2$-$MnO_2$ core-shell nanomaterials has demonstrated significant advantages in synergistic catalytic oxygen generation. In vitro experiments conducted by Pi et al revealed that this nanoplatform achieved an $H_2O_2$ scavenging rate of nearly 60% at a concentration of 100 μg/mL, resulting in a rapid increase in dissolved oxygen levels within 5 minutes. This swift oxygenation is beneficial for counteracting hypoxia-induced radioresistance. In environments with high GSH levels, $MnO_2$ undergoes further decomposition to release $Mn^{2+}$, thereby enhancing MRI contrast. Concurrently, the enhanced ROS generation, in conjunction with X-ray irradiation, significantly augments tumor cell eradication. These findings underscore the potential of this multifunctional nanoplatform for MRI-guided radiotherapy.[136]

In addition to the most extensively studied $MnO_2$ and $CeO_2$ systems, recent research has increasingly shifted its focus toward more complex oxide-based nanoplatforms. For example, $CoFe_2O_4$ multienzyme nanozymes possess catalase-, peroxidase-, and oxidase-like activities. In the TME, they can simultaneously alleviate hypoxia and enhance ROS-mediated therapeutic responses, showing excellent antitumor efficacy against refractory tumors such as osteosarcoma.[137] $Mn_3O_4$-based composite nanozymes have been used to induce immune activation and synergistically alleviate hypoxia,[138] while composite oxide nanozymes such as $CuMnO_x$ achieve functional coupling between oxygen production and ROS generation through multimodal catalytic pathways.[139] These multicomponent oxide platforms not only improve the efficiency of in situ oxygen generation but also provide novel design paradigms for combination therapies such as PDT, photothermal therapy (PTT), and immunotherapy. This suggests that future material innovation can be centered on multienzyme coexistence and microenvironment responsiveness to further enhance hypoxia relief and therapeutic sensitization.[176,177]

### Noble Metal and Single-Atom Nanozymes

Noble metal-based nanozymes (eg, Au,[140,178] Ag,[141] Pt,[179] Pd,[180,181] Ir,[142] Ru,[150] Rh[143,182]) have emerged as ideal candidates for alleviating tumor hypoxia and enhancing oxygen-dependent therapies due to their excellent catalytic activity, high chemical stability, and photothermal, optical, and X-ray responsive properties. These nanozymes effectively emulate the functions of natural enzymes, including peroxidase (POD), catalase (CAT), oxidase (OxD), and superoxide dismutase (SOD). Their catalytic activity, selectivity, and multifunctional synergy can be precisely tailored through the rational manipulation of particle size, exposed crystal facets, structural defects, surface ligands, and heterostructure engineering. Furthermore, the distinctive plasmonic and photothermal properties of noble metal nanozymes facilitate their application in PDT, PTT, and CT/PAI imaging, thereby offering highly customizable solutions for in situ oxygen generation and TME modulation.[183–185]

As a prominent example of noble metal-based nanozymes, gold nanozymes have been extensively employed in the regulation of the TME due to their superior catalytic activity, chemical stability, and biocompatibility.[178] Zhang et al utilized disulfide-containing mesoporous silica nanoparticles (SS-MSN) as a framework to anchor gold nanozymes onto the pore surfaces via $NaBH_4$ reduction, followed by encapsulation with bovine ovarian membranes (BOM) to construct the biomimetic nanozyme structure SS-MSN-Au@BOM. The Au nanozymes exhibited multiple catalytic activities in the TME, including glucose oxidase (GOx)-like, POD-like, and CAT-like functions. This enables the decomposition of endogenous $H_2O_2$ into $O_2$ while simultaneously producing ROS. The CAT-like oxygen-generating function of SS-MSN-Au@BOM supplied sufficient oxygen to sustain the GOx-like cascade reaction. The underlying mechanism is illustrated in Figure 4. This system not only effectively alleviated tumor hypoxia in vivo but also promoted immunogenic cell death, enhanced dendritic cell maturation, and activated T cells, thereby demonstrating significant tumor growth inhibition with favorable biocompatibility and circulatory stability. It provides a novel strategy for constructing nanotherapeutic platforms with dual functions of oxygen generation and immune modulation.[144]

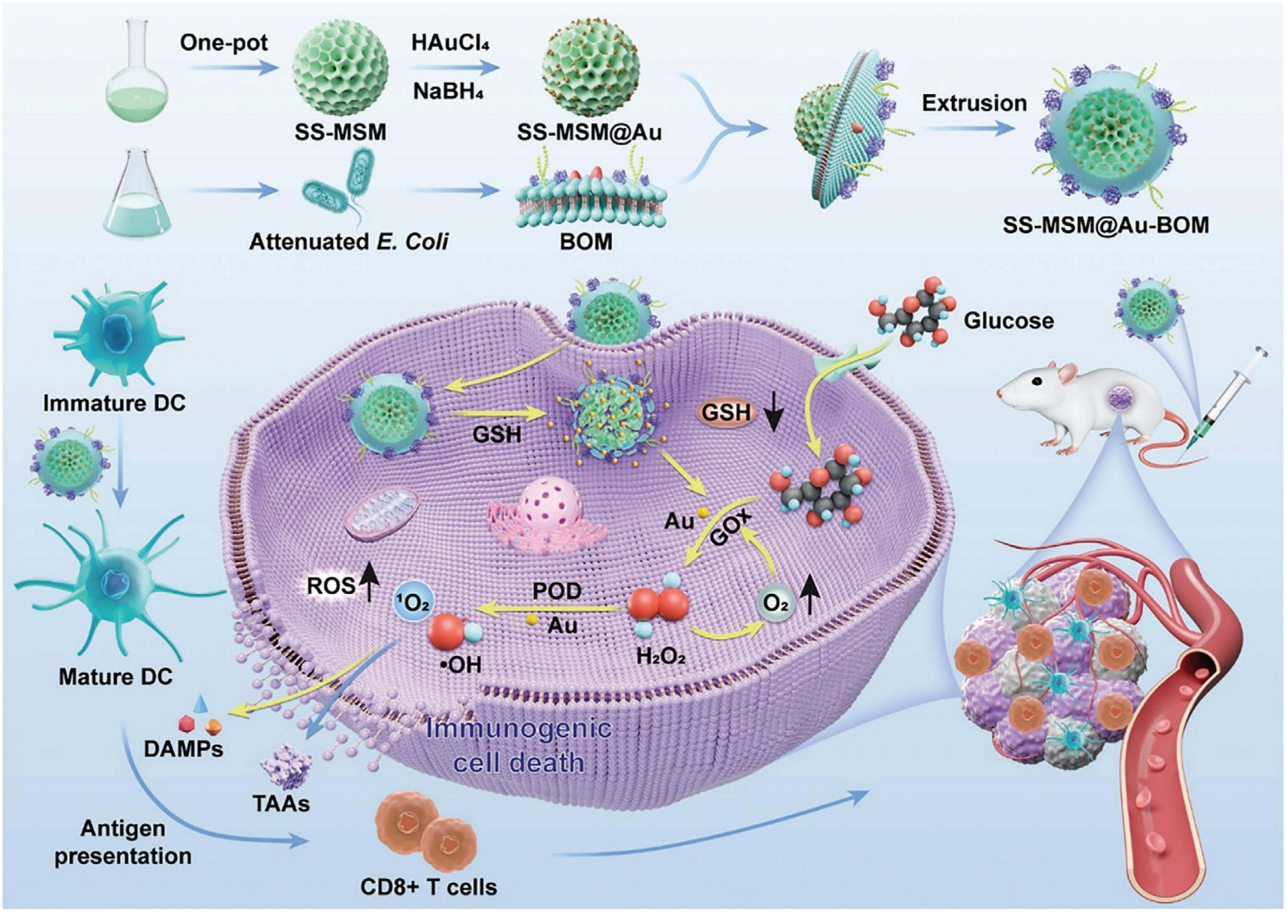


**Figure 4** Schematic illustration of the synthesis of the self-oxygenated biomimetic nanozyme SS-MSN@Au-BOM and its mechanism for alleviating tumor hypoxia via catalytic generation of reactive oxygen species to promote immune responses in tumor catalytic immunotherapy. In this schematic, upward arrows (↑) indicate elevated levels or upregulation of corresponding biological indicators; downward arrows (↓) indicate decreased levels or downregulation of corresponding biological indicators. Reproduced with permission.[144] Copyright © 2026 Wiley.

Silver nanomaterials have also been demonstrated to exhibit multiple enzyme-like activities. Their CAT-like and POD-like activities facilitate their involvement in the catalytic conversion of $H_2O_2$ within the TME, thereby enabling in situ oxygen generation and modulating ROS levels to a certain degree. In the context of tumor therapeutic applications, Ag is predominantly utilized as a structural or optical functional unit, often in conjunction with CAT or other highly efficient oxygen-generating components, to enhance tumor oxygenation and downregulate hypoxia-associated pathways. At present, Ag-based nanomaterials primarily serve an auxiliary role in the modulation of hypoxia, and their potential as standalone, highly efficient oxygen-generating nanozymes requires further systematic investigation and validation.[141,186]

Beyond the commonly studied nanomaterials like Au and Ag, other noble metal-based nanomaterials such as Pt, Pd, and Ru are also gained significant research attention due to their unique electronic structures and surface plasmon resonance effects. These materials exhibit robust catalytic activity and stability, enabling the rapid generation of ROS. Additionally, they have been reported to exhibit remarkable antibacterial properties.[187] Yang et al immobilized ultrasmall Pt nanoparticles onto MOF-derived carbon supports via in situ reduction. The catalase-like activity of Pt effectively enhanced oxygen generation at the tumor site, thereby boosting the synergistic antitumor effect of PTT and PDT. In vivo experiments demonstrated that this platform effectively suppressed tumor growth, providing compelling evidence for the practical efficacy of Pt-catalyzed oxygenation in cancer treatment.[145] Zhang et al designed a Pt@Au nanozyme by combining Pt and Au, which further exhibited an oxygen pump function. Its GOx-like activity first oxidizes glucose to generate $H_2O_2$, and the subsequent catalase-like activity of Pt decomposes $H_2O_2$ into $O_2$, achieving a self-oxygen-supplying cycle via cascade catalysis. This strategy greatly alleviates tumor hypoxia and improves radiosensitivity.[140]

Wang et al reported a Pd-modified nanozyme (Pd/H-$TiO_2$-PEG nanosheets) constructed by decorating $TiO_2$ with Pd atoms. The integration of Pd conferred the nanomaterial with enhanced catalytic activity towards endogenous $H_2O_2$, facilitating its conversion into $O_2$ and thus ensuring a continuous oxygen supply at the tumor site. In vivo experiments revealed a significant reduction in hypoxia due to the Pd/H-$TiO_2$-PEG nanosheets. Compared to the control group, there was a substantial increase in tumor oxygen saturation levels, which was associated with synergistically improved SDT and chemodynamic therapy (CDT) effectiveness. Additionally, this Pd-based nanozyme system significantly augmented ROS production and effectively inhibited tumor growth, all while demonstrating excellent biocompatibility and no detectable systemic toxicity. These findings suggest that palladium-based nanozymes not only ameliorate tumor hypoxia through oxygen generation but also significantly enhance oxygen-dependent therapeutic responses within the TME.[146]

