



The development of live microorganism-based oxygen shuttles for enhanced hypoxic tumor therapy



Dandan Han^{a,b}, Xing Zhang^b, Yichuan Ma^b, Xinjian Yang^{b,**}, Zhenhua Li^{a,c,*}

^a Affiliated Dongguan Hospital, Southern Medical University, Dongguan, 523059, China

^b College of Chemistry & Environmental Science, Key Laboratory of Medicinal Chemistry and Molecular Diagnosis of Ministry of Education, Chemical Biology Key Laboratory of Hebei Province, Hebei University, Baoding, 071002, China

^c Guangdong Provincial Key Laboratory of Shock and Microcirculation, Guangdong, 510515, PR China

ARTICLE INFO

Keywords:

Oxygen shuttles
Hypoxic tumor
Photosynthesis
Engineered bacteria

ABSTRACT

Hypoxia is a prominent feature of malignant tumors and contributes to tumor proliferation, metastasis, and drug resistance in various solid tumors. Therefore, improving tumor oxygenation is crucial for curing tumors. To date, multiple strategies, including oxygen delivering and producing materials, have been designed to increase the oxygen concentration in hypoxic tumors. However, the unsustainable supply of oxygen is still the main obstacle, resulting in a suboptimal outcome in treating oxygen-deprived tumors. Thus, a sufficient oxygen supply is highly desirable in the treatment of hypoxic tumors. Photosynthesis, as the main source of oxygen in nature through the conversion of light energy into chemical energy and oxygen, has been widely studied in scientific research. Moreover, photosynthetic microorganisms have been increasingly applied in cancer therapy by increasing oxygenation, which improves the therapeutic effect of oxygen-consuming tumor therapeutic tools such as radiotherapy and photodynamic therapy. In this review, we summarize recent advances in the design and manufacture of live bacteria as oxygen shuttles for a new generation of hypoxic tumor treatment strategies. Finally, current challenges and future directions are also discussed for successfully addressing hypoxic tumor issues.

1. Introduction

Solid tumor interior is far from the blood vessels and is in a state of hypoxia, which is caused by the rapid growth of the tumor [1,2]. Hypoxia not only confers tumor tolerance to conventional therapies, such as radiotherapy (RT) [3,4], chemotherapy [5] and photodynamic therapy (PDT) [6–8], but also facilitates tumors more invasive and metastasis. To overcome tumor hypoxia, various strategies have been developed in recent years. For example, hyperbaric oxygen (HBO) and oxygen (O₂)-binding haemoglobin (Hb) has been developed to deliver O₂ into the anoxic area for improved tumor oxygenation. In addition, the combination of HBO with RT has also been used for improved RT in clinic [9–11]. However, HBO treatment has serious side effects such as air pressure trauma, lung injury and oxygen poisoning, leading to that HBO has not been widely used in RT [12]. Therefore, novel O₂ delivering strategies for the treatment of hypoxic tumors are highly desirable.

With the emergence of nanotechnology, functionalized nanomaterials

are gradually being used as adjunctive agents for oxygen-dependent therapies [13,14]. Researchers have designed a variety of nanoscale oxygen shuttles with unique physicochemical properties for increasing intertumoral oxygenation [15–17]. Recent studies have shown that oxygen shuttles with a high affinity for oxygen such as Hb, perfluorocarbon (PFC) and metal-organic framework (MOF) [18,19] could deliver O₂ directly to the tumor, and significantly improve the efficacy of oxygen dependent PDT and RT. For example, Cai et al. combined human serum albumin (HSA) with Hb through intermolecular disulfide bonds to obtain a hybrid protein as an oxygen nanocarrier. Photosensitizer chlorin e6 (Ce6) was then encapsulated for enhanced PDT [20]. The nanodrug (C@HPOC) significantly enhanced the effect of PDT while relieving tumor oxygen. In addition, our group has used zirconium (Zr (IV))-based MOF (UIO-66) as an oxygen storage carrier and constructed self-sufficient oxygenated nanoparticles to successfully deliver oxygen and photosensitizer into hypoxic tumor [21]. Under 808 nm laser irradiation, the photothermal agent indocyanine green (ICG) promoted the

* Corresponding author. Affiliated Dongguan Hospital, Southern Medical University, Dongguan, 523059, China.

** Corresponding author.

E-mail addresses: jianxinyang123@163.com (X. Yang), zhenhuali@hbu.edu.cn (Z. Li).

<https://doi.org/10.1016/j.mtbio.2022.100517>

Received 19 October 2022; Received in revised form 8 December 2022; Accepted 9 December 2022

Available online 10 December 2022

2590-0064/© 2022 Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

release of O₂ from UIO-66. The released O₂ significantly improved the treatment efficiency of PDT against hypoxic tumors. In addition to the improved PDT, increasing the oxygen content in tumors could also increase the sensitivity of RT to hypoxic tumors. For example, Wang et al. built a graded nanodroplet system using perfluorooctyl bromide (PFOB) as an oxygen reservoir [22]. Gold nanoparticles wrapped in nanodroplets could concentrate the radiation energy and cause significant DNA damage. Under ultrasound, the burst oxygen release was triggered to reserve the oxygen loss, thus strengthening the RT-induced DNA damage while simultaneously inhibiting DNA repair. In addition to O₂ delivering, O₂ production in situ by undergoing chemical reactions is also a promising strategy for improved chemotherapy and PDT [23,24]. Hydrogen peroxide (H₂O₂) has been indicated to over-produce in tumor tissue due to abnormal metabolic processes [25–29]. Some highly active compounds such as manganese dioxide (MnO₂) and cerium oxide (CeO₂) can react with H₂O₂ in the tumor microenvironment to produce O₂ for hypoxic tumor therapy [30–32]. Liu et al. synthesized a MnO₂ nanoparticle based on polyacryllamine hydrochloride (PAH), which was further coupled to the photosensitizer Ce6 to obtain a nanocatalytic drug [7]. This nanocatalytic drug used MnO₂ nanoparticles to catalyze the endogenous H₂O₂ to generate oxygen, thus effectively alleviating the tumor oxygen loss and further enhancing the effect of the PDT treatment of Ce6. Photocatalytic nanosystems based on BiO_{2-x} nanosheets (BiO_{2-x} NSs) were also prepared by Gu et al. [33]. Bismuth (Bi), as a high Z element, could effectively improve RT by depositing higher radiation doses in tumor sensibility. Moreover, the BiO_{2-x} NSs could catalyze the breakdown of the highly expressed H₂O₂ at the tumor site into O₂ to alleviate the tumor oxygen loss, thus enhanced the effect of RT. However, due to the low endogenous H₂O₂ concentration, the oxygen production efficiency is pretty low [34–36]. To overcome this limitation, previously, we have reported a calcium peroxide (CaO₂)-based and pH-responsive nanocatalytic for enhanced chemotherapy. In our system, cobalt (Co)-based MOF (ZIF-67) was used to coat doxorubicin (DOX)-loaded CaO₂ (CaO₂@DOX@ZIF-67) [37]. In tumor acidic environments, CaO₂, DOX, and Co²⁺ would be released rapidly as the outermost ZIF-67 decomposes. Unprotected CaO₂ were then reacted with H₂O to produce O₂ and H₂O₂, and the increased O₂ levels alleviated the intertumoral oxygen deficiency, thus further improving the therapeutic effect of DOX. Although promising, the above oxygen enhancement strategies usually induced a burst release of oxygen within a very short time, and thus the oxygen enhancing capacity was limited. This restricted the improvement of tumor oxygen deficiency through endogenous oxygen production strategies. Another big challenge is that the accumulation of nanodrugs in the hypoxic tumor area is affected by physical barriers such as the dense extracellular matrix, high intratissue fluid pressure and an irregular blood supply [38–40]. The efficient penetration into hypoxic tumor tissue through passive targeting is very limited, which leads to the failure of the desired therapeutic effect [41,42]. Thus, developing hypoxia-targeting oxygen shuttles with efficient tumor penetration and controllable oxygen release ability is highly desirable.

