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Review

Recent Advancements of Nanotechnology-Based Strategies for Overcoming Tumor Microenvironment Hypoxia

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Abstract

Hypoxia is a typical characteristic of most solid malignancies, which has multiple effects on malignant phenotypes and biological behaviors of tumors including epithelial-mesenchymal-transition (EMT), invasion, migration, metastasis, autophagy, stem cell maintenance, pathological angiogenesis, drug resistance, and immunosuppression. Rcentlyumoand reversing the tumor hypoxic environment via nanotechnology has emerged as a novel therapeutic approach for the treatment of malignancies. The main strategies related to nanotechnology to alleviate or ameliorate hypoxic environment are as follows: (1) Bringing external oxygen to tumor hypoxic microenvironment; (2) Generating oxygen based on nanotechnology *in situ*; (3) Regulating the structure of the tumor microenvironment; (4) Decreasing oxygen consumption in the tumor microenvironment. In this review, we will discuss these nanotechnologies in detail.

Keywords: nanotechnology; tumor microenvironment; hypoxia; metal-organic frameworks; photodynamic therapy

1. Introduction

Most solid malignancies are characterized by hypoxic tumor microenvironment (TME) due to the malformed blood vessel that cannot provide adequate oxygen or the imbalance between oxygen support and consumption in tumor cells [1–6]. Intratumoral hypoxia leads to increased activity of hypoxia-inducible factors (HIFs), which plays an important role in tumor progression and affect malignant tumor hallmarks including but not limited to cell proliferation, differentiation, apoptosis, genetic instability, tumor metabolism, vascularization/angiogenesis, immunosuppression, and metastasis [7]. In addition, tumor hypoxic microenvironment is a significant obstacle to oxygen-dependent cancer therapy such as radiotherapy, chemotherapy, photodynamic therapy (PDT), immunotherapy, and so on [8].

Overall, hypoxia is regarded as a critical role in tumor progression and resistance to tumor therapy, which makes it a novel target for cancer therapy [9]. Recently, many researchers have tried to target hypoxia TME via nanotechnology. In this review, we focused on the recent advancements of nanotechnology-based strategies for overcoming hypoxia in TME. The main strategies related to nanotechnology to alleviate or ameliorate hypoxic environment are as follows: (1) Bringing external oxygen to tumor hypoxia microenvironment; (2) Generating oxygen based on nanotechnology *in situ*; (3) Regulating the structure of the TME; (4) Decreasing consumption of oxygen in the TME (Fig. 1). These strategies are shown in Table 1 (Ref. [10–35] and will be discussed in detail in the following sections.

2. Discussion

2.1 The Mechanisms of Hypoxia Promoting Tumor Progression

The hypoxic condition has pleiotropic effects on malignancy phenotypes and biological behaviors of tumors including such as EMT, invasion, migration, metastasis, cancer stem cell maintenance, autophagy, pathological angiogenesis, drug resistance, and immunosuppression [36–40]. For example, Hypoxia plays an important role in causing the EMT, invasion, migration, and metastasis of pancreatic ductal adenocarcinoma (PDAC) [37]. Tumor cells ac-

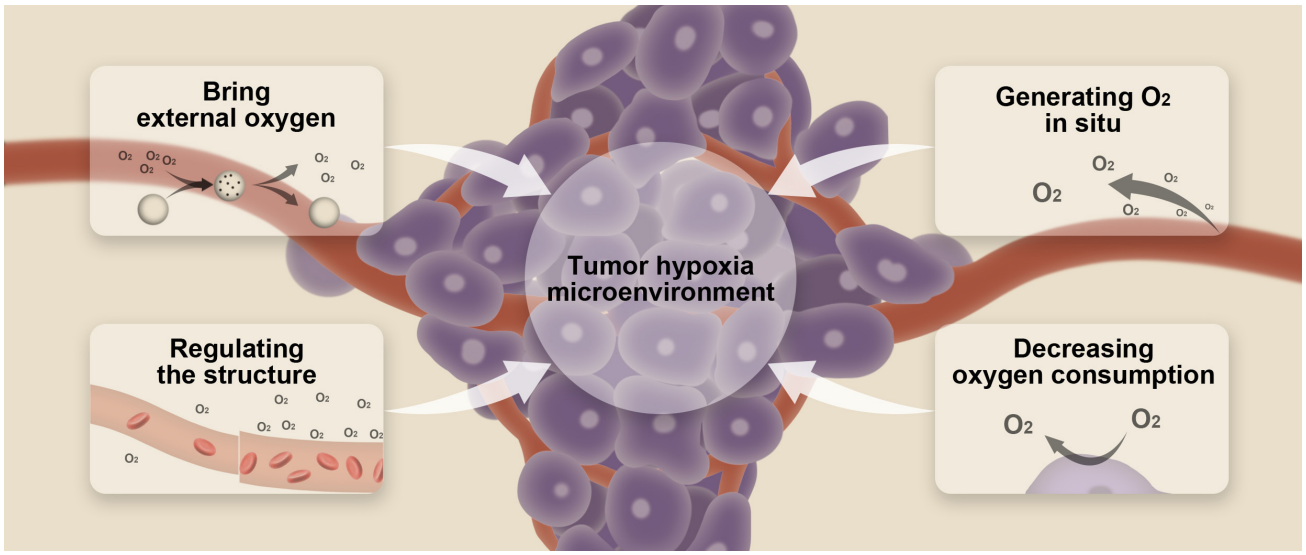

Fig. 1. Schematic illustration of the strategies based on nanotechnology for overcoming tumor hypoxia microenvironment.

Table 1. Nanotechnology-based strategies for overcoming tumor microenvironment hypoxia and typical examples *in vivo*.