Hu et al designed bimetallic RuCu nanozymes (RuCu NPs), which combine the high atomic number of Ru and the catalytic properties of Cu modification, exhibiting both peroxidase-like and catalase-like activities. In the acidic TME, RuCu NPs enhanced ROS production and relieved tumor hypoxia under X-ray irradiation, thus improving radiosensitivity in the MDA-MB-231 breast cancer model. Both simulated kinetic analyses and in vitro/in vivo results demonstrated that, compared with single-metal nanomaterials, the RuCu composite nanozyme achieved higher catalytic efficiency in decomposing $H_2O_2$ into $O_2$, thereby further improving therapeutic outcomes. These findings provide experimental evidence supporting the use of noble metal composite nanozymes to surmount hypoxia tolerance in tumor therapy.[147,188]

Noble metals and single-atom nanozymes facilitate the enhancement of biocompatibility and in vivo selectivity through the precise modulation of size, ligands, and heterostructures. Nevertheless, their long-term metabolic fate in vivo has yet to undergo systematic and comprehensive evaluation, posing a significant challenge to the clinical translation of these materials. Current research indicates that non-biodegradable noble metal nanomaterials are not readily excreted through conventional metabolic pathways in vivo and tend to accumulate in MPS organs, such as the liver and spleen, resulting in prolonged retention.[189] Recent research has demonstrated that the degradation and clearance of nanoparticles within biological systems are significantly influenced by their material composition, size, and surface chemical properties. Noble metal nanozymes, characterized by their inherent chemical inertness and structural stability, typically lack well-defined biodegradation pathways and predictable excretion mechanisms. Conversely, single-atom nanozymes, with their atomically dispersed structures and molecule-like properties, may exhibit enhanced metabolic potential under specific conditions. Nonetheless, the structural stability, evolution of coordination environments, and potential metal ion release behavior of these nanozymes in complex physiological environments remain largely uncertain.

Additionally, the long-term retention of inorganic nanomaterials may lead to chronic inflammatory responses, cumulative oxidative stress, and potential organ toxicity. Despite these concerns, most current studies focus on short-term toxicity assessments over periods of 14 to 30 days, which are insufficient for evaluating biosafety over extended durations of several months or even years. Therefore, existing conclusions regarding the "favorable biocompatibility" of noble metal-based and single-atom nanozymes are largely based on short-term toxicity assessments. This limited evidence is insufficient to meet the stringent safety standards required for long-term clinical applications. Future research should extend beyond the "functional stacking" phase. Instead, advanced detection techniques such as radioisotope tracing or ICP-MS should be utilized to develop pharmacokinetic models that encompass the entire life cycle of these nanozymes. Concurrently, the development of metallic alloys with biologically programmable degradability, or the engineering of bio-triggered dissociation platforms utilizing removable ultrasmall noble metal components, is crucial. These approaches aim to fundamentally resolve the ultimate metabolic fate of non-degradable inorganic constituents in vivo, thereby representing an essential pathway for advancing these nanozymes toward clinical translation.

## Photocatalytic Oxygen-Generating Nanoplatforms

Unlike enzymatic reactions that depend on the endogenous concentration of $H_2O_2$ within tumors, photocatalytic oxygen generation emulates the process of natural photosynthesis. When exposed to light, semiconductor materials produce electron-hole pairs ($e^-/h^+$), which directly facilitate the oxidation of water or hydrogen peroxide, resulting in oxygen production. This approach, which generates oxygen exclusively under illumination and halts in the absence of light,

demonstrates exceptional spatiotemporal control, thereby effectively mitigating the risk of off-target oxidative damage.[128,190]

### Visible Light-Responsive Oxygen-Generating Nanoplatforms

Visible light-responsive photocatalytic systems absorb light in the visible range (400–700 nm) to generate electron-hole pairs. The photogenerated holes facilitate water oxidation reactions, whereas the electrons contribute to the decomposition of $H_2O_2$, thus enabling continuous in situ oxygen production within tumor tissues. Graphitic carbon nitride (g-$C_3N_4$) is a layered polymeric semiconductor composed of carbon and nitrogen atoms connected through covalent bonds, and it possesses a graphite-like π-conjugated network. This distinctive structure provides g-$C_3N_4$ with a moderate bandgap (~2.7 eV) in the visible light region, which is conducive to effective light absorption, as well as high thermal and chemical stability. As a metal-free and environmentally benign photocatalyst, g-$C_3N_4$ has become a pivotal material in this domain.[148,191,192] Zheng et al constructed a carbon dot-modified g-$C_3N_4$ nanocomposite (PCCN), which increased intracellular $O_2$ levels through photocatalytic water splitting even under hypoxic conditions, thereby enhancing ROS generation and partially reversing hypoxia-induced resistance to PDT.[149] Sun et al constructed a composite system (PPIC) by covalently anchoring indocyanine green (ICG) and Ce6 onto Janus mesoporous Pt-organosilica (JMPO) nanoparticles. Under 660 nm visible light irradiation, this system leverages the catalase-like catalytic activity of the Pt component to decompose excess intratumoral $H_2O_2$ into $O_2$, significantly enhancing tumor oxygenation. In the group receiving PPIC-mediated PDT in combination with other treatments, 4 out of 6 mice (66.7%) demonstrated complete tumor regression, a result that was markedly superior to those observed in the control groups. These findings underscore the critical role of visible light-induced in situ oxygen generation in alleviating tumor hypoxia and enhancing the efficacy of PDT.[193]

However, the evaluation of such platforms should not be limited to their instantaneous oxygen-generating efficiency; instead, it is essential to assess their long-term effects on tumor vascular biology. In PDT, oxygen metabolism exhibits pronounced dynamics and stage dependence. The persistent consumption of oxygen during photosensitization reactions, coupled with ROS-mediated microvascular damage, can lead to localized secondary hypoxia. Although a high availability of oxygen is a fundamental prerequisite for $^1O_2$ generation, in vascular-targeted PDT (V-PDT) strategies, premature or excessive in situ oxygen production may inadvertently support the survival of endothelial cells. This, in turn, could mitigate the desired "ischemic necrosis" effect that results from vascular shutdown.[194,195] Furthermore, if oxygen generation occurs only during light irradiation, the subsequent post-treatment rebound in $pO_2$ often activates pro-angiogenic signaling pathways, triggering compensatory proliferation of residual tumor cells.[196] Consequently, an optimal visible-light-driven oxygen-generating system should deliver an oxygen supply profile that aligns precisely with the specific PDT modality. This alignment is crucial to prevent the unintended restoration of tumor interstitial fluid pressure and microvascular homeostasis that can result from excessive reoxygenation.

### Near-Infrared (NIR-I/II) Driven Oxygen-Generating Nanoplatforms

Near-infrared (NIR) light exhibits a tissue penetration depth ranging from 1 to 2 cm. Through the upconversion process, it can be excited by light in the NIR-I (700–1000 nm) or NIR-II (1000–1700 nm) spectral windows, resulting in visible light emission.[197] NIR-II, due to its deeper tissue penetration and lower light scattering background, offers unique advantages for in situ photocatalytic oxygen generation in deep-seated tumors.[151,152] Wang et al developed a Z-Scheme photocatalytic platform based on $FeS_2$/$CoS_2$@PEG nanosheets (FCs@PEG) for alleviating tumor hypoxia and enhancing therapy under NIR-II (1064 nm) irradiation. FCs@PEG (~80 nm) exhibited a high photothermal conversion efficiency of 50.5% and enabled effective separation of photogenerated electron-hole pairs upon NIR-II excitation. $FeS_2$ (1.16 eV) and $CoS_2$ (1.37 eV) were simultaneously excited under low-energy NIR-II laser irradiation and generated high-energy holes and electrons via the Z-scheme photocatalytic mechanism. The generated holes were utilized for water oxidation to produce oxygen, while the electrons participated in ROS generation, thus enhancing the effects of PDT and photothermal therapy.[153]

Liu et al constructed self-assembled Ru-based nanozymes (CS–DA@Ru NPs) for NIR-II photoacoustic imaging (PAI)-guided PTT/PDT. The system generated Ru nanoparticles on chitosan-based carriers via dopamine-mediated

reduction of $RuCl_3$ and exhibited significant catalase-like activity. In the mildly acidic TME, CS–DA@Ru NPs efficiently decomposed excess $H_2O_2$ into $O_2$, effectively alleviating hypoxic regions. By employing NIR-II PAI to monitor changes in blood oxygen saturation, the study demonstrated a significant increase in the oxyhemoglobin signal within the tumor region over time following injection, peaking at 12 hours, in contrast to the control group (saline), which exhibited negligible changes. This result provides robust evidence for the in situ oxygenation capability of Ru nanozymes in vivo. In 4T1 tumor-bearing mouse models, CS–DA@Ru NPs under 1064 nm laser irradiation elevated the tumor temperature to approximately 57 °C and markedly enhanced $^1O_2$ production and therapeutic efficacy. These findings highlight the dual advantages of hypoxia alleviation through oxygenation and the synergistic killing effects of PDT/PTT.[150]

From a clinical translation standpoint, the effectiveness of these nanoplatforms should not be assessed solely based on baseline $pO_2$ prior to treatment. Instead, it is crucial to consider the dynamic oxygenation profiles throughout the entire treatment course. Current research often lacks systematic monitoring of oxygen levels at critical post-treatment intervals, such as 24 and 72 hours. Notably, rapid oxygen consumption and vascular damage during PDT can lead to a sustained hypoxic state, which is closely linked to blood flow obstruction and tumor control in V-PDT.[198] Based on this, the design of oxygen-generating nanoplatforms should consider the synchronization of pharmacokinetics and oxygen kinetics (PK/OK). The oxygen production rate should be dynamically matched to oxygen consumption during PDT to sustain efficient ROS generation. In the later stages of treatment, it is also necessary to evaluate whether the nanoplatforms interfere with therapeutically beneficial vascular occlusion by modulating oxygen levels. Existing studies suggest that post-treatment reoxygenation may activate HIF-1α-related signaling and promote angiogenesis, thereby influencing the risk of tumor recurrence.[199] Consequently, future research should transition from solely focusing on maximizing peak oxygen generation to quantitatively regulating oxygen exposure over time. This can be achieved by developing dynamic evaluation systems that incorporate oxygenation trajectories at various time intervals (eg, 24–72 hours). Such process-based, dynamic assessment strategies are more effective in determining whether a nanoplatform can achieve complete tumor eradication or, alternatively, facilitate therapeutic escape and subsequent recurrence due to insufficient oxygenation management. This approach would thereby offer more predictive evidence for its clinical translation.