Among the existing targeted therapies, bacterial therapy has been used for more than a century [43,44]. Furthermore, hybrid biological microswimmers have recently been shown to play an active role in targeted delivery and in vitro biomedical applications [45,46]. We have also constructed hypoxia-targeting systems based on facultative anaerobic bacteria and photosynthetic bacteria (PSB) for the treatment of hypoxic tumors [47]. This work was the first report to discover and confirm that PSB has a photothermal transformation capability. Therefore, PSB could be used as both a photothermal agent and hypoxia-targeting carrier to achieve efficient treatment against hypoxic tumors without any post-modification or drug introduction. Moreover, our results showed that PSB with hypoxia and near-infrared chemotactic capabilities could target tumor core regions. In addition to playing a role as a carrier in cancer therapy, bacteria were also widely used for immunotherapy since William Coley injected heat-killed bacteria (“Coley’s Toxins”) into tumor patients to activate the immune system to fight cancer in the late

nineteenth century [48,49]. Bacterial-derived molecules such as peptidoglycan, lipopolysaccharide (LPS) and lipophosphoric acid could provide powerful immunostimulatory signals. They mainly bind to the pattern recognition receptors (PRR) expressed by innate immune cells such as dendritic cells (DCs) and macrophages to activate immune cells for tumor cell elimination [50,51]. For example, Wei et al. attached resiquimod (R848), a toll-like receptor 7/8 (TLR7/8) agonist, on ethylene glycol chitosan-modified *Escherichia coli* (*E. coli*) (EcPR848) to enhance the antitumor effect of cancer therapy [52]. EcPR848 could target hypoxic tumors and release R848 after phagocytosis by M2 macrophages. Both R848 and *E. coli* could polarize M2 macrophages into M1 type for enhanced immunotherapy. In addition, bacteria were also used as tumor vaccine adjuvants. Jing et al. coupled the neoantigen peptide with yeast polysaccharide shell particles by click chemistry to synthesize a novel tumor vaccine delivery system [53]. Bacteria-based tumor vaccines could stimulate the body to produce a potent antigen-specific CD8⁺ T cell immune response. There are at least two advantages of live bacteria-based oxygen shuttles for enhanced hypoxic tumors therapy: 1) photosynthetic microorganisms can produce oxygen via photosynthesis under light and hypoxic conditions, providing a green and efficient biological oxygen source for hypoxic tumors, and 2) anaerobic or facultative anaerobic bacteria can use their hypoxic properties to target tumors. Thus, the combination of bacterial hypoxia targeting and continuous oxygen production can effectively reverse the hypoxic microenvironment of the tumor and thus achieve the desired therapeutic effect. In this review, we systematically describe the design of live bacteria-based shuttles, including how bacteria increase tumor oxygenation, their underlying mechanisms, their effect on tumor oxygenation and their efficacy for improving various cancer treatments (see Fig. 1 and Table 1).

2. Oxygen shuttles produced oxygen for enhanced tumor therapy

2.1. Cyanobacteria-based oxygen production system

2.1.1. Cyanobacteria improved PDT efficiency

On primitive earth, oxygen began to accumulate in the atmosphere due to bacterial photosynthesis. Algae are among the earliest

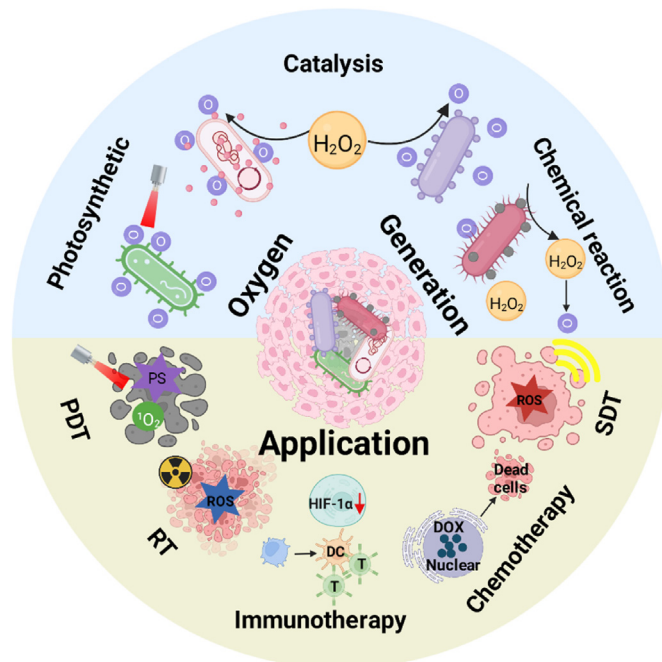


Fig. 1. Microorganism-based oxygen shuttles for enhanced hypoxic tumor therapy.

Table 1

Representative applications and strategies of microorganism-based oxygen shuttles in the treatment of hypoxic tumors.

Microorganism type	O ₂ generation mechanism	Mode of cancer therapy	References
Cyanobacteria	Photosynthesis	PDT SDT RT	[6,64,65,67,68,71,79,80,82] [83] [88,89]
<i>Chlorella</i>	Photosynthesis	PTT and Chemotherapy PDT RT CDT	[96] [99] [101,102] [105]
<i>Escherichia coli</i>	Engineered <i>E. coli</i> overexpressed CAT to catalyze endogenous O ₂ production by H ₂ O ₂ . Magnetic Fe ₃ O ₄ nanoparticles on the surface of <i>E. coli</i> would catalyze O ₂ production by H ₂ O ₂ in situ. <i>E. coli</i> was directly used as the reducing agent to react with the KMnO ₄ aqueous solution via ultrasonication, and the generated MnO _x can react with H ₂ O ₂ to produce O ₂ .	PDT and PTT RT CDT PDT and Chemotherapy	[110] [111] [116] [120]
<i>Shewanella oneidensis</i>	The MnO ₂ nanosheets were modified on the MR-1 surface to catalyze the endogenous H ₂ O ₂ .	Immunotherapy	[114]
<i>Spirulina platensis</i>	Photosynthesis	RT and PDT	[117]