Strategy	Nanoparticles	Tumor model (cell line)	References
Bring external oxygen to tumor hypoxia microenvironment	Oxy-PDT	Colon carcinoma (CT26)	[10]
	HMSNs-GOx-Ce6@CPPO-PFC/O_2	Melanoma lung metastasis (B16 F10)	[11]
	PFC@PLGA-RBCM	Breast carcinoma (4T1)	[12]
	IPH@RBC	Colon carcinoma (CT26)	[13]
	PCN-224-Pt	Liver carcinoma (H22)	[14]
	O_2@UiO-66@ICG@RBC	Breast carcinoma (MCF-7)	[15]
	IR780@O_2-SFNs/iRGD	Breast carcinoma (4T1)	[16]
	ZDZP@PDA–PEG	Breast carcinoma (4T1)	[17]
	Polydopamine-nanoparticle-stabilized oxygen microcapsules	Pancreatic carcinoma (KPC)	[18]
Generating O_2 based on nanotechnology *in situ*	LipoMB/CaO_2	Breast carcinoma (4T1)	[19]
	A-MnO_2	Breast carcinoma (EMT6)	[20]
	BSA-MnO_2/IR820@OCNC	Esophageal carcinoma (KYSE 30)	[21]
	HSA-MnO_2-Ce6&Pt	Breast carcinoma (4T1)	[22]
	Fuco-MnO_2	Pancreatic carcinoma (BxPC-3)	[23]
	CAT@Pt (IV)-liposome	Breast carcinoma (4T1)	[24]
	HA-CAT@aCe6	Breast carcinoma (MDA-MB-231)	[25]
	mCMSNs	Breast carcinoma (MCF-7)	[26]
	PDA-Pt-CD@RuFc	Breast carcinoma (4T1)	[27]
	PCCN	Breast carcinoma (4T1)	[28]
	FA-WN-Ce6	Colon carcinoma (CT26)	[29]
Regulating the structure of TME	SPION@hMSN	Breast carcinoma (4T1)	[30]
	α-CD-Ce6-NO	Breast carcinoma (MCF-7)	[31]
	DiR-hCe6-liposome	Breast carcinoma (4T1)	[32]
Decreasing oxygen consumption in the TME	PV-TS	Breast carcinoma (4T1)	[33]
	Mito-OxE	Breast carcinoma (4T1)	[34]
	SORgenTAM	Breast carcinoma (4T1)	[35]

quire and maintain cancer stem cell (CSC) phenotype under hypoxic conditions, which has increased self-renewal and invasion potential [41,42]. Autophagy is associated with cellular response to stresses such as hypoxia in the TME [43–46]. Evidence suggested that enhanced autophagy promoted tumor survival [45]. Angiogenesis is another im-

portant component in the TME under hypoxic conditions [47], and HIF-1α is essential to hypoxia-induced angiogenesis via the expression of VEGF in the tumor [48]. Under hypoxic conditions in PDAC, cancer-associated fibroblasts (CAFs) and dense extracellular matrix (ECM) components were deposited to induce extrinsic resistance for drugs [49]. The strategy of blocking immune checkpoints by immune checkpoint inhibitors (ICIs) has achieved great success in melanoma and lung cancer [50–52]. However, this strategy is limited due to its low response rate in some types of cancers in clinics such as PDAC, which is characterized by hypoxic conditions in TME [53]. Thus, tumor hypoxic microenvironment is a significant impediment to the efficacy of tumor therapy [8]. Relieving the hypoxia status of TME is a promising strategy for tumor treatment.

2.2 Recent Advancements about the Strategies for Overcoming Tumor Hypoxic Microenvironment Based on Nanotechnology

2.2.1 Bring External Oxygen to Tumor Hypoxia Microenvironment

Delivering oxygen to a hypoxic microenvironment by nanomaterials is the most common method to alleviate tumor hypoxia. Recently, various nanotechnology-based methods have been developed to bring external oxygen to the tumor hypoxic microenvironment.

2.2.1.1 Artificial Red Blood Cells Substitutes (RBCSs). The most important function of natural Red Blood Cells (RBCs) is to transfer oxygen (O_2) from the oxygen-enriched tissues to oxygen-deficient tissues. Each RBC contains thousands of hemoglobin (Hb) molecules and each Hb molecule combines with four oxygen molecules. In a hypoxic microenvironment, Hb releases oxygen very quickly to improve the condition of hypoxia [54].

Many researchers are devoted to assembling semi-synthetic RBCs with Hb as the oxygen carrier, which are called Hb-based oxygen carriers (HBOCs) (Fig. 2i). There are several different HBOC systems such as cell-free Hb [55,56] and particle-encapsulated Hb [57–59]. Cell-free Hb has some disadvantages including short circulation time, poor stability, and potential side effects, due to the dissociation of Hb tetramer, binding to plasma haptoglobin, and clearance by liver, kidney, and spleen [60,61]. By chemical modification or encapsulation with biodegradable materials, Hb-based O_2 carriers could reduce the disadvantages of cell-free Hb system and the capability to carry oxygen was similar to natural RBCs [62–66].

Compared with natural RBCs, Hb-based O_2 carriers can infiltrate into tumor tissues through the narrow vascular structure and provide enough O_2 in hypoxic tumors [67]. Nonetheless, the switch of Hb into non-functional methemoglobin (metHb) occurs in the HBOC system, which is prevented in natural RBCs by a multi-enzyme system. Therefore, next-generation HBOCs are desired to create a nanomaterial system with excellent oxygen-carrying capacity and reduced conversion of Hb into metHb [68].

2.2.1.2 PFC-Based Oxygen Carriers (PFOCs) and Fe^{2+} Porphyrin Systems. To alleviate the disadvantages of HBOCs, many investigators have focused on synthetic molecules to replace the function of natural Hb. Perfluorocarbons (PFCs) have a great potential to carry gases and are used as oxygen carriers due to their stability and biosafety [10,11].