### X-Ray Activated Radiodynamic Oxygen-Generating Nanoplatforms

Due to their superior ability to penetrate deep tissues and their well-established clinical use in RT, X-rays are considered a crucial external energy source for addressing the hypoxic microenvironment characteristic of deep-seated solid tumors. Traditional RT predominantly utilizes X-rays to directly cause DNA damage and generate free radicals, thereby leading to tumor cell death. However, the biological effectiveness of this approach is significantly influenced by the $pO_2$, a phenomenon known as the oxygen enhancement effect. Consequently, tumor hypoxia emerges as a principal factor contributing to suboptimal RT outcomes and the development of radioresistance. To overcome this limitation and enable PDT in deep-seated tissues, nanoscintillators have emerged. Nanoscintillators are a class of nanomaterials capable of generating detectable photon emission upon exposure to ionizing radiation, such as X-rays or γ-rays. This luminescent phenomenon, known as scintillation, involves the absorption of high-energy radiation followed by the rapid re-emission of energy in the form of ultraviolet or visible light photons.[200,201] In recent years, the field of radiodynamic therapy (RDT) has advanced through the integration of X-rays with nanomaterials and photosensitizers to improve therapeutic outcomes. This approach involves the introduction of nanoscintillators or radiosensitizers enriched with high atomic number (high-Z) elements, which serve as energy conversion centers. These centers facilitate the transformation of high-energy X-rays into secondary photons or excited-state electrons, thereby initiating catalytic reactions.[155,202] In this process, researchers have developed nanoplatforms with water-splitting activity to achieve in situ oxygen generation during RT. This real-time oxygenation strategy not only elevates the local oxygen concentration to alleviate hypoxia-induced radioresistance but also amplifies oxidative stress damage through oxygen-mediated free radical cascade reactions.[203]

Zhu et al proposed a low-dose X-ray RDT platform based on gold nanoclusters (AuNC@DHLA). This system uses gold nanoclusters encapsulated by dihydrolipoic acid (DHLA) as RDT sensitizers, which can efficiently generate ROS under low-dose (0.5–2 Gy) X-ray irradiation without the need for additional scintillators or photosensitizers. In vitro experiments revealed that AuNC@DHLA, when subjected to 4 Gy X-ray irradiation, significantly enhanced the

production of $^1O_2$ and hydroxyl radicals (·OH), sustaining ROS generation even under hypoxic conditions to effectively induce cell death. In deep hypoxic solid tumor-bearing mouse models, either single or fractionated low-dose X-ray irradiation combined with AuNC@DHLA significantly inhibited tumor growth and enhanced tumor-infiltrating immune responses. These findings suggest that this strategy not only directly kills tumors but also improves overall therapeutic efficacy through ROS-mediated immunomodulatory effects.[156]

To further optimize energy conversion efficiency and biocompatibility, Gu et al developed an organic phosphorescent nanoscintillator (BPT-HOF@PEG) based on a hydrogen-bonded organic framework (HOF), which can emit phosphorescence upon X-ray exposure. Unlike traditional complex systems that rely on heavy metal inorganic scintillators and photosensitizers, BPT-HOF@PEG integrates the functions of both a scintillator and a photosensitizer. It can efficiently absorb X-rays and directly generate $^1O_2$, thus achieving deep PDT in tumor tissues. In vitro and in vivo results demonstrated that this nanosystem effectively produced a substantial amount of $^1O_2$ under X-ray irradiation. Through the synergistic effects of direct DNA damage and ROS cascade reactions, it significantly inhibited tumor growth in HCC models, achieving an in vivo inhibition rate of up to 90.4%. In addition, this organic material exhibited high biocompatibility, which effectively reduced the toxicity risks associated with traditional metal scintillators. This study demonstrates the potential of organic HOF nanoscintillators in efficient, low-toxicity, and deep-tumor X-ray-induced PDT, providing a reference for the design of novel energy conversion nanomaterials in the future.[157]

Furthermore, several studies have reported that pure organic phosphorescent nanoscintillators can achieve efficient $^1O_2$ generation even at extremely low X-ray doses (0.4 Gy). These materials effectively convert X-ray energy into usable energy to activate local oxygen for ROS generation via highly efficient electronic excitation and enhanced intersystem crossing (ISC) processes. Such findings further demonstrate the feasibility of non-metallic materials in mediating X-ray-triggered oxygen/ROS production.[155]

## Hydrolysis-Driven Oxygen-Releasing Nanoplatforms

Hydrolysis-driven oxygen-releasing nanoplatforms alleviate hypoxia by leveraging the chemical hydrolysis of metal peroxides or related precursor materials in the TME. These systems provide a sustained and controllable local oxygen source to support oxygen-dependent therapies. The fundamental principle of this approach is based on the exploitation of the instability of metal peroxides (MPs), such as $CuO_2$, $CaO_2$, $MgO_2$, and $ZnO_2$, in acidic conditions. These materials react with protons to directly release $O_2$ or its precursor, $H_2O_2$. This active oxygen-supplying strategy eliminates dependence on endogenous hydrogen peroxide levels within tumors and enables stable oxygen perfusion even in extremely hypoxic deep tissues.[204,205]

### Stimuli-Responsive Metal Peroxide Nanoplatforms

In research concerning responsive MP nanoparticles, the primary challenge lies in achieving an optimal balance between the rate of oxygen generation and systemic biosafety. Given that MPs tend to undergo spontaneous hydrolysis under neutral physiological conditions, it is a common practice among researchers to utilize pH-sensitive polymers, MOFs, or polyphenol-based protective layers to encapsulate the core.[206–208]

Tang et al developed a tumor pH-responsive nanoreactor based on $CuO_2$, utilizing human serum albumin (HSA) as a scaffold to achieve stable encapsulation of $CuO_2$ via biomineralization. In the mildly acidic TME (pH ~6.5), the nanoreactor rapidly dissociates. During hydrolysis, it instantaneously releases $Cu^{2+}$, $H_2O_2$, and $O_2$, supplementing the insufficient oxygen supply in tumors while providing $H_2O_2$ substrate for CDT to generate highly cytotoxic ·OH radicals. This enhances oxidative stress and significantly improves the therapeutic efficacy of PDT/photosensitizer-mediated therapy. In vitro experiments confirmed that $O_2$ produced from $CuO_2$ notably ameliorated the photosensitive response of hypoxic cells.[158] Chen et al developed a functional material (DOX-TAPP-$CaO_2$@OA@PAA, DTCOP) by coating $CaO_2$ with polyacrylic acid (PAA). This material achieves stable oxygen release under low pH conditions and can synergize with photosensitizers to significantly enhance PDT efficiency and alleviate tumor hypoxia. The acid-triggered $O_2$ release addresses the reduced activity of photosensitizers caused by hypoxia, offering potential to improve the response of oxygen-dependent therapies.[159] Similarly, Mo et al designed a pH-responsive nanoplatform $CaO_2$@CUR@ZIF-Cu, in which the $CaO_2$ core releases $H_2O_2$ and $O_2$ in the acidic TME, while ZIF-Cu serves as

a pH-sensitive encapsulation shell to prevent premature hydrolysis in normal tissues. Under acidic conditions, this nanoplatform effectively releases oxygen and provides $H_2O_2$ substrates, significantly amplifying Fenton-like ROS generation. This cascade enhances the outcomes of both CDT and immunotherapy while maintaining low systemic toxicity.[160]

Qiao et al engineered polydopamine-coated $ZnO_2$@PDA nanoparticles capable of undergoing hydrolysis within the acidic TME to release $H_2O_2$ and $O_2$. Additionally, the liberated $Zn^{2+}$ ions interfere with the metabolic-redox equilibrium of tumor cells, offering an alternative mechanism for tumor growth inhibition. This innovative design illustrates the strategic application of shell functionalization to regulate the acid-responsive hydrolysis of MPs, thereby augmenting oxygen production while maintaining the biostability and biosafety of the nanoparticles.[161]

### Cascade Catalytic Oxygen-Generating Nanoplatforms

To overcome the challenges posed by insufficient $H_2O_2$, low pH, and high antioxidant capacity within the TME, cascade catalytic oxygen-generating systems utilize multiple chemical and enzymatic reaction pathways to continuously enhance the local oxygen supply. Li et al developed a PFC nanoemulsion to construct a PFC-$H_2O$ "liquid–liquid" interfacial system. Their study confirmed that during high-frequency liquid–liquid contact/separation processes induced by ultrasonic vibration, oxygen atoms in water molecules lose electrons to generate ·OH. Under ultrasound assistance, oxygen in water can also extract electrons from negatively charged PFC (PFC*), producing superoxide anion radicals ($\cdot O^{2-}$). The researchers applied this ROS generation mechanism to cancer therapy. By employing human serum albumin (HSA)-modified perfluorotributylamine (PFTBA) PFC nanoemulsions, ROS were generated under ultrasound irradiation, triggering immunogenic cell death in tumor cells. This work provides a promising strategy for cancer therapy.[162]

Yu et al developed a H-$MnO_2$/GOX&CQ-iRGD cascade nanoamplifier, a responsive cascade system specifically designed for pancreatic cancer. The hollow $MnO_2$ shell undergoes decomposition in the acidic TME, resulting in the release of $Mn^{2+}$ ions and $O_2$. The encapsulated glucose oxidase (GOx) facilitates the conversion of intracellular glucose into $H_2O_2$, which is then either reconverted into $O_2$ through the catalytic action of $MnO_2$ or participates in Fenton-like reactions to generate ·OH. This cyclical process markedly enhances the efficacy of CDT and mitigates hypoxia within the TME. The cascade nanosystem not only significantly augments the production of $H_2O_2$ and $O_2$ but also demonstrates a robust capability for ·OH generation in a simulated TME, as evidenced by changes in UV-visible absorption and methylene blue (MB) probe assays. Both in vitro and in vivo studies demonstrate that this "targeting–decomposition–catalysis–inhibition" cascade mechanism substantially improves tumor suppression while maintaining excellent biosafety and selectivity.[163]

Zhang et al developed a hybrid nanozyme that integrates mineralized $MnO_2$ with a MOF carrier. In the multilayered architecture of $Fe_3O_4$@ZIF-8/GOx@$MnO_2$, the ZIF-8 shell undergoes acid-induced decomposition within the TME, releasing GOx and $Fe_3O_4$. The $H_2O_2$ generated through GOx catalysis is converted into $O_2$ by $MnO_2$ to alleviate hypoxia. Concurrently, the $Mn^{2+}$ ions released from $MnO_2$ decomposition facilitate the Fenton reaction, producing ·OH and thereby enhancing the CDT effect. This platform amalgamates multiple synergistic functionalities, such as oxygen supply, inhibition of glucose metabolism, and ROS generation, demonstrating augmented antitumor activity and immunomodulatory effects in both in vitro and in vivo settings.[164] Despite the significant advantages of cascade oxygen-generating systems in amplifying in situ oxygen supply efficiency and synergistic sensitization, their intricate multi-component structures present challenges related to the controllability of reaction pathways, biosafety, and the assessment of in vivo metabolic behavior.[163] Future research should prioritize the precise regulation of reaction kinetics, emphasizing the integration of self-regulatory or feedback inhibition mechanisms and the development of biodegradable or low-loading catalytic units. These approaches have the potential to facilitate the creation of intelligent, self-sensing kinetic regulatory networks characterized by improved controllability, reproducibility, and clinical relevance, as opposed to the mere aggregation of multiple independent catalytic events to achieve therapeutic outcomes.