photosynthetic autotrophs on earth and can efficiently produce O₂ by photocatalysis [54]. Microalgae, as photoautotrophs, have recently been used as unique oxygenators for wound healing and hypoxia-related tumor therapy [47,55]. In particular, microalgae have been widely used in the fields of food, biofuels, health products and environmental control [56,57]. Recently, microalgae have been of considerable use in biomedical fields for applications such as bioanalysis, tissue engineering, drug delivery and tumor therapy, and they exhibit high biocompatibility both in vivo and in vitro [58–60]. Studies by Woo et al. used the cyanobacterium *Synechococcus elongatus* to increase tissue oxygenation, maintain myocardial metabolism, and greatly improved cardiac function [61]. It was also suggested that cyanobacteria therapy was nontoxic and would not cause a meaningful immune response. In addition, Zhou et al. designed *Spirulina platensis*-based oral drugs in the treatment of two intestinal diseases, colon cancer and colitis [62], which expanded medical microalgae agents' application. Thus, there was an increasing interest in advances in photosynthetic biomaterials and therapies. However, no previous study has demonstrated their safety in human patients. This gap was a major obstacle to translating photosynthetic therapies into clinical practice. In an early clinical trial, researchers implanted photosynthetic scaffolds containing high concentrations of *Chlamydomonas reinhardtii* into eight patients with full-thickness skin wounds [63]. Over the subsequent 90 days, the photosynthetic scaffolds did not trigger any harmful local or systemic immune responses and allowed full tissue regeneration. It was the first demonstration that photosynthetic cells could be safely implanted in human patients for tissue regeneration. Therefore, algae could be used as green oxygen donors to improve the oxygenation of the tumor microenvironment (TME). Inspired by this, Shi et al. first injected the photosensitizer Ce6 into cyanobacteria (*Syne7942*) for enhanced PDT [64]. Fig. 2A showed that under irradiation of 660 nm laser, the biological hybrid carried out continuous photosynthesis through the cyanobacteria, achieved continuous oxygen release and rapid and efficient production of singlet oxygen (¹O₂), which proved that oxygen production in microbial nanomedicine could enhance PDT for tumor treatment. In addition, Cai et al. used an autotrophy *Syne7942* as an oxygen-producing carrier for ICG-coated HSA nanoparticles (HSA/ICG NPs) delivery [65]. Under irradiation with a 660 nm laser, the cyanobacteria produced a large quantity of oxygen through photosynthesis. The oxygen producing in situ effectively reversed the immunosuppressive TME and enhanced the antitumor immune response mediated by ICD (Fig. 2B). In 2015, *Synechococcus elongatus* UTEX 2973 (S.2973) was isolated, showing the advantages of rapid growth and good light resistance. More importantly, S.2973 exhibited a robust and promising chassis for biomedical applications because its optimal growth temperature was similar to that of humans [66]. Therefore, Zhang et al. encapsulated mesoporous

nanoparticles and an S.2973-mediated biologic oxygen pump in a hydrogel (ALG-MI-S.2973) [67]. First, after intratumoral injection of ALG-MI-S.2973, S.2973 efficiently produced O₂ under a 640 nm laser, thus relieving the hypoxic TME. After the release of ICG, efficient PDT and tumor growth inhibition were found under an 808 nm laser. In this system, the growth of S.2973 and the triggering PDT were chosen two different lasers, which avoided killing S.2973 with PDT-induced reactive oxygen species (ROS) in the early stage, thus ensuring maximum oxygen production. The 808 nm laser-induced PDT simultaneously cleared S.2973, further ensuring the biosafety of the system. Hao et al. integrated Ce6-containing cyanobacteria onto a 3-dimensional (3D) printed calcium carbonate (CaCO₃-PCL) scaffold to build a multifunctional, delicate photosynthetic oxygen autologous platform [68]. First, Ce6 was internalized into photosynthetic cyanobacteria (CeCyano) and then the 3D-printed CaCO₃-PCL scaffold was constructed and customized based on personalized data with the assistance of computer-aided design software. The constructed CeCyano cells were then decorated on the cap scaffold to complete the final treatment platform (CAPC). Under 660 nm laser irradiation, the engineered CAPC scaffold generates oxygen through photosynthesis and subsequently activates Ce6, resulting in enough ¹O₂ production for efficiently combating osteosarcoma (OS) in vivo (Fig. 2D). More importantly, the excess oxygen produced could also promote cell proliferation and differentiation, thus promoted bone regeneration after the synergistic action of OS with the 3D-printed scaffolds. Furthermore, along with the repair of bone injury, the scaffold gradually degraded and released CaCO₃ to support new bone generation. Enhanced osteosarcoma PDT efficiency was achieved by enabling photosynthetic oxygenation-induced tumor hypoxia remission and promoting bone regeneration with subsequent local oxygenation.

However, traditional photosensitizers (such as porphyrin derivatives) are prone to self-aggregation because of their hydrophobicity under physiological conditions, resulting in low bioavailability and photodynamic yield [69,70]. Black phosphorus nanosheets (BPNSs) have attracted wide attention because of their unique two-dimensional layered structure and physical-chemical properties. Owing to their broad absorption in ultraviolet and visible light, good biocompatibility, and high efficiency of PDT [71,72], two-dimensional BPNSs have broad application prospects in the field of biomedicine, particularly in tumor therapy [73]. Consequently, Shi et al. hybridized cyanobacteria (Cyan) with inorganic nanophotosensitizer BPNSs to obtain a new type of bioreactor (Cyan@BPNSs) (Fig. 3A) [74]. Under irradiation with a 660 nm laser, Cyan continued to produce oxygen in situ through photosynthesis. As shown in Fig. 3B–F, BPNSs induced a large amount of oxidative stress at the tumor site with strong cytotoxicity to tumor cells. However, the application of visible light in vivo is seriously limited due to the short

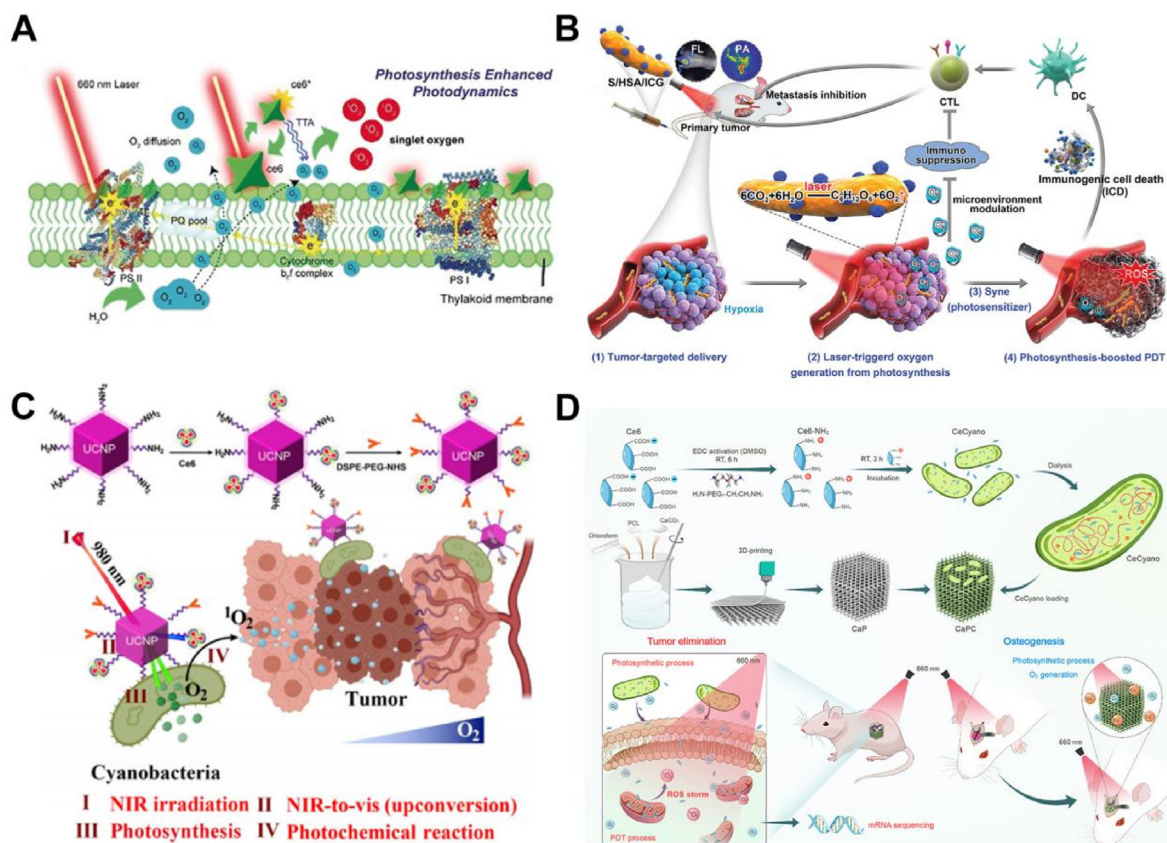


Fig. 2. A. Mechanistic diagram of CeCyan generating oxygen and $^1\text{O}_2$ by CeCyan under 660 nm laser [64]. B. Schematic illustration of HSA/ICG conjugated Syne as an in situ photocatalyzed oxygen generation system for metastatic tumor immunogenic PDT [65]. C. Schematic illustration of S-UCNP-Ce6 for enhanced PDT of hypoxic tumors [6]. D. The CeCyan-based 3D printed CaCO_3 -PCL scaffold was used for enhanced PDT of osteosarcoma [66]. Adapted with permission from Ref. [64] Copyright 2019, Wiley-VCH; adapted with permission from Ref. [65] Copyright 2020, Wiley-VCH; adapted with permission from Ref. [6] Copyright 2020, Springer Nature; adapted with permission from Ref. [66] Copyright 2021, Elsevier.