PFCs are inert liquids, and the shape can be cyclic or linear so that PFCs can easily dissolve tremendous amounts of O_2 and exchange gases with high efficiency. Nevertheless, PFCs are not water-soluble and will formulate into emulsions *in vivo*. Another advantage of PFCs is that oxygen load can be precisely controlled [69].

Because of the rapid growth of the tumor, the center of the tumor is often hypoxic, which prohibits the production of reactive oxygen species (ROS) and leads to the tolerance of tumor cells to radiotherapy [70,71]. PFOCs can promote oxygen concentration at the hypoxic site of the tumor to increase the sensitivity of tumor cells to radiotherapy [8,72,73]. For example, Gao *et al.* [12] reported that biocompatible PFC@poly (d,l-lactide-co-glycolide) (PLGA) nanoparticles, which were further coated with a red-blood-cell membrane (RBCM) to create PFC@PLGA-RBCM nanoparticles (Fig. 2ii).

PFC@PLGA-RBCM nanoparticles can availably deliver oxygen to the oxygen-starved interior of the tumor, which greatly relieves tumor hypoxia and thus enhance the treatment efficacy of radiotherapy [12,74]. Furthermore, PFOCs can be used in enhancing the efficacy of PDT and chemotherapy. Although PFOCs have the outstanding oxygen-carrying ability, the hydrophobic features of PFOCs block their application in tumors [11]. In addition, extensive and enduring exposure to PFOCs may lead to some adverse reactions, including elevated central venous pressure, cutaneous flushing, pulmonary hypertension, chest tightness, fever, and hypotension [75].

Fe^{2+} protoporphyrin IX (heme), which comes from Hb, can stably bind oxygen. Therefore, another design of oxygen carriers was to explore the Fe^{2+} porphyrins. Many studies synthesized an amphiphilic Fe^{2+} porphyrin and encapsulated Fe^{2+} porphyrin into liposomes. These vesicles showed reversibly binding and releasing oxygen, similar to Hb [76].

2.2.1.3 Metal–Organic Frameworks (MOFs). In recent years, metal-organic frameworks (MOFs) (Fig. 2iii) are a useful material in many domains for their catalytically active sites, large porosity, and flexible structure [77,78]. In addition, MOFs are appropriate candidates for gas storage and separation due to the large surface area and uniform pore size.