## Microbial or Biomimetic Photosynthetic Nanoplatforms

With an enhanced comprehension of the pathogenic mechanisms associated with hypoxia in the TME, microbial or biomimetic photosynthetic nanoplatforms have been proposed as innovative light-driven strategies for in situ oxygen

production. These systems are designed to continuously improve the hypoxic microenvironment, facilitate oxygen-dependent therapies, and initiate robust immune responses. In nature, photosynthetic organisms such as algae and cyanobacteria efficiently convert light energy into chemical energy, releasing oxygen through photosynthesis, and are characterized by high quantum efficiency and excellent biocompatibility. This approach not only ensures sustained and controllable oxygen delivery but also utilizes carbon dioxide produced by tumor metabolism through photosynthesis, thereby mitigating hypoxia and modulating the local acidic TME.[165,166,209]

### Living Photosynthetic Microorganism-Based Nanoplatforms

Living microbial platforms leverage the metabolic pathways of intact organisms, offering potential for self-replication and environmental sensing. Among these platforms, cyanobacteria and Chlorella are the most extensively studied vectors. Their integrated photosystem I (PS I) and photosystem II (PS II) complexes facilitate efficient oxygen evolution, even under conditions of extremely low light intensity.[210] For example, Zhang et al described the development of an in situ formed microalgae-integrated living hydrogel (ACG gel), comprising alginate, *Chlorella sorokiniana* (C. soro), and GOx, which undergoes crosslinking directly at the tumor site. The incorporated microalgae continuously generated substantial amounts of oxygen under visible light through photosynthesis, thereby increasing intratumoral oxygen saturation and enhancing GOx-catalyzed glucose depletion to disrupt the energy supply. This mechanism ultimately converts the immunosuppressive TME into an immunoresponsive state. In vitro studies demonstrated that 4T1 cells in the hypoxic PBS group exhibited pronounced red fluorescence of HIF-1α. Conversely, in the group co-cultured with C. soro-containing gels under illumination, the red fluorescence of HIF-1α was absent, indicating that the ACG gel effectively mitigated hypoxia through photosynthetic oxygenation. In vivo experiments using the 4T1 tumor model further demonstrated that the ACG gel significantly inhibited tumor growth and effectively prevented postoperative recurrence, thereby confirming the potential of living photosynthetic microorganisms as natural oxygenators.[165]

Zhong et al enhanced the biocompatibility and in vivo retention of photosynthetic microalgae by encapsulating them with biomineralized calcium phosphate (CV@CaP). In mouse tumor models, this system significantly alleviated hypoxia through sustained photosynthetic oxygen generation, enhanced RT efficacy, and triggered infrared-mediated synergistic PTT/PDT, demonstrating the application potential of living microalgae delivery platforms in multimodal cancer therapy.[167] However, the introduction of such living exogenous microorganisms into the human body inevitably presents substantial biosafety concerns. Lipopolysaccharide (LPS) present on the surface of prokaryotes, such as cyanobacteria, along with the unique cell wall components of microalgae, are readily recognized by the host's innate immune system, leading to significant complement activation or systemic inflammatory responses (SIRS).[211] Furthermore, live microorganisms have the potential to proliferate and migrate unintentionally within the intricate in vivo environment. They may also acquire genetic mutations through horizontal gene transfer, which can lead to deviations from their intended therapeutic design and result in unpredictable ecological impacts. Additionally, in immunocompromised cancer patients, microorganisms generally considered non-pathogenic may display conditional pathogenicity, leading to uncontrollable infections.[212] Therefore, to advance the clinical translation of such living microbial platforms, priority should be given to constructing "genetic kill switches" via synthetic biology approaches, or to developing engineered microbial systems that are metabolically active but replication-deficient.[213] These strategies aim to preserve photosynthetic activity while eliminating self-replication capacity, rather than drawing conclusions regarding biosafety solely based on oxygen-generating performance.

### Plant-Derived Biomimetic Thylakoid Nanoplatforms

Plant-derived nanothylakoids or nanovesicles utilize photosynthetic organelles or membranes to construct biomimetic oxygen carriers. Upon exposure to light at the tumor site, these systems can be activated to produce oxygen, thereby improving the efficacy of photosensitizers and facilitating immune activation.[214] Mei et al systematically utilized the endogenous chlorophyll system within plant-derived nanovesicles as an "in vivo photosynthetic oxygenator" for on-demand oxygen generation at the tumor site, precisely amplifying the PDT effect. The researchers developed a multifunctional nanoplatform based on spinach-derived nanovesicles (SDNVs) encapsulated with aggregation-induced emission luminogens (AIEgens), denoted as AIE@SDNVs, integrating drug delivery, oxygen production, and

immune activation. The construction of AIE@SDNV and the underlying mechanism of its synergistic photoimmunotherapy are depicted in Figure 5. Utilizing their inherent photosynthetic capabilities, SDNVs release significant amounts of oxygen upon exposure to light, serving as a substrate for AIEgens and thereby enhancing the generation of ROS. This sequential process intensifies lipid peroxidation and disrupts calcium homeostasis in tumor cells, ultimately inducing ICD. Notably, this approach of photosynthetic nanovesicle-mediated photoimmunotherapy not only inhibited the growth of primary tumors in a bilateral tumor model but also effectively suppressed distant, non-irradiated tumors and extended survival. These findings highlight the significant potential of plant-derived photosynthetic vesicles in alleviating tumor hypoxia and reversing the immunosuppressive TME.[168] Compared with conventional synthetic nanocarriers, plant-

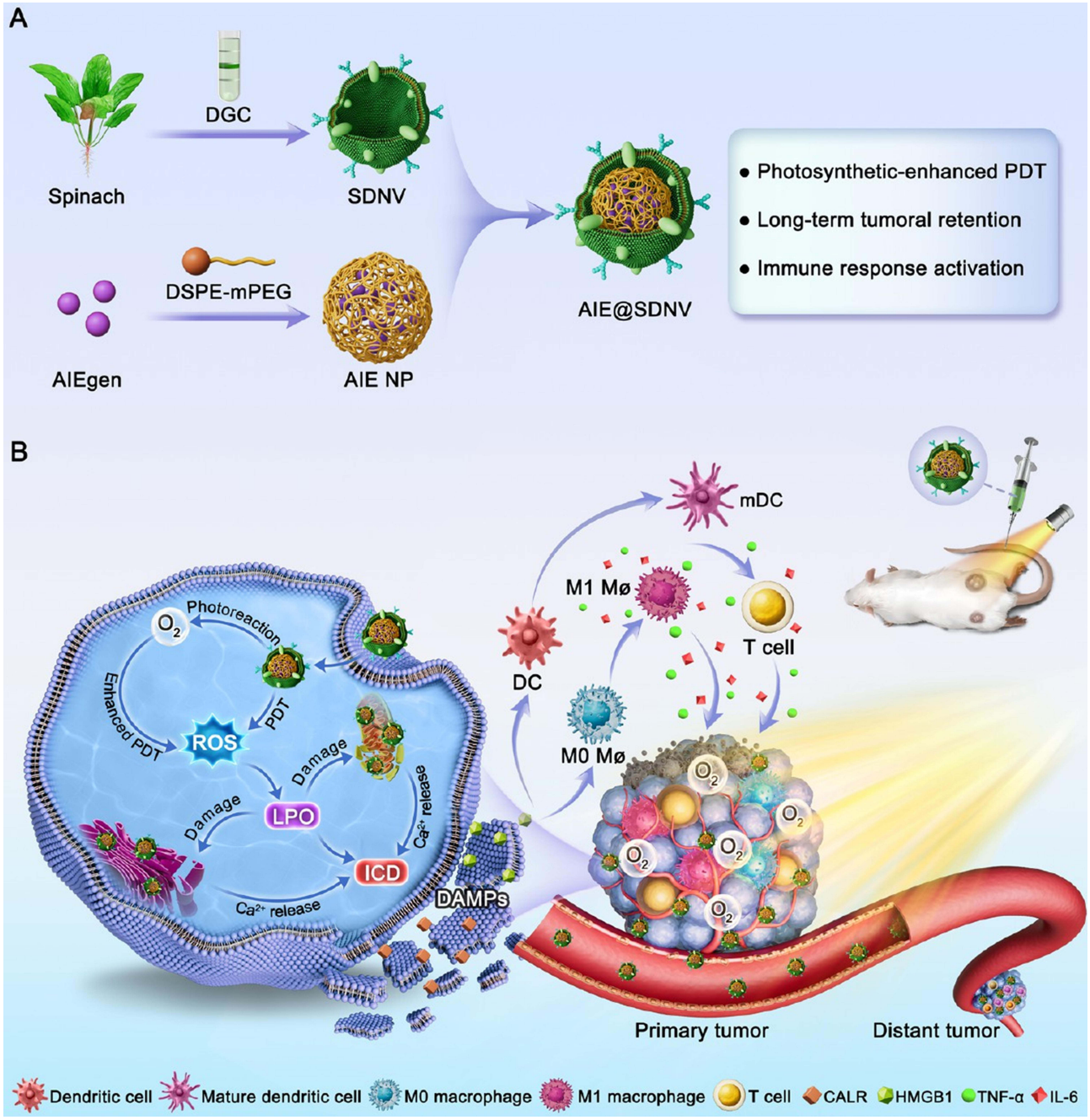


**Figure 5** Construction and photoimmunotherapeutic mechanism of the biomimetic nanoplatform AIE@SDNV. (**A**) Preparation of AIE@SDNV nanoparticles. (**B**) Light-triggered photosynthetic oxygen generation and AIEgen delivery by SDNV enhance PDT, induce ICD, and activate antitumor immune responses in a bilateral tumor model. Reproduced with permission.[168] Copyright © 2026 American Chemical Society.


https://doi.org/10.2147/IJN.S615263

derived biomimetic systems offer multiple advantages, including superior biocompatibility, intrinsically robust oxygen-generating capability, and high drug-loading capacity and photosensitizer activation efficiency. As emerging biomimetic photosynthetic nanoplatform, these systems hold the potential to yield groundbreaking outcomes in future integrated photo-immunotherapy strategies.