wavelength of visible light and poor penetrating ability. Compared with visible light, near-infrared light (NIR) could penetrate deep tissue and causes less damage to normal tissue [75]. Upconversion nanoparticles (UCNPs) had the ability to convert long wavelength light into short wavelength light, which effectively overcame the limitation of visible light [76–78]. Inspired by this, we have conjugated Ce6 and UCNPs on cyanobacteria to construct a self-oxygenated photodynamic system (Fig. 2C) [6]. As a light-trapping antenna, UCNPs could convert excited light of 980 nm into visible light and 660 nm light, which could be used for oxygen production by cyanobacteria and $^1\text{O}_2$ production by photosensitizers, respectively. Our near-infrared-driven self-oxygen nanosystem significantly improved the efficacy of PDT in the treatment of hypoxic tumors. Similarly, Wang and Shi also loaded UCNPs on the surface of cyanobacteria to convert 980 nm wavelength light into red luminescence suitable for inducing oxygen production in cyanobacteria, which greatly enhanced oxygenation in the deep tumor tissue [79,80]. Although UCNPs solved the problem of the low penetration depth of visible light in tissue, the overheating caused by long-term laser irradiation posed an unignored risk for in vivo applications [81]. Therefore, the optimal design of suitable light sources and their adaptability to cyanobacteria oxygen evolution was still a considerable challenge. Shi et al. introduced a new type of blue persistent luminescence material (PLM) into the oxygen production cyanobacteria to construct a novel exogenous radiation-free antitumor platform [82]. First, cyanobacteria were pre-treated with CaAl_2O_4 : Eu, Nd (CAO PLM) in vitro. In the process of UV lamp pre-excitation and LED re-excitation, the broad blue persistent emission was triggered due to the existence of the 5d-4f electron transition and electron trapping of Eu^{2+} . In addition, CAO PLM could

store part of the light energy and then act as a light source in vivo to achieve long-term excitation of cyanobacteria and continuous oxygen production while avoiding the side effects of long-term light excitation.

2.1.2. Oxygen-producing cyanobacteria for enhanced SDT and RT

Insufficient oxygen supply has become a major obstacle that restricts the efficiency of acoustic dynamic therapy (SDT). Hu et al. designed an oxygen self-sufficiency system (M@C) with cyan as an oxygen self-donor and ultrasmall anoxic double metal oxide $\text{Mn}_{1.4}\text{WO}_x$ nanoparticles as an acoustic sensitizer to improve the efficacy of SDT on hypoxic tumors (Fig. 4D) [83]. Under light irradiation, cyanobacteria could continuously produce oxygen to relieve tumor hypoxia. Fig. 4A–C showed that the acoustic sensitizer $\text{Mn}_{1.4}\text{WO}_x$ could produce ROS through ultrasound-activated SDT, and the high concentration of O_2 significantly improved the efficiency of ROS production to induce apoptosis in cancer cells. Importantly, the abundant photosynthetic oxygenation in tumors suppressed the gene expression of hypoxia-inducible factor-1 (HIF-1 α), ultimately achieving the goal of tumor eradication. As the traditional RT is ineffective in treating anaerobic tumors and will damage the normal tissue, many nanomaterials containing high atomic number elements have been used as RT sensitizers to enhance the production of free radicals and thus improve the efficiency of RT [84,85]. However, most of these RT sensitizers were oxygen dependent, and thus the continuous oxygen consumption in tumor tissue significantly limits the production of free radicals, making it difficult to exert the maximum effect [86,87]. Therefore, Zhang et al. introduced photosynthetic deoxygenic cyanobacteria into a radiosensitizing platform based on 2D bismuth nanosheets to effectively regulate the hypoxic TME tolerated by radiotherapy [88].