DeCoste *et al.* [79] systematically explored MOFs for

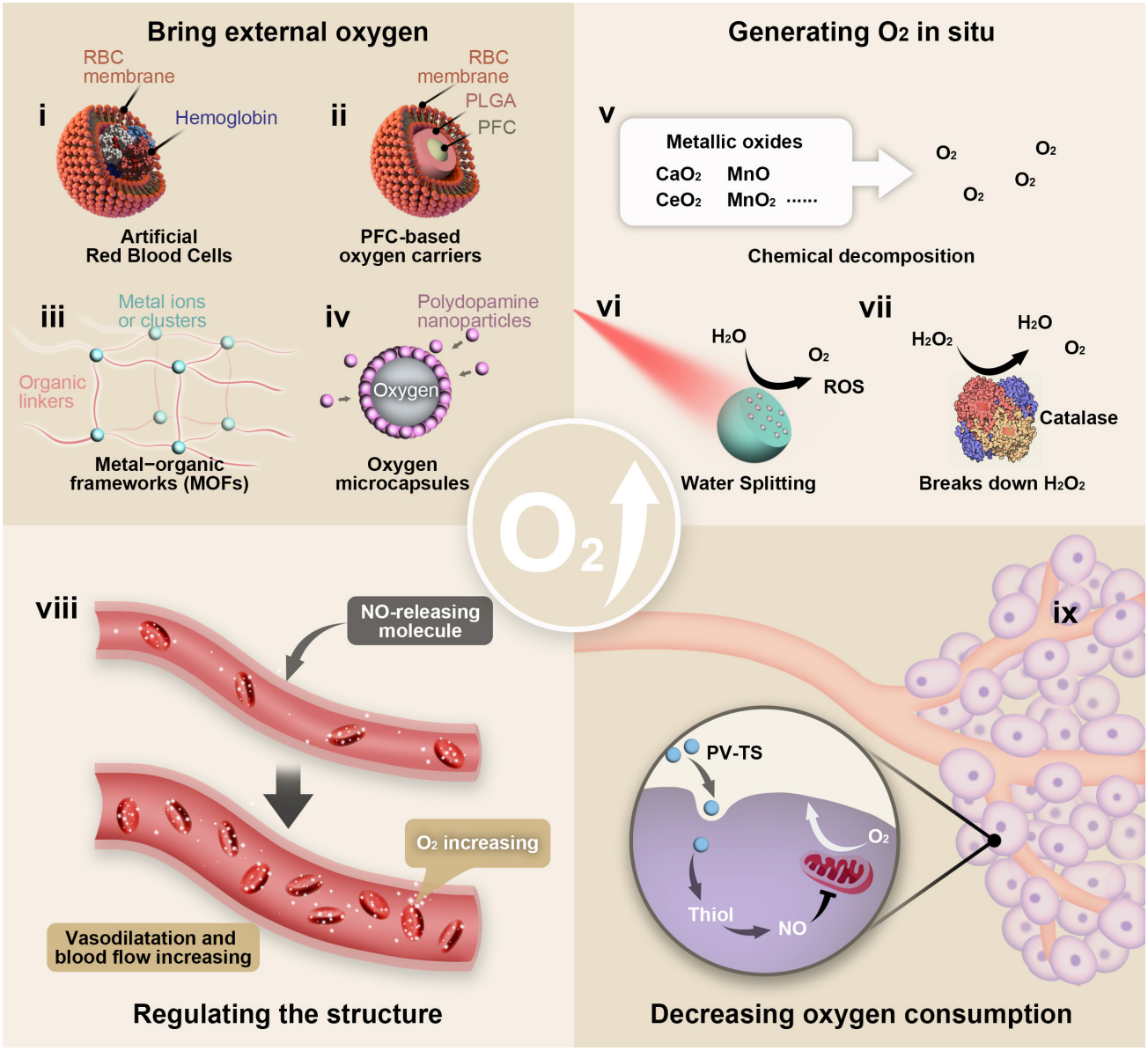

Fig. 2. Schematic illustration of the strategies based on nanotechnology for overcoming tumor hypoxia microenvironment. (i) The morphology and structure of artificial RBCs. (ii) The morphology and structure of PFC-based oxygen carriers. PFC was wrapped in PLGA shell and then coated with RBCM. (iii) The illustration of construction of a MOF and its building components. (iv) The morphology and structure of polydopamine-nanoparticle-stabilized oxygen microcapsules. (v) The illustration of Chemical decomposition like metallic oxides producing oxygen. (vi) The schematic diagram of water-splitting strategy breaks down water to produce oxygen. (vii) The schematic diagram of catalase breaks down H_2O_2 to produce oxygen. (viii) The schematic diagram of regulating the structure by increasing blood flow. (ix) The schematic diagram of decreasing oxygen consumption.

the adsorption of oxygen. The working capacity of MOFs was determined by high-pressure oxygen isotherms. Simulations were performed on the oxygen capacity of 10,000 hypothetical MOF materials in a database created using established high-speed MOF generation techniques, NU-125 was selected as prime candidate based on its superior ability to absorb oxygen and currently known synthesis techniques, and NU-125 was proved to have more capacity for oxygen than Norit activated carbon and zeolite NaX. These MOFs were proved to be useful for oxygen storage in different fields such as aerospace, military, and medicine [79]. Recently, Moghadam *et al.* [80] introduced a visualization concept to clarify the relationships between structural properties and oxygen adsorption ability. They employed high-throughput screening (HTS) techniques to explore oxygen storage in a database of 2,932 existing MOFs and discovered a top MOF material (UMCM-152). They further proved that UMCM-152 delivered 22.5% more oxygen than the material known.

Furthermore, MOFs have been explored to improve

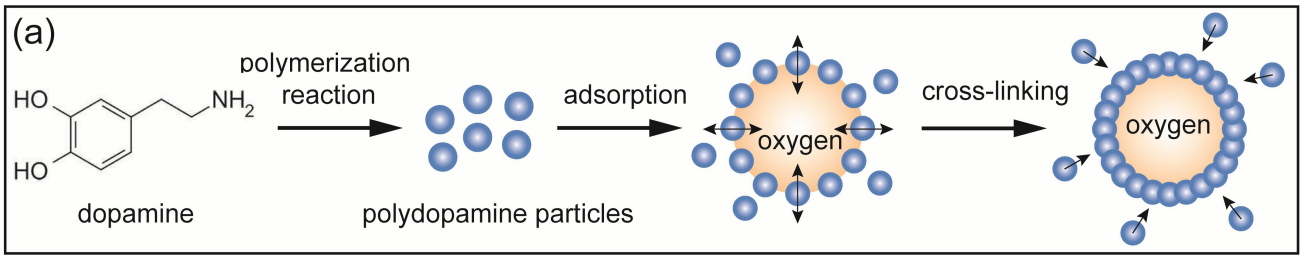

Fig. 3. Preparation of polydopamine-nanoparticle-stabilized oxygen microcapsules. Reproduced with permission [1].

the therapeutic efficacy of PDT in cancers in combination with photosensitizers (PS). Zhang *et al.* [14] reported a nanoplatform that could promote the production of O_2 in the tumor hypoxic microenvironment via H_2O_2-activated release of O_2, which achieved better therapeutic effects.

Gao *et al.* [15] reported a PDT nanoplatform that took full advantage of MOFs. As an oxygen carrier, Zirconium (IV)-based MOF (UiO-66) was combined with indocyanine green (ICG) and further loaded with the cytomembrane of RBCs. After laser irradiation, ICG would degrade the cytomembrane of RBC. Meanwhile, the photothermal characteristic of ICG could accelerate the release of oxygen from UiO-66 in the hypoxic TME. Subsequently, the production of O_2 could improve the effects of PDT in antitumor therapy, which provides a new therapy to kill hypoxic tumors. Ren *et al.* [17] reported a nanoplatform (ZDZP@PP) based on the zeolitic imidazolate framework-67 (ZIF-67) core with a pH-responsive catalase, and a polydopamine-poly (ethylene glycol) (PDA-PEG) layer for improved biocompatibility, which was proved to boost the efficiency of chemo-photodynamic therapy.

2.2.1.4 Oxygen Microcapsules. Recently, with the help of interfacial polymerization, our group created an effective oxygen delivery vehicle of polydopamine-nanoparticle-stabilized oxygen microcapsules (Fig. 2iv).

To prepare nanoparticle-stabilized oxygen microcapsules, at first, under vigorous and rapid shearing, dopamine, a neurotransmitter that assists cells to transmit pulses, was oxidized to form polydopamine nanoparticles at the oxygen/water interface. With the help of amino-rich polylysine and chitosan, uniform polydopamine nanoparticles were achieved and the overoxidation of polydopamine nanoparticles was prevented. By optimizing the interfacial adsorption kinetics of polydopamine nanoparticles, chitosan increases the life of oxygen microbubbles. Due to the decline of the interfacial tension, polydopamine nanoparticles temporarily assembled at the surface of oxygen microbubbles. Then, to achieve stable polydopamine-nanoparticle-stabilized oxygen microcapsules, glutaraldehyde was added to permanently crosslink polydopamine nanoparticles. After removing excess solvents and residual polydopamine nanoparticles, nanoparticle-stabilized oxygen microcapsules were well dispersed in oxygen-enriched water. Due to the solid shells availably enclosing oxygen in the core and effectively keeping oxygen microbubbles from coalescing, the oxygen microcapsules keep stable without observable changes for at least one week (Fig. 3, Ref. [1]). We created an effective oxygen delivery vehicle of polydopamine-nanoparticle-stabilized oxygen microcapsules, which effectively improves the hypoxic microenvironment. Gemcitabine (GEM) is a first-line chemotherapy drug for pancreatic cancer. Oxygen microcapsules combined with GEM drugs achieve a synergetic therapeutic effect in pancreatic cancer treatment [18].