### Bio-Inorganic Hybrid Photosynthetic Microrobots

Bio-inorganic hybrid photosynthetic systems represent an innovative integration of photosynthetic microorganisms or biological components with inorganic nanomaterials to develop microrobotic platforms. These platforms facilitate a synergistic interaction between photosynthetic oxygen production and functional inorganic elements, such as magnetic responsiveness, photothermal effects, and radiation enhancement. A typical representative is a composite platform combining cyanobacteria with radiotherapy-sensitizing nanoparticles. Li et al synthesized $La_2O_3$ NPs via a solid-phase reaction method. The particle surfaces were coated with membrane structures formed from extracellular substances (eg, polysaccharides and proteins), with visible thylakoid stacks inside and an average diameter of 145.17 ± 58.49 nm. This nanoplatform alleviates tumor hypoxia through laser-activated cyanobacterial photosynthesis, while $La_2O_3$ enhances radiation-induced ROS generation and triggers pyroptosis via the ROS-NLRP3-GSDMD pathway. This process is further enhanced after RT, promoting the secretion of immune factors such as IL-1β and IL-6. In vivo studies using LLC and CT26 tumor models confirmed that this dual-enhanced RT platform exhibits excellent antitumor efficacy, offering a promising strategy for treating hypoxic solid tumors. Despite these encouraging results, clinical translation faces challenges, including the long-term stability of cyanobacterial components, standardized preparation of nanoparticle-hydrogel systems, and individual differences among patients. Beyond colorectal cancer, this platform also demonstrated efficacy in hypoxic lung cancer models, suggesting potential applications for other hypoxic solid tumors. Future studies will explore combination therapies with chemotherapy or immune checkpoint inhibitors and assess long-term safety.[169]

In situ oxygen-generating nanoplatforms have demonstrated a substantial capacity to elevate local oxygen partial pressure and improve the efficacy of oxygen-dependent therapies across various tumor models. However, their further development is impeded by several critical challenges. Notably, there is inadequate efficiency of externally driven energy in penetrating deep tumors, coupled with a lack of comprehensive evaluations of their long-term metabolic behavior and immunological compatibility. Consequently, future research may benefit more from focusing on the development of programmable, on-demand oxygen generation systems integrated with therapeutic processes, rather than merely enhancing oxygen production efficiency. For instance, aligning oxygen release with radiotherapy dosage, light irradiation intervals, or stages of immune activation could be advantageous. Additionally, simplifying material composition, minimizing the proportion of non-degradable components, and incorporating systematic pharmacokinetic and immunological safety assessments at an early stage are likely to be pivotal steps in advancing in situ oxygen-generating strategies from laboratory research to clinical application.

## Oxygen-Economization Nanoplatforms for Tumor Hypoxia Alleviation

The development of a hypoxic TME arises not only from an inadequate supply of oxygen but also from the elevated oxygen consumption rate (OCR) of tumor cells, the latter of which represents a significant limiting factor for the effectiveness of oxygen-dependent therapeutic interventions. Conventional nanoplatforms, such as oxygen-carrying and in situ oxygen-generating nanoplatforms, primarily concentrate on augmenting oxygen supply. However, these methodologies encounter challenges related to the efficiency and duration of oxygen delivery, as well as maintaining a balanced interaction with the metabolic oxygen consumption of tumors. Consequently, the concept of oxygen-economization nanoplatforms has emerged in recent years. This strategy is centered on either reducing oxygen consumption within tumor tissues or enhancing the efficiency of oxygen utilization, thereby improving overall tumor oxygenation and bolstering the efficacy of oxygen-dependent therapeutic modalities.[128,215] Unlike conventional oxygen supplementation methods, this strategy emphasizes more efficient reversal of hypoxia by decreasing intracellular oxygen consumption, inhibiting oxidative metabolic pathways, or enhancing the rate of oxygen utilization in therapeutic reactions, rather than merely augmenting local oxygen supply. Within this context, nanoplatforms can serve multiple functions, such as delivering drugs that suppress oxygen consumption,[216] catalyzing the redirection of tumor metabolic pathways,[217,218] or integrating responsive functions to achieve on-demand regulation of oxygen utilization. Table 2 provides a summary of representative oxygen-economization nanoplatforms designed to alleviate tumor hypoxia.

**Table 2** Summary of Oxygen-Economization Nanoplatforms Construction Strategies

| Strategies | Therapeutic Agents | Tumor Cells | Therapy Methods | Refs. |
|---|---|---|---|---|
| Inhibition of Complex I | HA-P-$L_{BAY}$ | 4T1 | Chemotherapy | [219] |
| | IMMMF | 4T1 | CDT/SDT | [220] |
| | Met-HCe6-Lip | 4T1/CT26/SCC-7 | PDT/Chemotherapy | [221] |
| | LCM | CT26 | PDT/Immunotherapy | [222] |
| | PSCe6-PFH | 4T1 | Photoimmunotherapy | [223] |
| Inhibition of Complex III | TNPs/IA | HeLa | PDT | [224] |
| | HSA-ATO NPs | MC38 | Immunotherapy | [225] |
| | NPs-aPD-1/$HbO_2$/ATO | MC38 | Immunotherapy | [226] |
| Other inhibition strategies | CyOA NPs | 4T1 | PDT | [227] |
| | 3BP@PLGA-IR780 | 4T1 | PDT | [228] |
| Metabolic reprogramming interventions | CFMB | 4T1 | CDT/PTT | [229] |
| | PTSK@CRM | CT26 | Immunotherapy | [230] |
| | OAGO | 4T1 | PTT | [231] |
| Oxygen conservation | PTTD NPs | 4T1 | PDT | [232] |
| | ACSN/$Fe_3O_4$@MSNs-iRGD | MGC-803 | PDT | [233] |

## Mitochondrial Respiration Inhibitors

Inhibiting the activity of key complexes in mitochondrial oxidative phosphorylation (OXPHOS) is an effective strategy to reduce oxygen consumption in tumor cells, improve local oxygen availability, and sensitize tumors to oxygen-dependent therapies.[234,235] Complex I (NADH-CoQ reductase) and Complex III (CoQ-cytochrome c reductase) within the mitochondrial electron transport chain (ETC) serve as primary sites for oxygen consumption. Targeted inhibitors of these complexes can markedly reduce the OCR of tumor cells, consequently preserving oxygen to augment therapeutic efficacy.[236,237]

### Inhibition of Complex I

Complex I in the mitochondrial ETC serves as the initiating site of oxidative phosphorylation. It is responsible for oxidizing NADH and transferring electrons to ubiquinone (CoQ), accompanied by proton transmembrane translocation, making it one of the major oxygen-consuming sites in tumor cells.[238] Therefore, targeting Complex I with specific inhibitors can reduce intracellular oxygen consumption, induce an energy crisis, and alleviate the hypoxic microenvironment by modulating oxygen metabolism.[239] BAY 87–2243 is a notable inhibitor of Complex I, effectively suppressing its activity even at low nanomolar concentrations, which results in the disruption of the mitochondrial respiratory chain and a substantial reduction in OCR. Previous research has shown that BAY 87–2243 possesses significant antitumor efficacy across various cancer cell lines and xenograft tumor models. In models of BRAF-mutant melanoma, oral administration of approximately 9 $mg \cdot kg^{-1}$ notably reduced both tumor volume and weight. At the cellular level, treatment with BAY 87–2243 significantly decreased both basal and maximal OCR and induced a metabolic shift towards glycolysis, reflecting characteristics of mitochondrial reprogramming.[240] Su et al developed a hyaluronic acid (HA)-crosslinked liposomal nanocarrier system, HA-P-$L_{BAY}$, for delivering BAY 87-2243. By meticulously optimizing the physical integrity of the liposomal membrane, this system facilitates enhanced transcellular penetration of the drug within tumor tissues, thereby overcoming the limitations of conventional drug delivery systems that are often unable to penetrate deeply into tumors. The HA-mediated CD44 targeting enables the initial accumulation of liposomes in tumor tissues,

followed by active transcytosis to overcome elevated interstitial fluid pressure and deliver BAY 87–2243 to deep-seated tumor cells. Once internalized, the drug precisely inhibits mitochondrial respiratory chain Complex I, reducing endogenous OCR and effectively alleviating tumor hypoxia. Concurrently, it suppresses malignant tumor behavior by downregulating HIF-1α and its downstream target genes. This nanoplatform achieves a synergistic effect of oxygen conservation and deep drug delivery, underscoring the potential of modulating membrane integrity to optimize the antitumor efficacy of respiratory inhibitors.[219]

Metformin, a widely utilized antidiabetic medication, has been demonstrated to decrease the OCR of tumor cells by inhibiting Complex I activity, thereby mitigating hypoxia within the TME. This action subsequently ameliorates the immunosuppressive milieu and enhances the effectiveness of oxygen-dependent therapies.[220] Mechanistically, metformin inhibits mitochondrial Complex I to reduce oxygen consumption and activate the AMPK signaling pathway. This results in decreased stability of HIF-1α and downregulation of its downstream targets, such as CA9 and VEGF, thereby exerting dual regulatory effects on both tumor metabolism and the immune microenvironment.[216,221,222,241]

Dai et al engineered oxygen-carrying polymeric micelles, PSCe6-PFH, co-loaded with metformin and a photosensitizer, drawing inspiration from the biological circadian rhythm. Metformin, by inhibiting Complex I activity, significantly curtailed oxygen consumption in tumor cells, thereby reducing oxygen consumption at its source and prolonging local oxygen availability within tumors. Mechanistic investigations revealed that during the dark phase, the release of oxygen from the micelles, coupled with metformin-mediated suppression of mitochondrial respiration, mitigated tumor hypoxia, enhanced dendritic cell (DC) maturation by 1.5-fold, and decreased the infiltration of immunosuppressive Treg cells. In the subsequent light phase, the improved oxygen environment further augmented ROS generation and ICD induced by PDT/photoimmunotherapy (Figure 6A). In breast cancer mouse models, the group subjected to alternating light-dark treatment demonstrated significantly reduced tumor volume, extensive apoptosis within tumor tissue, and manageable systemic toxicity, thereby achieving a synergistic amplification effect characterized by "inhibiting oxygen consumption–alleviating hypoxia–sensitizing therapy". This study first highlights the critical role of the dark phase in photoimmunotherapy. By aligning biological rhythm with therapeutic rhythm through biomimetic design, it provides a new strategy for metformin-based nanotherapeutic approaches.[223]

### Inhibition of Complex III

Complex III facilitates the electron transfer from ubiquinone to cytochrome c and constitutes a crucial oxygen-utilizing component within the ETC. The strategic inhibition of Complex III with specific inhibitors can diminish oxygen consumption by obstructing electron flow, while concurrently promoting electron leakage and the generation of ROS. This dual action can potentiate the cytotoxic efficacy of therapies reliant on oxygen.[242,243]