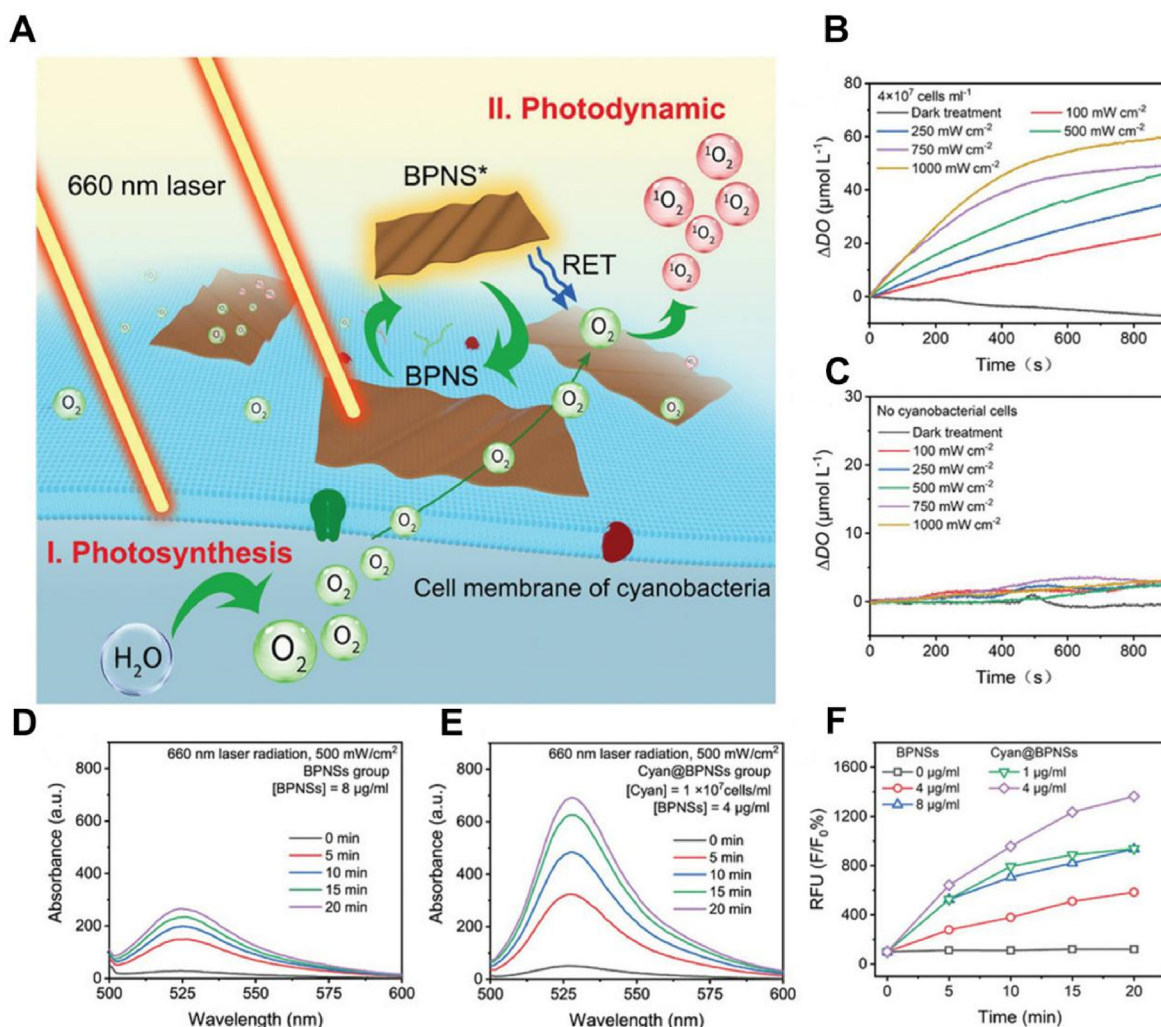


Fig. 3. A. The process of oxygen generation and photosensitization of Cyan@BPNSs in vitro. B. The relative dissolved oxygen concentration curves for solutions containing cyanobacteria C. and no cyanobacterial cells. D. Fluorescent map of singlet oxygen sensor green (SOSG) at BPNSs and E. Cyan@BPNSs group at different time under laser radiation (660 nm, 500 mW/cm²). F. Relative SOSG fluorescence intensity of different concentrations of BPNSs and Cyan@BPNSs under 660 nm laser irradiation [74]. Adapted with permission from Ref. [74] Copyright 2019, Wiley-VCH.

The continuous photosynthetic oxygen released from cyanobacteria effectively alleviated the hypoxic state of the tumor. Simultaneously, under continuous irradiation with X-rays, the radiosensitizer 2D bismuth produced large amounts of ROS and then broke DNA strands in tumor cells. Notably, newly generated oxygen in TME caused further DNA breaks, which significantly improved the effect of radiotherapy and inhibited tumor growth in vivo. Li et al. prepared photosynthesis microcapsules (PMC) by combining cyanobacteria with UCNP through electrostatic droplets in alginate microcapsules (MC) [89]. PMC were capable of photosynthesis under radiation from NIR and provided durable and controlled oxygen cooperation in a biological environment. PMC-supplemented O₂ inhibited HIF-1 α production in cancer cells and significantly inhibited cancer cell replication in a nontoxic manner. Subsequently, they combined PMC with X-rays to increase the sensitivity of malignant melanoma to ionizing radiation. This system could enhance the radiosensitivity of melanoma cells by activating lipid peroxidation and ferroptosis. Driven by NIR (980 nm), PMC could continuously photosynthesize in tumors to build a hyperoxia microenvironment. The combination with X-rays caused lipid peroxidation in melanoma cells and individual tumor graft cells in vivo (Fig. 4E). The accumulation of lipid peroxides would induce ferroptosis-induced cancer cell death that synergized with X-rays. Thus, combination therapy could overcome the

intrinsic and acquired drug resistance of melanoma and further suppress tumor metastasis. In conclusion, Cyanobacteria could produce large amounts of oxygen under the light to relieve hypoxic tumors, significantly improving the efficacy of oxygen-dependent therapy.

2.2. Small algae-based oxygen production system

2.2.1. *Chlorella* PDT

Chlorella pyrenoidosa is a unicellular autotrophic photosynthetic green alga rich in protein, fat, carbohydrates and vitamins, which plays an important role in reducing blood pressure, lowering blood lipids, and enhancing immunity, antioxidation and antitumor activity [90,91]. *Chlorella* contains a large amount of chlorophyll, which can absorb light over a wide range of wavelengths such that photosynthesis can be carried out at a particular wavelength [92]. *Chlorella* has been certified as a recognized safe (GRAS) organism by the FDA [93]. Zhao et al. designed a *Chlorella*-based live scaffold that adapted to irregularly shaped wounds and promoted their healing using an in situ microfluidic-assisted 3D bioprinting strategy [94]. Because photosynthetic protein nucleoli were introduced during 3D printing, this scaffold produced sustainable oxygen under light and promoted cell proliferation, migration and differentiation even under low oxygen conditions. Therefore, printing an active

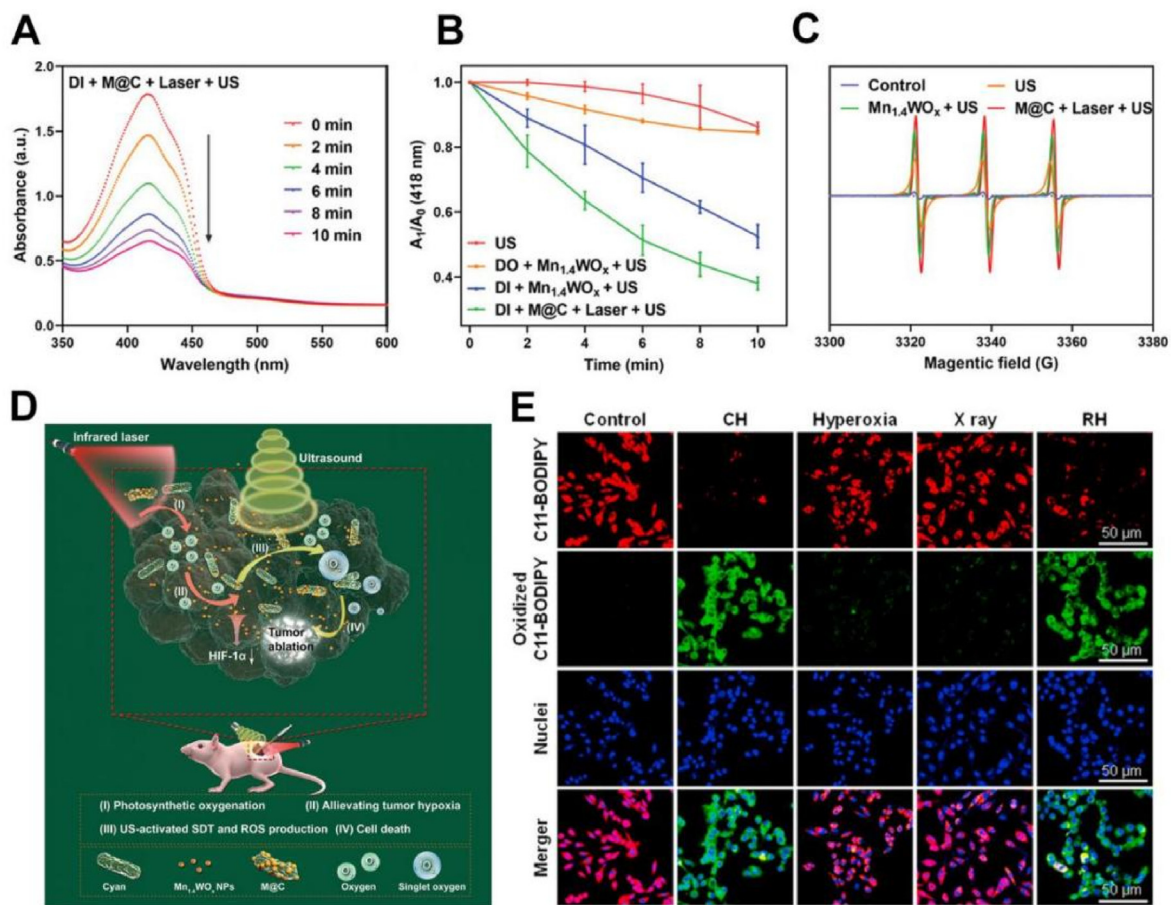


Fig. 4. A. The change of 1,3-diphenylisobenzofuran (DPBF) treated with M@C under laser and US irradiation for different times. B. Quantitative analysis of DPBF oxidation after different treatments. C. The electron spin resonance (ESR) spectroscopy detected ROS generation after different treatments. D. Schematic illustration of M@C for enhancing the SDT efficiency in hypoxic tumors [83]. E. Images of the radiation-hyperoxia-induced lipid-peroxidation in cells after different treatments [89]. Adapted with permission from Ref. [83] Copyright 2021, Wiley-VCH; adapted with permission from Ref. [89] Copyright 2019, Elsevier.