In addition, we reported that oxygen microcapsules can markedly improve radiotherapy efficacy in a mouse model of hepatocellular carcinoma (HCC). Combined treatments of oxygen microcapsules and radiotherapy can effectively decrease tumor-associated macrophages (TAMs) infiltration in tumors while promoting the transformation of pro-tumor type M2 TAMs to anti-tumor type M1 TAMs, which activates the immune responses of T cell against the tumor (Fig. 4, Ref. [2]) [81].

2.2.2 Generating O_2 Based on Nanotechnology *In Situ*

Another way to improve hypoxia in the TME is to produce oxygen *in situ*. Three major strategies are discussed here, including chemical decomposition system, catalase, and water splitting.

2.2.2.1 Chemical Decomposition System. The chemical decomposition system involves a highly reactive compound that can decompose H_2O_2 to generate oxygen, which increases the oxygen concentration in the tumor. These compounds are usually metallic oxides, such as CaO_2 [19,82], MnO [83,84], CeO_2 [85–87], MnO_2 [20–22,88], etc. (Fig. 2v). MnO_2 is the most common metal oxide to produce oxygen for tumor treatment *in situ*. Furthermore, MnO_2 can be degraded into harmless substances-hydrosoluble Mn^{2+} ions, which can improve T1-weighted magnetic resonance imaging (MRI) [89]. Different morphologies and structures of MnO_2 are used to generate O_2, such as nanodots, nanotubes, nanoparticles, nanosheets, and so on [23,90–93]. For example, Prasad *et al.* [20] created nanoparticles of polyelectrolyte-albumin complex with MnO_2 (A-MnO_2). These nanoparticles could produce O_2 by decomposing H_2O_2 in a hypoxic TME of murine breast

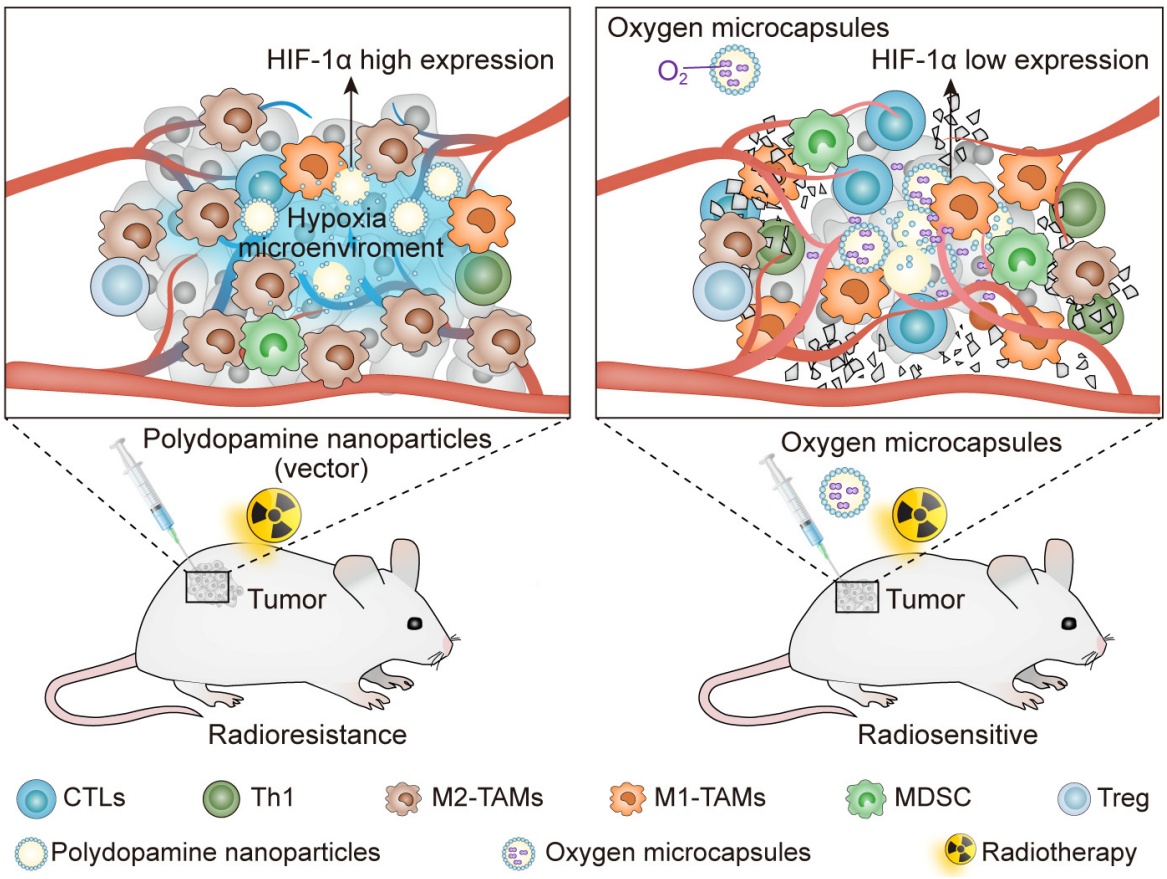

Fig. 4. Improving the efficacy of radiotherapy and anti-tumor immunity via using oxygen microcapsules. Reproduced with permission [2].

tumor model. In addition, these nanoparticles decreased the expression of HIF-1α, which restrains tumor progression and aggressiveness. Compare with radiation therapy alone, combination treatment of nanoparticles and radiation dramatically restrained breast tumor growth.