Atovaquone, an antimalarial agent structurally similar to coenzyme Q10, functions as a Complex III inhibitor and has demonstrated significant research potential in the regulation of cancer metabolism and the amelioration of hypoxia.[224] Ashton et al reported that atovaquone rapidly decreases the OCR by over 80% across various tumor cell lines, an effect considerably more pronounced than that elicited by other metabolic inhibitors. In tumor spheroid models of FaDu, HCT116, and H1299, atovaquone treatment notably reduced hypoxic regions, accompanied by a significant decrease in OCR, while also enhancing radiosensitivity.[244] In a clinical trial involving patients with non-small cell lung cancer (NSCLC), the administration of standard dosages of atovaquone resulted in a significant reduction in hypoxic volume, with a median change of −28%. Additionally, it led to the downregulation of hypoxia-related gene expression, all without notable adverse events. This represents the first clinical evidence that targeting tumor mitochondrial metabolism can alleviate tumor hypoxia and exert significant antitumor effects at the mRNA level.[245] In addition, atovaquone exhibits significant OCR inhibition and induces metabolic reprogramming in cell lineages highly dependent on mitochondrial metabolism, such as breast cancer stem cells.[246] Its ability to reduce hypoxia and enhance radiosensitivity has also been validated in refractory diffuse midline glioma models.[247]

To enhance the bioavailability and tumor-targeting efficacy of atovaquone and to further augment its immunotherapeutic potential, Wang et al engineered nanoparticles composed of human serum albumin and atovaquone (HSA-ATO NPs). The utilization of this nanocarrier markedly increased systemic drug accumulation and ameliorated the hypoxic

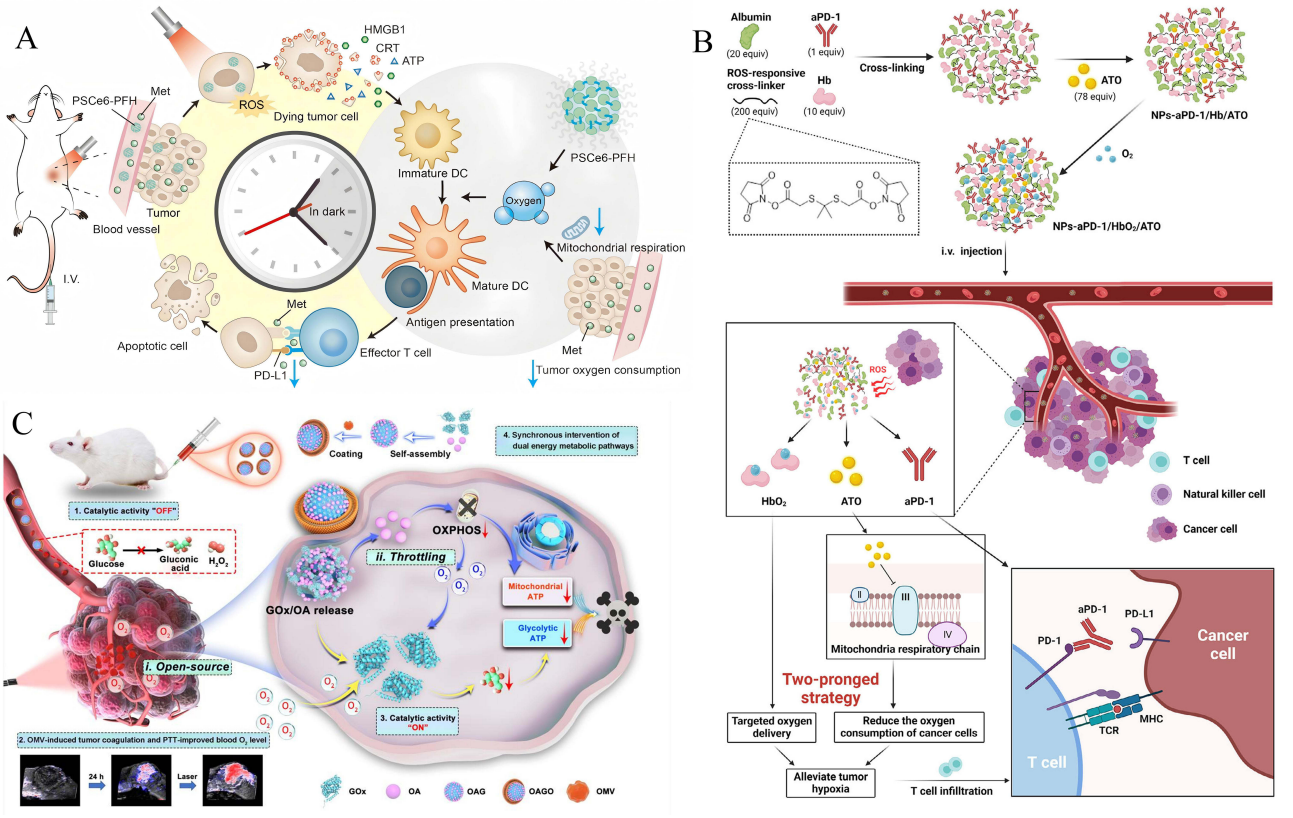


**Figure 6** Oxygen-economization nanoplatforms. (**A**) Schematic illustration of the PSCe6-PFH nanoplatform for establishing irradiation-darkness therapeutic rhythms to enhance photodynamic immunotherapy in hypoxic tumors through amplification of the cancer-immunity cycle. Reproduced with permission.[223] Copyright © 2026 Tsinghua University Press Ltd. (**B**) Synthesis and function of NPs-aPD-1/$HbO_2$/ATO. Reproduced with permission.[226] Copyright © 2026 Wiley. (**C**) Schematic illustration of a synergistic oxygen modulation nanoplatform that enhances oxygen supply and reduces oxygen consumption for improved antitumor therapy. Reproduced with permission.[231] Copyright © 2026 Elsevier. In this schematic, solid arrows indicate activation or cascading progression of biological processes; blunt-ended inhibitory lines represent the blockade of relevant pathways; downward arrows (↓) indicate downregulation of corresponding biological indicators; cross symbols denote the inhibition of related biological processes.

**Abbreviations**: CRT, calreticulin; HMGB1, high-mobility group box 1 protein; ATP, adenosine-5′-triphosphate; Met, metformin; aPD-1, PD-1 antibody; Hb, hemoglobin; ATO, atovaquone; i.v., intravenous; $HbO_2$, oxygenated hemoglobin; ROS, reactive oxygen species.

TME. By alleviating hypoxia, these nanoparticles promoted the infiltration of $CD8^+$ T cells, thereby enhancing the antitumor efficacy of PD-1 immune checkpoint blockade therapy.[225] In addition, Zhang et al developed a multifunctional nanoplatform (NPs-aPD-1/$HbO_2$/ATO) by integrating atovaquone with oxygenated hemoglobin ($HbO_2$) and an anti-PD-1 antibody, thereby achieving the triple functions of "inhibiting oxygen consumption, direct oxygen supplementation, and immune activation". Figure 6B illustrates the preparation method and mechanism of action of NPs-aPD-1/$HbO_2$/ATO. In vivo experiments showed that the nanoaggregate significantly alleviated tumor hypoxia by inhibiting Complex III-mediated oxygen consumption, and synergized with $HbO_2$ to provide additional oxygen, thus enhancing the immunotherapeutic response. This system achieved synergy between oxygen conservation and oxygen supplementation. Notably, NPs-aPD-1/$HbO_2$/ATO exhibited distinct tumor-targeting capability in vivo, with tumor accumulation levels 4.2-fold higher than those observed in the liver. This study holds substantial significance for achieving targeted drug delivery, overcoming tumor hypoxia, and advancing immunotherapy, providing valuable references for the development of cancer treatment strategies.[226]

These studies illustrate that strategies for economizing oxygen can optimize the tumor's oxygen metabolic environment by decreasing mitochondrial oxygen consumption and enhancing the effective utilization of local oxygen under conditions of limited overall oxygen supply. Given that the most used type II photosensitizers in clinical settings exhibit high sensitivity to oxygen concentration, their efficacy is constrained by the kinetics of molecular oxygen conversion into $^1O_2$. Therefore, enhancing oxygen utilization efficiency by reducing endogenous oxygen consumption offers a viable approach to improving the efficacy of PDT. Although oxygen-economization strategies present certain


https://doi.org/10.2147/IJN.S615263

limitations compared to other alternative approaches aimed at reducing the oxygen dependence of PDT, type I photosensitizers, which can generate free radicals through electron transfer mechanisms, are less reliant on oxygen concentration. This characteristic allows them to fundamentally circumvent the limitations associated with $^1O_2$ generation.[248] V-PDT prompts occlusion of tumor vasculature, resulting in rapid and sustained ischemic necrosis, and its therapeutic effectiveness is independent of maintaining elevated oxygen levels during irradiation.[195] In addition, fractionated irradiation strategies can effectively alleviate acute oxygen depletion during treatment by restoring tissue oxygenation during the intervals between light exposures.[249] Conversely, oxygen-economization strategies do not inherently augment the total oxygen content; their effectiveness is contingent upon the initial $pO_2$ and the degree of respiratory inhibition, and they may be constrained in regions of severe hypoxia. Consequently, contemporary research increasingly advocates for the integration of these approaches with oxygen-carrying or oxygen-generating strategies to achieve a coordinated regulation of oxygen supply and demand, thereby optimizing the overall efficacy of PDT and other oxygen-dependent therapies.

### Other Inhibition Strategies

In addition to targeting Complexes I and III of the electron transport chain, an increasing body of research has concentrated on disrupting other critical mitochondrial oxygen metabolic enzymes or associated metabolic pathways to modulate oxygen consumption and energy metabolism. A typical example is the multifunctional hemicyanine-based nanoplatform (CyOA NPs) reported by Wang et al By targeting succinate dehydrogenase (SDH) within Complex II of the mitochondrial respiratory chain, CyOA NPs inhibit OXPHOS, enabling oxygen-economization PDT that enhances phototoxicity against cancer stem cells (CSCs). By inhibiting SDH activity, the nanoformulation significantly decreases oxygen consumption in tumor cells. Concurrently, as a photosensitizer, it generates ROS upon light irradiation. This synergy between oxygen conservation and explosive ROS production results in an approximately 50.4-fold increase in phototoxicity compared to non-targeted systems, alongside remarkable tumor inhibition in breast cancer stem cell models. Owing to its self-assembly capability and integrated dual functionality, this SDH-inhibiting nanoplatform offers a carrier-free, easily prepared, and highly effective design strategy for mitochondrial metabolic inhibition.[227]

Other researchers have employed nanocarriers to deliver specific mitochondrial metabolic disruptors. Wen et al developed a nanoplatform by co-assembling 3-bromopyruvate (3BP) with a carrier polymer and a photosensitizing dye. This system preferentially accumulates in mitochondria, where it concurrently decreases cellular oxygen consumption and reduces the ROS threshold. This dual action enhances the therapeutic efficacy of PDT and addresses the limitations posed by hypoxia. Consequently, this strategy facilitates a dual-targeted disruption of tumor cell energy metabolism, thereby improving overall antitumor efficacy.[228]

## Metabolic Reprogramming-Based Oxygen Conservation Strategies

Metabolic reprogramming is a fundamental characteristic of cancer, facilitating malignant tumors in maintaining energy supply, synthesizing essential macromolecules, and withstanding therapeutic stress amidst conditions of rapid proliferation, nutrient scarcity, and microenvironmental challenges. This metabolic adaptation includes the well-known Warburg effect,[250,251] glutamine addiction,[252] alterations in lipid metabolism, and remodeling of OXPHOS pathways.[253] Tumor metabolic reprogramming provides ATP and intermediate metabolites for rapid proliferation, and drives therapeutic resistance and recurrence by modulating redox balance, regulating signaling pathways (such as PI3K/AKT/mTOR and HIF-1α), and interacting with the immune microenvironment.[229,230,254,255] Consequently, intervention strategies targeting these metabolic pathways have emerged as a pivotal direction in cancer therapy research.