scaffold loaded with microalgae directly onto diabetic wounds could significantly accelerate the closure of chronic wounds by reducing local hypoxia, increasing angiogenesis, and promoting the synthesis of the extracellular matrix (ECM). Wu et al. used live *Chlorella* and bacteria to fabricate hydrogel patches that produced hydrogen and oxygen and promoted the healing of chronic diabetic wounds by reducing oxidative stress and inflammation [95]. It has been proven that *Chlorella* possessed good biological safety and great clinical application prospects. Therefore, a new self-oxygen supplying nanosystem based on *Chlorella* could be constructed to overcome tumor hypoxia. Youn et al. first reported that the characteristics of photosynthetic oxygen production by *Chlorella* could be used in the treatment of hypoxic breast cancer [96]. First, *Chlorella vulgaris* produced high levels of oxygen under 660 nm light exposure. The gold nanorods in this system could increase the tumor ambient temperature to 41–42 °C in response to an 808 nm near-infrared laser, which significantly dilated tumor blood vessels and promoted the transport of the chemotherapeutic drugs DOX and oxygen to hypoxic tumors (Fig. 5A). However, the growth factors in *Chlorella* may be phagocytized by macrophages, resulting in a decline in oxygen production efficiency. Alginate is a type of natural polysaccharide with high adhesion, good biocompatibility and degradability and is therefore widely used in cell transport [97,98]. Jiang et al. coated calcium alginate onto *Chlorella* and protected *Chlorella* from being phagocytized, thus realizing a long-term standby oxygen supply (Fig. 5B) [99]. As shown in Fig. 5C, D, F, the system produced oxygen from the decomposition of water and energy conversion after light triggering, which effectively alleviated tumor hypoxia. And then large amounts of ROS could be

produced to effectively kill tumor cells in vitro (Fig. 5E, G). It has been demonstrated that *Chlorella* has excellent potential in hypoxia-tolerant photodynamic therapy.

2.2.2. *Chlorella* in RT and SDT

The oxygen production system based on *Chlorella* plays an important role in PDT-based antitumor strategy, and researchers have further explored their potential applications in tumor RT. Zhou et al. first designed an erythrocyte membrane-modified microalgae (RBCM-Algae) to enhance the therapeutic efficacy of RT-mediated hypoxia-tolerant tumors [100]. Fig. 6B showed that RBCM-Algae could produce O₂ when stimulated by red light, which increased the oxygenation of the local tumor tissue. Furthermore, under laser irradiation, RBCM-Algae would breakdown, resulting in the release of chlorophyll from the microalgae. Subsequently, under 650 nm irradiation, free chlorophyll could be used as a photosensitizer to produce ROS, thus enhancing PDT efficiency. They found that microalgae coated with calcium phosphate had good biocompatibility compared with silicon dioxide (SiO₂), which could continuously supply oxygen and significantly improve the RT effect [101, 102]. Both photosynthesis and PDT required photoexcitation while the poor penetration of light into biological tissues limited their efficiency. Generally, the construction of heterojunction structures (type II heterojunctions) is the most direct and effective means to improve the efficiency of light energy conversion [103,104]. Mei et al. constructed functionalized Chl cells (Chl-BP-Fe) of BPNSs through the Lego building block method and improved the oxygen production of Chl cells, which then enhanced the photodynamic effect of BPNSs [105]. The BPNSs

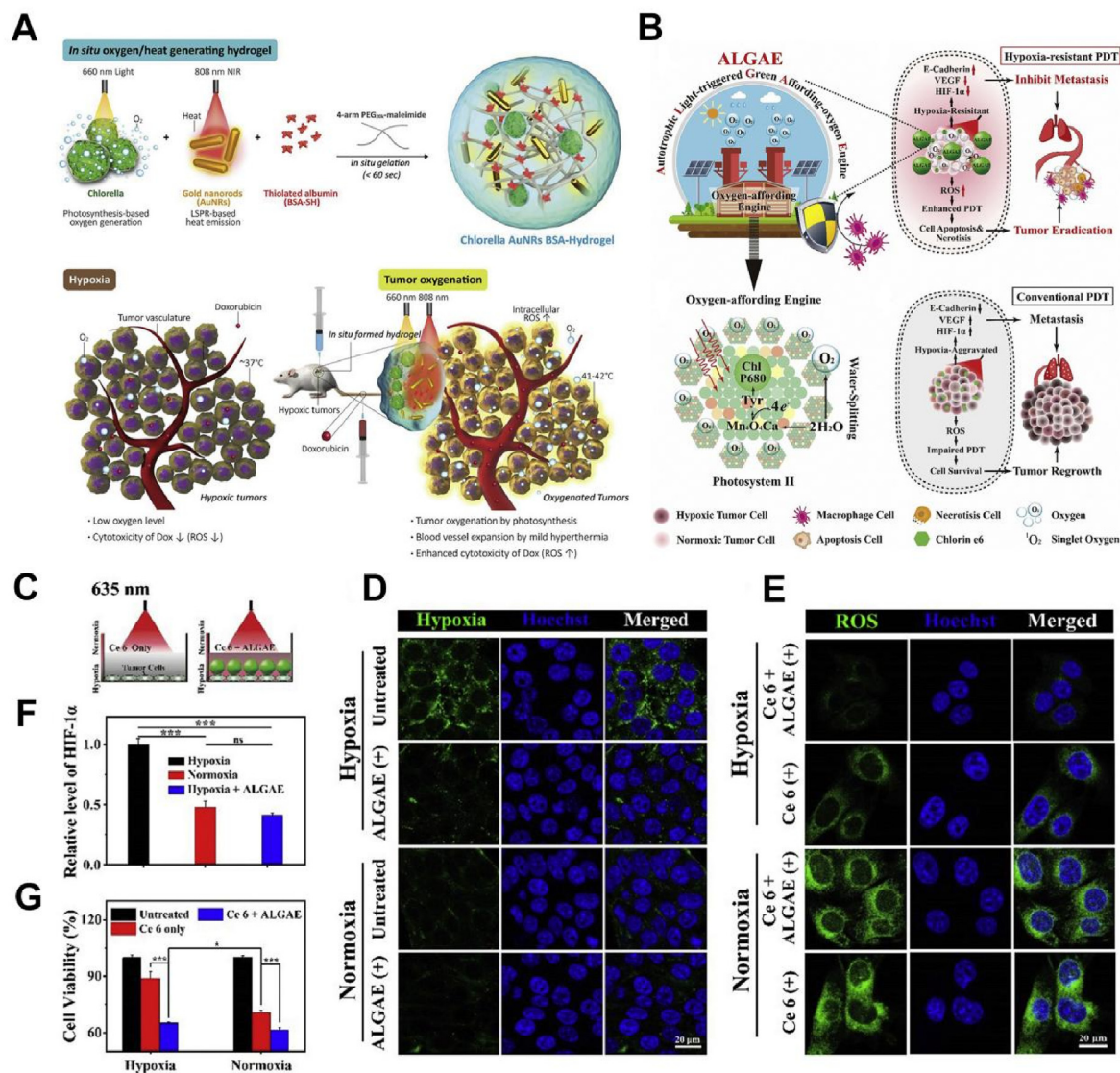


Fig. 5. A. Scheme showing in situ rapid gelation of *Chlorella* AuNRs BSA-Gel that generated oxygen for overcoming hypoxia [96]. B. Schematic diagram of the hypoxia-resistant PDT induced by the ALGAE system. C. Schematic illustration of the cellular experiment with 4T1 cells treated with Ce6, Ce6-ALGAE under 635 nm laser light. D. The images that were stained by the hypoxic probe in cells irradiated with or without ALGAE by confocal microscopy (LSCM). E. The cellular expression of HIF-1 α with or without ALGAE after irradiation. F. LSCM images of the intracellular ROS production. G. Cell viability of conventional PDT with or without ALGAE under hypoxic and normoxic conditions [99]. Adapted with permission from Ref. [96] Copyright 2019, Elsevier; Adapted with permission from Ref. [99] Copyright 2019, Elsevier.