Yang *et al.* [94] developed a multifunctional nanoplatform (MONs-GOx@MnO_2-Ce6) consisting of glucose oxidase (GOx)-coated mesoporous organosilica nanoparticles (MONPs) and MnO_2 nanosheets-chlorin e6 (Ce6). When MONPs-GOx@MnO_2-Ce6 entered the TME, it could catalyze the glucose to H_2O_2, which was decomposed by MnO_2 nanosheets to produce O_2 in the TME. Tseng *et al.* [95] designed a hypoxia-responsive carrier based on the characteristics of lactate accumulation in tumors to achieve effective and specific delivery of antitumor viruses. The carrier was loaded with lactate oxidase (LOX), and lactate in tumors could penetrate into the carrier and be oxidized into pyruvic acid and H_2O_2. We think these produced H_2O_2 can be used as materials for the O_2-producing compounds of chemical decomposition system. This provides a mechanistic basis for the combined application of LOX-loaded carriers with H_2O_2-related O_2-producing chemical decomposition system in tumor therapy.

2.2.2.2 Catalase Breaks Down H_2O_2 to Produce Oxygen. In living cells, catalase is a critical enzyme that prevents cells from oxidative damage via catalyzing H_2O_2 to generate O_2 and water (Fig. 2vii). It is well-known that tumor cells tend to contain higher levels of H_2O_2 than normal cells, which may result in DNA damage, metastasis, abnormal proliferation, and angiogenesis [96–98]. However, the instability of catalase limits its use in the production of oxygen due to its short half-life *in vivo* [89].

A lot of researchers are dedicated to improving the stability of catalase via encapsulating them to various nanoplatforms [24,99,100]. For example, Phua *et al.* [25] created catalase-encapsulated hyaluronic-acid (HA)-based nanoparticles loaded with an adamantane-modified photosensitizer to improve the therapeutic effect of PDT. The adamantane-modified Ce6 (aCe6) was created by combining Ce6 with adamantane. The HA-CAT@aCe6 nanoparticles containing catalase can increase the therapeutic effect of PDT by decomposing endogenous H_2O_2 into water and oxygen. The cell viability experiment manifested that HA-CAT@aCe6 showed high cytotoxicity under 660 nm light exposure at normoxic conditions. HA-CAT@aCe6 also showed high cytotoxicity in a hypoxic microenvironment due to the oxygen production capability of catalase.

Therefore, HA-CAT@aCe6 showed an outstanding potential to overcome hypoxic conditions for the treatment effect of PDT.

Liu *et al*. [101] wrapped the catalase in outer layers of MOFs. The integrated MOF system with characteristics of tandem catalysts can decompose endogenous H_2O_2 into water and oxygen. The treatment effect of PDT was improved by 8.7-fold than the treatment lack of catalase, which displayed an increased therapeutic effect against tumor cells in tumor hypoxic microenvironment. They reported tumor cell membrane coated mesoporous copper/manganese silicate nanospheres (mCMSNs). mCMSNs can increase ROS generation and reduce glutathione-activated Fenton reaction, which shows outstanding synergistic therapeutic effects. mCMSNs can reduce tumor hypoxic microenvironment via decomposing endogenous H_2O_2 into water and oxygen and further react with oxygen to release ROS under laser irradiation. Importantly, alleviating hypoxia conditions and reducing ROS scavenger achieves additional therapy effects *in vitro* and *in vivo*. In addition, the Mn^{2+} can play an important role in tumor MRI [26].

Li *et al*. [100] created a tumor-targeted cascade bioreactor (mCGP) which can increase targetability and retention capacities in the tumor. Once mCGP entered the tumor cell, it can catalyze the endogenous H_2O_2 to produce oxygen and water, which would next increase the disintegration of intracellular glucose and fortify the generation of cytotoxic singlet oxygen ($^1O_2$) under photon exposure. As a result, mCGP showed enhanced therapeutic efficacy due to the combined effect of PDT and cell starvation. Carbon dots (CDs) can effectively produce $^1O_2$ for PDT in oncotherapy. Jia *et al*. [102] created magnetofluorescent Mn-CDs by utilizing manganese (II) phthalocyanine as a precursor. Mn-CDs can not only produce $^1O_2$ but also decompose H_2O_2 to release oxygen.

Recently, a multifunctional nano-platform PDA-Pt-CD@RuFc was developed, which consisted of platinum-decorated and cyclodextrin (CD)-modified polydopamine (PDA) nanoparticles combined with a ferrocene-appended ruthenium complex (RFC). PDA-Pt-CD@RuFc nanoparticles combined PDT with photothermal therapy (PTT), which can kill tumor cells in an anoxic microenvironment in several aspects. Firstly, the PDA-Pt-CD@RuFc nanoparticles can decompose H_2O_2 to release oxygen and water. Secondly, photothermal heating can stretch the blood vessels and then increase oxygen supplement. Thirdly, PDT based on RuFc can also occur through a non-oxygen-dependent Fenton reaction. In addition, combined therapy can reverse the hypoxic microenvironment of the tumor to acquire a better combination therapy effect [27].