Jiang et al designed an oxygen-regulated enzymatic nanoplatform (OAGO) that integrates GOx with the mitochondrial inhibitor oligomycin A, facilitating simultaneous intervention in both glycolysis and OXPHOS. In 4T1 mouse tumor models, this strategy enhanced intratumoral oxygen availability and GOx reaction efficiency while impairing mitochondrial function, thus imposing a dual blockade on tumor energy supply. It markedly inhibited tumor proliferation and improved the efficacy of combination therapy (Figure 6C). The study clearly demonstrates the mechanistic advantage of continuously targeting the two major energy metabolism pathways while regulating oxygen utilization, representing a promising approach for efficient antitumor therapy.[231] In models of colorectal and gastric cancer, Aisu et al developed

a small-molecule dual inhibitor that concurrently targets OXPHOS and lactate metabolism. This intervention disrupts the complementary interaction between these two principal energy-generating pathways, resulting in energy depletion and degradation of the TME, thereby augmenting the overall therapeutic efficacy. High-resolution metabolic imaging (HP-MRSI) offers the capability to monitor these metabolic alterations in real time, underscoring the potential of this strategy as a prospective option in cancer treatment.[256]

### Oxygen Conservation and Enhanced Oxygen Utilization Strategies

In the complex TME, oxygen is not only rapidly consumed by proliferating tumor cells but also inefficiently utilized by cancer-associated fibroblasts, immune cells, and various non-therapeutic redox reactions. This results in the non-targeted, dispersed utilization of limited oxygen resources, weakening the actual efficacy of oxygen-dependent therapies. In light of this understanding, strategies have been proposed to conserve oxygen and enhance its targeted utilization. The central concept involves regulating oxygen diffusion, retention, and preferential usage, thereby obstructing non-target oxygen-consuming pathways and facilitating precise spatiotemporal management of oxygen within the tumor.[232,257]

Situ et al developed an oxygen-economization, tumor-targeted photosensitive magnetic nanomaterial (ACSN/$Fe_3O_4$@MSNs-iRGD) for the integrated diagnosis and therapy of gastric cancer. This system co-delivers atovaquone (ATO) and the photosensitizer ACSN via a nanocarrier. The two components are integrated into a composite photosensitive functional unit, in which ATO is used to inhibit oxygen consumption and ACSN participates in the photodynamic reaction. Upon internalization into tumor cells, ATO specifically targets the mitochondria, inhibiting cellular aerobic respiration and thereby diminishing unnecessary oxygen consumption within the tumor. This oxygen-economization strategy enables the photosensitizer to more efficiently convert the remaining oxygen molecules into ROS upon laser irradiation, markedly improving the efficiency of PDT against hypoxic tumors. Studies demonstrated that this nanoplatform remarkably boosts ROS generation and augments the tumor-killing effect of PDT both in vitro and in vivo, achieving effective oxygen retention and preferential utilization.[233]

Nonetheless, compared with direct oxygen-carrying or in situ oxygen-generating strategies, oxygen-economization approaches present both advantages and limitations. These strategies do not rely on exogenous oxygen or substrates, thereby enhancing their potential for system simplification and applicability in deep tumor regions. However, they do not intrinsically increase overall oxygen levels, and their effectiveness is significantly influenced by the initial tumor $pO_2$ and the degree of metabolic inhibition. Consequently, in regions characterized by severe hypoxia, a singular oxygen-economization strategy may be insufficient to fully restore therapeutic efficacy. Therefore, there is an increasing research emphasis on integrating oxygen-economization strategies with oxygen-carrying or oxygen-generating methods to achieve a coordinated regulation of oxygen supply and demand, thereby optimizing the overall efficacy of oxygen-dependent therapies.

## The Advances of Key Nanoplatforms Effective Against Tumor Hypoxia

Tumor hypoxia is not an isolated microenvironmental feature, but is highly coupled with multiple resistance mechanisms including radioresistance, failure of photo/sonodynamic therapy, immunosuppression, and metabolic adaptation.[20] Consequently, strategies aimed solely at alleviating hypoxia or employing isolated therapeutic modalities often demonstrate limited efficacy within the complex tumor ecosystem.[258] In recent years, research has progressively transitioned from focusing on single-module hypoxia alleviation to utilizing hypoxia-relieving nanoplatforms as central components for combination therapy. By strategically integrating these platforms with RT, PDT, SDT, chemotherapy, immunotherapy, and other treatment modalities, therapeutic responses are enhanced across both spatial and temporal dimensions.[259,260] Under this framework, alleviating hypoxia is no longer merely an auxiliary function. Instead, it serves as a pivotal driver that directly governs key therapeutic processes, including ROS generation efficiency,[172,261,262] the extent of DNA damage,[263] induction of immunogenic cell death (ICD),[264,265] and remodeling of the tumor immune microenvironment.[170] A plethora of studies have illustrated that the strategic integration of oxygen regulation with multiple therapeutic modalities can overcome the limitations of monotherapy in hypoxic conditions. This synergistic approach results in markedly enhanced tumor suppression and can even trigger a systemic antitumor immune response in solid tumor models.[266] Consequently, this trend has catalyzed the rapid advancement of multifunctional nanoplatforms

designed for triple or higher-order combination therapies, establishing a critical pathway for the translation of tumor hypoxia-relieving strategies into clinical applications.[267]

## Dual-Mode Synergistic Antitumor Therapy

The integration of chemotherapy and PDT has demonstrated significant advancements in preclinical studies. Lee et al engineered Hb-based self-assembled nanoclusters, designated as DOX@HPBC, with an approximate diameter of 220 nm. In this system, Hb was conjugated with PEG-biotin and the photosensitizer Ce6, while also incorporating the chemotherapeutic agent DOX. In hypoxic HeLa cell models, this nanoplatform reduced hypoxia levels by approximately 64.8% and significantly restored the expression of hypoxia-related markers, such as HIF-1α and MDR1. In xenograft mouse models, it achieved a tumor volume reduction of approximately 96.6%, demonstrating excellent hypoxia alleviation and potent synergistic efficacy of chemo-PDT (Figure 7A).[268]

While the advent of chemotherapy has improved cytotoxic effects, the pronounced oxygen dependency of PDT continues to constrain its therapeutic effectiveness in deep-seated tumor areas. Conversely, integrating PDT with oxygen-

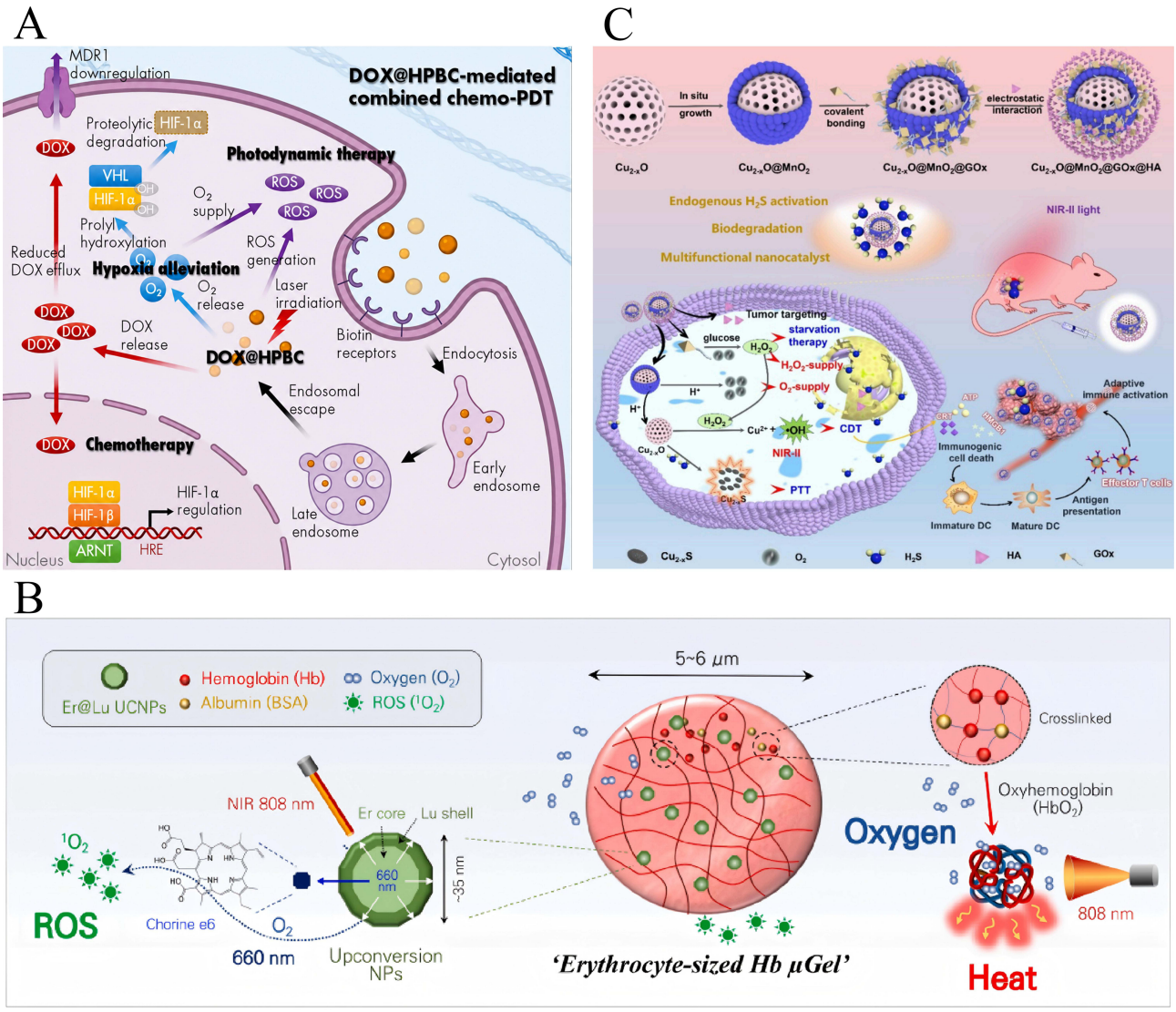


**Figure 7** Illustrates the following processes: (**A**) Chemo photodynamic therapeutic mechanism of DOX@HPBC. Reproduced with permission.[268] Copyright © 2026 Elsevier. (**B**) Hemoglobin microgels with erythrocyte size capable of generating heat, oxygen and reactive oxygen species. Reproduced with permission.[269] Copyright © 2026 Elsevier. (**C**) Structural design and therapeutic mechanism of the TME responsive $Cu_{2-x}O@MnO_2@GOx@HA$ nanoenzyme. Reproduced with permission.[154] Copyright © 2026 Elsevier.