adsorbed by polyaspartate (PASP) was first used as Lego building blocks and then loaded onto the Chl surface by the complexation reaction of Fe³⁺ with PASP. Under 658 nm laser irradiation, Chl cells were able to reduce tumor hypoxia and improve the efficiency of PDT through their own photosynthesis system. Importantly, the type of heterojunction with a suitable band structure was cleverly constructed between BPNs and chlorophyll from Chl cells, greatly improving the efficiency of light penetration into the tissue. Moreover, Fe³⁺ between Lego blocks could both consume glutathione and reduce the resistance of tumor cells to ROS. This also catalyzed the reaction of Fe²⁺ with H₂O₂ to produce hydroxyl radicals, thus improving the efficiency of chemodynamic therapy (CDT)-mediated death of tumor cells. In summary, *Chlorella* could not only produce oxygen via photosynthesis, but also have reliable biosafety. Therefore, the *Chlorella*-based oxygen shuttle has the most potential in clinical applications.

2.3. Bacteria engineering for oxygen supplying

Researchers have combined the ability of facultative anaerobic bacteria or obligatory anaerobic bacteria to colonize tumors with the oxygen production performance of photosynthetic bacteria to greatly increase the intratumor oxygen content [106]. To expand bacterial therapy, researchers have focused on genetically engineered common bacteria for O₂ producing [107,108]. For example, bacteria were genetically engineered to produce enzymes that could catalyze H₂O₂ to generate O₂. The facultative anaerobic bacterium *E. coli* DH5 α is a genetically modified competent and it's easy to absorb exogenous genes, which makes it suitable for gene modification and targeted delivery [109]. Zhao et al. genetically modified *E. coli* by plasmid transfection to obtain overexpressed human catalase (CAT) in *E. coli*, which catalyzed O₂ production from endogenous H₂O₂ in situ to enhance the PDT effect [110]. In

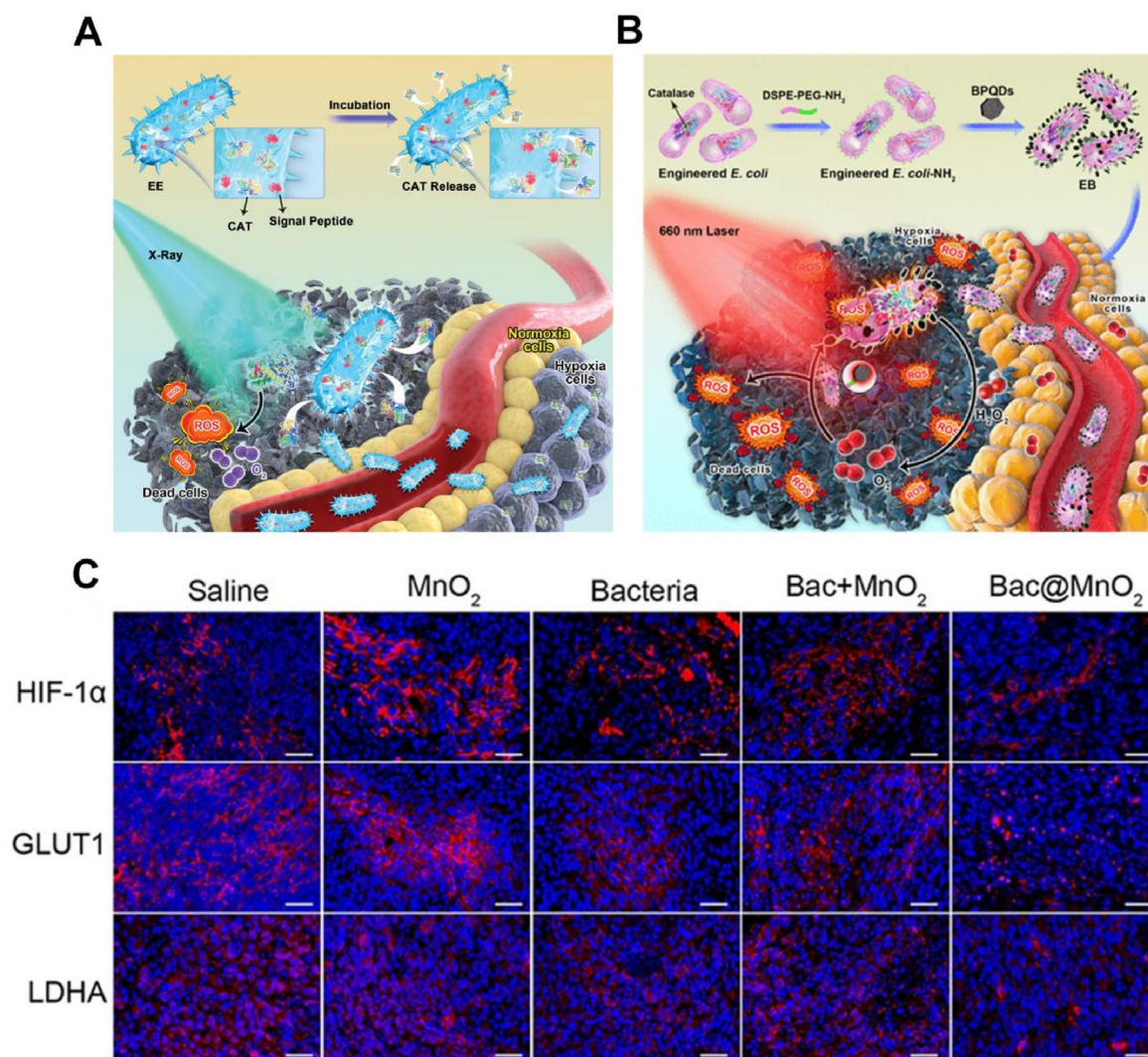


Fig. 6. A. Engineered *E. coli* of secreted CAT for the treatment of hypoxic tumors [112]. B. Bacteria carrying CAT could relieve tumor hypoxia and thus enhance PDT [112]. C. Immunofluorescence staining of GLUT1, HIF-1 α , and LDHA of mice tumor tissues after different treatments [114]. Adapted with permission from Ref. [114] Copyright 2021, Wiley-VCH; Adapted with permission from Ref. [112] Copyright 2020, American Chemical Society; Adapted with permission from Ref. [114] Copyright 2020, Wiley-VCH.

addition, PDT mediated by bacterial surface-loaded nanodopamine (pDA) also selectively ablated tumors under near-infrared irradiation. The integration of transgenic bacteria and pDA/Ce6 showed a potent antitumor effect. At the same time, Zhao et al. also used these engineered bacteria to achieve continuous oxygen supply in solid tumors and obtained positive RT effects (Fig. 6A) [111]. In addition to the genetic modification of bacteria to express CAT, bacteria could also be engineered nanoenzymes on their surface to catalyze O₂ production (Fig. 6B) [112]. Under natural environmental conditions, facultative anaerobic *Shewanella oneidensis* MR-1 (*S. oneidensis* MR-1) could transfer electrons from some organic compounds (such as formic acid, amino acids, and lactic acid) to the terminal electron receptors of redox-active minerals (Fe³⁺ and Mn⁴⁺) and then respire in the absence of molecular oxygen [113]. Given this unique property of MR-1, Zhang et al. modified MnO₂ nanosheets on MR-1 to construct a biohybrid bacterium (Bac@MnO₂) [114]. MnO₂ nanoflowers with larger surface areas could serve as electron acceptors to provide larger reaction regions for lactate. Simultaneously, MnO₂ could catalyze the conversion of H₂O₂ into O₂, which both improved tumor hypoxia and prevented lactate production by down-regulating the expression of glucose transporter type 1 (GLUT1), HIF-1 α ,

and interfering lactate dehydrogenase A (LDHA), thus effectively inhibited tumor growth (Fig. 6C).