2.2.2.3 Generating O_2 by Water Splitting. Catalase and catalase-like material can effectively decompose H_2O_2 to release oxygen and water in the tumor hypoxic microenvironment. However, in bioactive cells, the levels of endogenous H_2O_2 are limited, which limits the use of H_2O_2 decomposition strategies in tumors [103,104]. Therefore, recently, some studies attempted to produce oxygen via splitting water rather than H_2O_2 to enhance the level of oxygen in the tumor hypoxic microenvironment [105–107]. The water-splitting strategy can take full advantage of unlimited raw materials to generate oxygen *in vivo* (Fig. 2vi). Moreover, the usage of water-splitting materials shows a powerful ability to raise oxygen levels *in vivo*, which improves the PDT effect. For example, by combining carbon dots with C3N4, a carbon nitride (C3N4)-based multifunctional nanocomposite (PCCN) can perform water splitting. Carbon dots were first combined with C3N4 to increase its red-light absorption. Under light exposure, PCCN could increase the intracellular level of oxygen and ROS in the tumor hypoxic microenvironment [28]. Analogously, Ce6 combined with tungsten nitride nanoparticles (WN NPs) decorated with folic acid (FA) modification to produce FA-WN-Ce6 (FWC) nanoparticles. FWC nanoparticles can increase PDT against the hypoxic TME. The WN in FWC plays an important role in water splitting to produce oxygen, which markedly improves the ROS generation ability of Ce6 in hypoxic TME both *in vitro* and *in vivo*. Furthermore, FWC nanoparticles can decrease the invasion and metastasis of cancer cells due to increased oxygen levels in the hypoxic TME [29]. Nonetheless, the water-splitting strategy can't be applied in tissues with limited light source penetration.

2.2.3 Regulating the Structure of TME

In addition to directly carrying oxygen to the tumor hypoxic microenvironment or producing oxygen *in situ*, regulating the structure of TME can elevate oxygen levels in the tumor hypoxic microenvironment [89].

Increasing Blood Flow. Due to the abnormal blood vessels in the area of the tumor, inadequate blood flow is a common characteristic of solid tumors. Therefore, improving blood flow would be an effective method to increase the oxygen level in the hypoxic TME [108]. For example, Nitric oxide (NO) can mediate the relaxation of the blood vessel. Blood flow can be regulated by controlling the release of NO (Fig. 2viii).

Jin *et al*. [30] synthesized a novel BNN-type NO-releasing molecule (NORM) activated by ultrasound and a nano-carrier of superparamagnetic iron oxide-encapsulated mesoporous silica nanoparticles (SPION@hMSN) to create a novel nanomaterial (BNN6-SPION@hMSN). BNN6-SPION@hMSN demonstrated excellent tumor-killing ability and ultrasound-triggered NO release to mediate relaxation of the blood vessel. BNN6-SPION@hMSN can efficiently control the release of NO to improve the hypoxia of the TME.

Analogously, Deng *et al.* [31] invented a nanocarrier with GSH-sensitive NO prodrug. The nanocarrier was fabricated by LEGO-like self-assembly for efficient intracellular delivery of NO, NO released by the nanocarrier can not only improve hypoxia in the tumor by mediating vasodilation, but also increase the concentration of ROS generated by PDT through GSH depletion and generate cytotoxic peroxynitrite anions ($ONOO^-$), resulting in a significant synergistic therapeutic effect with PDT in tumor therapy.

It is well known that the blood flow of cancer can be augmented by mild heating [109,110]. Brizel *et al.* [110] created a nanomaterial that can increase blood flow in a hypoxic tumor environment by mild photothermal heating. This is achieved through a near-infrared (NIR) exposure combined with intravenous injection of DiR-hCe6-liposome and then leads to mild photothermal heating, which would increase blood flow in a hypoxic tumor environment and enhance the therapeutic effect of PDT in the hypoxic TME [32].

2.2.4 Decreasing Oxygen Consumption in the TME

Diminishing oxygen consumption is also an alternative treatment strategy to increase oxygen levels in hypoxia of the TME [111]. Therefore, strategies for inhibiting oxidative respiration to decrease tumor oxygen consumption also have been designed to solve the hypoxia issues in tumors [108] (Fig. 2ix). For example, Denko et al put forward an "O_2-economizer" concept by preventing cell oxidative respiration to spare endogenous O_2 and then overcome the hypoxia barrier. A NO donor and a photosensitizer were combined with poly (D, L-lactide-co-glycolide) nanovesicles to create a PDT-specific O_2 economizer. When PDT-specific O_2 economizer aggregated into the tumor, the NO donor released NO to restrain cellular respiration, which reserved more oxygen to support the therapeutic effect of PDT. This concept of O_2-economizer provides an alternative strategy to reduce hypoxia in the TME [33–35].

2.3 Characteristics and Comparison of Four Strategies

For strategy of bringing external oxygen to tumor hypoxia microenvironment, due to the existence of membrane protein complexes that are crucial for long-term blood circulation, the RBCM-encapsulated nanoparticles have significantly prolonged blood half-life and biocompatibility. They can be used as long-circulating oxygen carriers to alleviate tumor hypoxia and enhance therapeutic effects [11,66–68]. Studies have shown that hypoxia affects the function and phenotype of immune cells in the TME, and RBCs are closely related to immune cells in the liver, such as Kuffer cells. Therefore, RBCM-coated nanoparticles with both immune regulation and oxygen-carrying functions shows research potential for anti-tumor immunotherapy in liver cancer [112,113]. The advantages of MOFs are high porosity, large surface area and tunable structure, various modifying groups have been introduced into the system to improve the performance and functions of this particle. In addition, single therapeutic way of MOFs doesn't work very well. Therefore, it's an urgent need for more combination therapy. For example, MOFs can be combined with more other therapies like immunotherapy to acquire a synergistic effect. Furthermore, the synthesis processes of these well-designed MOFs are often difficult to control. In different tumor microenvironments, different modifying component may alter the kinetic behavior of delivery and release of MOFs, which need to be further clarified in the future [114].