independent PTT can significantly expand tumor vasculature through localized hyperthermia induced by the photothermal effect. This approach enhances blood oxygen supply, thereby fundamentally mitigating the oxygen deprivation challenge associated with PDT.[270–272] Kim et al designed a representative erythrocyte-sized Hb microgel system (Hb μGels) composed of Hb, upconversion nanoparticles (UCNPs), and a photosensitizer. This platform can not only supply oxygen but also generate heat and ROS under NIR irradiation, thereby achieving highly efficient PDT and PTT under extremely hypoxic conditions. The system is composed of Hb, bovine serum albumin (BSA), Ce6, and Er@Lu UCNPs. The UCNPs are designed to convert an 808 nm laser into visible light, thereby activating the photosensitizer to produce $^1O_2$, while Hb releases oxygen to mitigate tumor hypoxia, enabling multimodal synergistic antitumor effects (Figure 7B). In 4T1 mouse models, the Hb μGels demonstrated a significant inhibition of hypoxic tumor spheroid growth and an improvement in tumor $pO_2$, with hypoxic regions ($pO_2 < 5$ mmHg) being notably alleviated. These findings underscore the potent synergistic efficacy of PDT/PTT and confirm that Hb encapsulation can effectively alleviate tumor hypoxia, thereby enhancing the therapeutic efficacy of oxygen-dependent treatments.[269]

To overcome the limitations imposed by the hypoxic TME on SDT and immunotherapy, Huang et al encapsulated perfluorohexane (PFH) as an oxygen reservoir together with the photosensitizer Ce6 into liposomes, constructing a functional PFC-based oxygen-carrying nanodroplet PCL@$O_2$. This nanosystem demonstrated a substantial enhancement in ROS generation both in vitro and in vivo, facilitating SDT to induce a higher rate of apoptosis through an oxygen-dependent mechanism. Furthermore, it effectively alleviated tumor hypoxia by supplying additional oxygen. Notably, this study integrated the nanoplatform with immune checkpoint inhibitors, specifically the PD-1 antibody, to treat residual lesions following insufficient radiofrequency ablation (iRFA). In vivo experiments revealed that this combination therapy not only significantly inhibited the growth of primary and metastatic tumors but also markedly increased the proportion of antitumor immune cells, enhanced immune memory responses, reduced the number of Tregs, and improved long-term survival rates. This research provides a preclinical proof-of-concept for ultrasound-guided, self-oxygen-enriching SDT to augment cancer immunotherapy post-iRFA in solid tumors, offering a novel therapeutic strategy.[273]

## Multi-Modal Cascade Synergistic Therapeutic Strategies

To enhance therapeutic outcomes, recent research has transcended bimodal synergy by focusing on the development of integrated, multidimensional triple or even quadruple therapeutic paradigms, alongside cascade catalytic synergistic therapies. These approaches are designed to expand the therapeutic window by achieving cascade amplification effects at each stage, thereby offering innovative technical pathways for the effective eradication of complex solid tumors. Chen et al constructed a TME-mediated NIR-II light-activated multifunctional cascade nanoenzyme system ($Cu_{2-x}O$@$MnO_2$@GOx@HA) to achieve intratumoral self-supply of $O_2$/$H_2O_2$ and combine multiple therapeutic modalities. This nanoenzyme exploits the acidic conditions of the TME to selectively decompose the $MnO_2$ layer, resulting in the release of $Mn^{2+}$ ions and oxygen, thereby effectively mitigating TME-associated hypoxia. The released oxygen subsequently acts as a substrate for GOx, catalyzing the production of $H_2O_2$ and thereby enhancing the GOx-mediated self-supply of $H_2O_2$. Upon exposure to NIR-II (1064 nm) laser irradiation, $Cu_{2-x}O$ is transformed into $Cu_{2-x}S$, facilitating photothermal effects that synergize with CDT to augment tumor cell eradication (Figure 7C). In summary, this NIR-induced photocatalytic and cascade-reaction nanoenzyme not only alleviates tumor hypoxia but also enhances the efficacy of GOx-mediated starvation therapy and CDT. Additionally, the generated ROS induce ICD, thereby activating adaptive immune responses to achieve a multimodal synergistic antitumor effect, encompassing PTT, CDT, starvation therapy, and immunotherapy.[154]

Similarly, Tang et al constructed a TME-responsive self-oxygenating nanoplatform $CaO_2$@Cu-TCPP/DSF/HA ($CaO_2$-MD), which integrates in situ oxygen generation, sonodynamic therapy, cuproptosis induction, and immunotherapy activation into a single system to achieve deep multi-module synergy. The nanoplatform is activated by endogenous $H_2O_2$ and the dysregulated copper metabolism characteristic of the TME, resulting in continuous in situ oxygen production. This process effectively mitigates tumor hypoxia and significantly enhances the efficiency of ROS generation during SDT. Concurrently, the platform facilitates mitochondrial accumulation of copper ions, which induces cuproptosis marked by an imbalance in lipoylated proteins, thereby disrupting the metabolic survival mechanisms of tumor cells. The

oxidative stress induced by SDT further exacerbates mitochondrial damage, creating a positive feedback loop with cuproptosis for synergistic cytotoxicity. Both in vitro and in vivo experiments demonstrated that this approach substantially counteracted the inhibitory effects of hypoxia on SDT and cuproptosis, achieving a 96% tumor inhibition rate in the 4T1 breast cancer model. When combined with PD-L1 immune checkpoint blockade, the complete tumor regression rate reached 80%, and long-term immune memory was induced to prevent recurrence, providing a novel platform for multimodal therapy that breaks through the hypoxia limitation of solid tumors.[274]

In order to address the complex pathological issues associated with hypoxia and oxidative stress, Choi et al developed an innovative metal-free polyphenol-enzyme cascade nanoplatform (EGCG-catalase complex, EC), which is designed to autonomously scavenge ROS and continuously produce oxygen within hypoxic and oxidative microenvironments. The fundamental mechanism of this platform is based on a "scavenging-conversion-regeneration" cascade logic. By leveraging the multi-enzyme-mimetic activities (SOD/POD/GPx) of EGCG in conjunction with catalase, the system effectively transforms deleterious superoxide anions into hydrogen peroxide, which is subsequently decomposed into oxygen and water, thereby establishing a closed-loop antioxidant and oxygen-supplying system. In vitro experiments have demonstrated that the EC significantly decreases ROS levels in hypoxic endothelial cells, inhibits cellular senescence, and enhances angiogenesis. In a model of glucocorticoid-induced muscle atrophy, administration of the antioxidant malotilate through the EC platform effectively restored muscle fiber area and function. In a diabetic hindlimb ischemia model, the EC platform mitigated tissue necrosis and fibrosis, while synergistically interacting with VEGF to significantly enhance blood flow reperfusion. This study presents a comprehensive therapeutic strategy for hypoxia-related diseases, addressing both inadequate oxygen supply and oxidative damage concurrently.[275]

## Challenges and Perspectives for Clinical Translation

Research on mitigating tumor hypoxia is experiencing a paradigm shift from straightforward oxygen supplementation to systemic remodeling.[276–278] It is important to note, however, that although these multicomponent cascade nanosystems offer considerable benefits in terms of functional integration and therapeutic synergy, their complex structural design introduces new challenges for clinical translation. The precise assembly of multiple components necessitates multistep synthesis and stringent control of reaction conditions, which may complicate the maintenance of batch-to-batch consistency in compliance with Good Manufacturing Practice (GMP) guidelines.[279] Simultaneously, variables such as the preservation of enzymatic activity, regulation of inorganic component ratios, and interfacial stability may exhibit variability during large-scale production, potentially impacting the therapeutic efficacy and safety of the final product. Furthermore, the scale-up of multicomponent systems may face additional challenges, including intricate manufacturing processes, elevated production costs, and the absence of well-defined quality control standards.[280] Consequently, future research should not only focus on enhancing the therapeutic performance of these nanoplatforms but also prioritize the development of scalable fabrication strategies, streamlined component design, and the establishment of standardized quality control systems to facilitate their successful translation into clinical applications.

# Outlook

Future research on hypoxia-alleviating nanoplatforms should focus on designs that are both clinically translatable and dynamically regulated. Despite significant progress in enhancing intratumoral oxygen delivery, production, and retention, critical barriers continue to hinder clinical translation. The structural complexity of many existing nanoplatforms presents substantial challenges for scalable manufacturing, batch-to-batch reproducibility, and adherence to GMP standards. This underscores the necessity for simplified, modular, and robust design strategies. Furthermore, the long-term in vivo fate of nanomaterials, particularly those incorporating inorganic or non-degradable components, remains inadequately understood. Comprehensive investigations into pharmacokinetics, biodistribution, metabolic pathways, and long-term biosafety are therefore crucial to thoroughly evaluate their clinical applicability and safety profiles. Furthermore, contemporary oxygen-regulation strategies predominantly depend on static oxygen supplementation or modulation of consumption. In contrast, tumor oxygenation is intrinsically dynamic and spatially heterogeneous. Future research should prioritize the development of intelligent, self-adaptive systems that can synchronize oxygen regulation with the real-time metabolic

demands of tumors. Additionally, standardized quantitative in vivo methods for oxygen detection are essential for reliable cross-platform comparisons and preclinical validation. Building on promising early-phase clinical data from studies on pancreatic and breast cancers, the next generation of nanomedicine should incorporate highly biocompatible and bioresponsive platforms alongside innovative combination regimens. Precisely remodeling the dynamic TME through these synchronized strategies offers significant potential for overcoming therapeutic resistance and optimizing anticancer clinical outcomes.

## Data Sharing Statement

No datasets were generated or analyzed during the current study.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Funding

This study was supported by Natural Science Foundation of Hunan Province (No. 2025JJ80119), the Excellent Youth Project of Hunan Provincial Department of Education (No. 23B0362), the General Subjects of Hunan Provincial Administration of Traditional Chinese Medicine (No. B2024015), the Key Discipline Project on Chinese Pharmacology of Hunan University of Chinese Medicine [202302].

## Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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