For strategy of Generating O_2 based on nanotechnology *in situ*. MnO_2 nanoparticles is the most widely used chemical decomposition nanoparticles, which have outstanding performance for improving the treatment of tumors. MnO_2-based nanoplatforms with excellent biodegradability can be gradually broken down into Mn^{2+} ions, which may cause potential toxicity especially under higher concentrations. In addition, the introduction of other functional groups, including anti-cancer drugs and biomolecules will cause great troubles in the process of massive production. Simple and reliable methods to produce MnO_2-based nanosystems would helpful for their applications in the future [115].

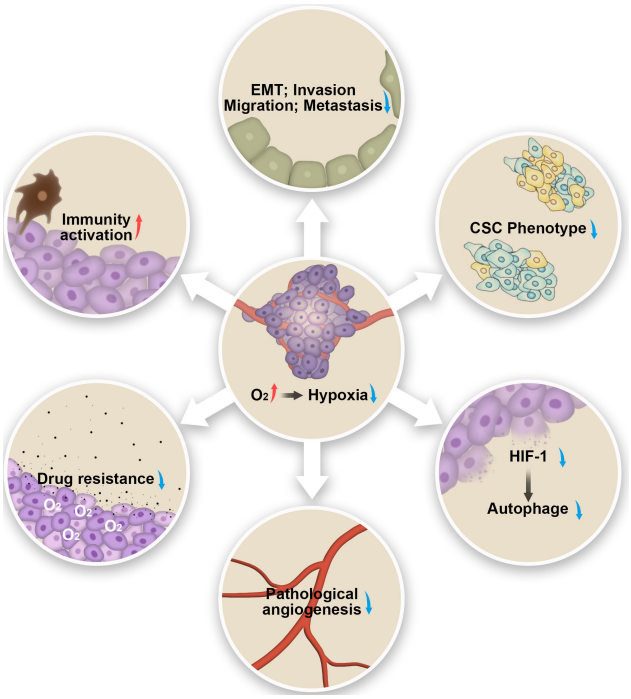

Fig. 5. Schematic illustration of the possible antitumor mechanism by alleviating hypoxia.

For strategy of regulating the structure of TME. Nanoparticles mainly mediate vasodilation in tumors through NO releasing and tissue heating to increase blood flow and oxygen supply in TME. In addition, the release of NO from nanoparticles can also enhance the effect of pho-

todynamic therapy through GSH depletion and reactive nitrogen species generation [30,31]. It is well known that intravenous injection is one of the main application methods of anti-tumor drugs. The increased blood supply in TME helps improve drug infiltration into the tumor, which offers the possibility of combining these nanoparticles with antitumor drug treatments such as chemotherapy. However, the increased blood flow may lead to adjacent dissemination and distant metastasis of the tumor, this risk requires further study and evaluation.

For strategy of decreasing oxygen consumption in the TME. The nanoparticles mainly target the respiration process of tumor cells, thereby reducing the consumption of oxygen in the tumor and enhancing the effect of PDT. Metabolic reprogramming is a key hallmark of cancer, in which aerobic glycolysis is an important feature [116], so targeting aerobic respiration to reduce oxygen consumption in tumors may have limited effect. In addition, O_2-economizer also affect aerobic respiration of immune cells, stromal cells, etc. in TME. These effects may require further research.

3. Conclusions

The tumor hypoxic microenvironment is a major obstacle to oxygen-dependent cancer therapy such as radiotherapy, chemotherapy, PDT, immunotherapy, and so on. Currently, the strategies of nanotechnology for increasing the oxygen level mainly include the following aspects: (1) Bring external oxygen to tumor hypoxia microenvironment. (2) Generating O_2 based on nanotechnology *in situ*. (3) Regulating the structure of the TME. (4) Decreasing oxygen consumption in the TME. These nanotechnologies have ameliorated the hypoxia of certain tumors and achieved enhanced anti-tumor effects, which may reduce malignancy phenotypes and biological behaviors of tumors including EMT, invasion, migration, metastasis, cancer stem cell maintenance, autophagy, pathological angiogenesis, drug resistance, and immunosuppression (Fig. 5).

Although nanotechnology targeting hypoxia has been researched and developed for a long time, the clinical applications associated with it have lagged behind. A variety of nanotechnology have been tried to improve tumor hypoxia, however, there are no FDA-approved treatments to reverse tumor hypoxia. On the one hand, tumor heterogeneity is the most important factor because different tumors have phenotypic features and genetic mutations. This requires that different tumors should be treated in different ways. On the other hand, the size, shape, surface charge and mechanical properties, as well as unstable biocompatibility and safety, also negatively affect the clinical application of these nanoparticles. Further research is needed to improve these aspects. In addition, multifunctional composite nanoparticles with complementary mechanisms have shown encouraging research prospects. The existing nanoparticles targeting hypoxic TME mainly focus on radiotherapy, chemotherapy and PDT and other treatments. The immunomodulatory effects of these nanoparticles and the prospect of combination with immunotherapy deserve further attention.

Abbreviations

PDT, photodynamic therapy; PTT, photothermal therapy; MRI, magnetic resonance imaging; EMT, epithelial-mesenchymal-transition; TME, tumor microenvironment; PDAC, pancreatic ductal adenocarcinoma; HCC, hepatocellular carcinoma; HIF, hypoxia-inducible factor; HBOC, Hb-based oxygen carrier; PFOC, PFC-based oxygen carrier; MOF, Metal–organic framework; NU-125, Northwestern University-125; UMCM-152, University of Michigan Crystalline Material-152; GSH, glutathione; MONP, mesoporous organosilica nanoparticle; ROS, reactive oxygen species.

Author Contributions

JW, JSo wrote the manuscript and contributed equally. XY, JT, JZ, XW, YJ, YZ, and DC provided help and advice on the manuscript, JSh, XB, and TL reviewed the manuscript and secured the funding. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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