However, due to the limited content of endogenous H₂O₂ limiting the application of CAT and nanowaves in situ catalysis, the introduction of exogenous H₂O₂ is crucial to improve the treatment of hypoxic tumors [115]. Inspired by magnetic bacteria, Zhang et al. modified magnetic ferrous oxide (Fe₃O₄) nanoparticles (MNPs) on the *E. coli* surface and developed an engineered bacteria-based integrated bioreactor (Ec-pE@MNPs) (Fig. 7A) [116]. The engineered bacterium overexpressed the respiratory chain enzyme NDH-2, which received electrons from nicotinamide adenine dinucleotide (NADH) and then transferred the electrons to O₂ to produce H₂O₂ (Fig. 7B). Subsequently, the MNPs on the surface of *E. coli* catalyzed H₂O₂ to produce O₂ in situ via a Fenton-like reaction. Moreover, *E. coli*-pE produced continuous H₂O₂ while producing large amounts of hydroxyl radicals (\bullet OH) to induce tumor cell apoptosis. This bacterial manipulation allowed a bacterium to deliver different drugs for different situations to treat hypoxic tumors. Zhou et al. modified magnetic Fe₃O₄ NPs on the surface of magnetically engineered *Spirulina platensis* via a dip-coating process and developed a photosynthetic biohybrid nanopolymer system (PBNs) [117]. This

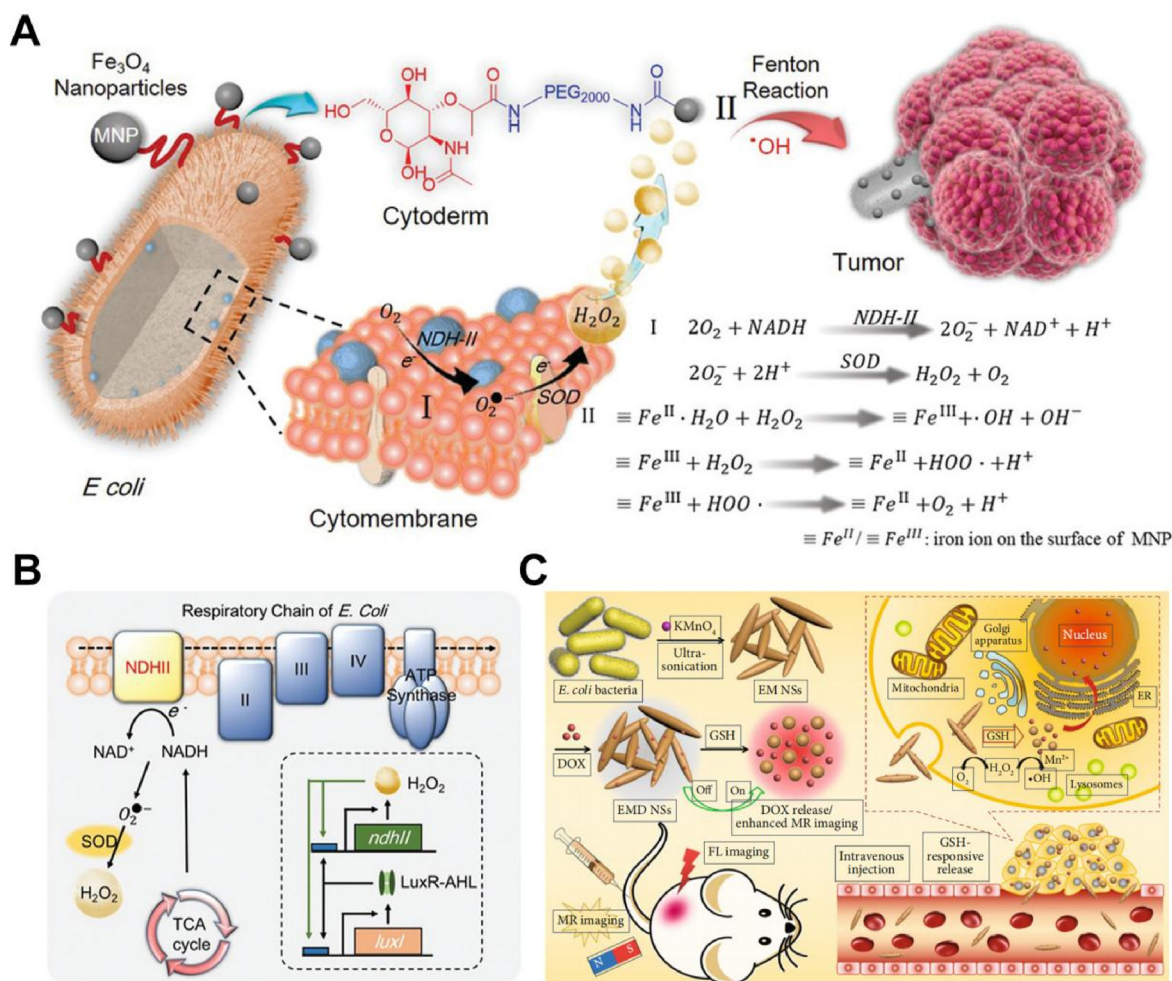


Fig. 7. A. The scheme of bacteria-based Fenton-like bioreactor was capable of oxygen production and used for enhanced CDT [115]. B. Mechanism of NDH-2 expression based on synthetic biology, and the function of NDH-2 played in the respiratory chain of bacteria [115]. C. Schematic illustration of the fabrication of EMD NSs that enhanced CDT combination therapy [120]. Adapted with permission from Ref. [115] Copyright 2019, Wiley-VCH; adapted with permission from Ref. [120] Copyright 2020, Science Partner Journals.

system had a high tumor aggregation rate due to the presence of magnetic Fe₃O₄ NPs. Subsequently, PBNs that colonize the anoxic region of the tumor could regulate the tumor TME by forming oxygen in situ through photosynthesis. In addition, the chlorophyll released from PBNs treated with RT can act as photosensitizers to produce cytotoxic reactive oxygen species under laser irradiation, thus achieving powerful PDT. Inspired by the strong oxidant potassium permanganate (KMnO₄), MnO₄⁻ is reduced to MnO₂ [118,119]. For the first time, Wu et al., used *E. coli* as a template and reducing agent to build a tumor microenvironment-responsive nanospindle (EM NSs) at room temperature and loaded the chemotherapeutic drug DOX (EMD NSs) by ultra-sonication with (KMnO₄) at room temperature (Fig. 7C) [120]. The MnO_x structure in the EMD NSs could react with GSH in the TME to cause EMD NSs breakdown with the simultaneous release of DOX and Mn²⁺. Subsequently, the released DOX could eliminate cancer cells, and Mn²⁺, with Fenton-like properties, could convert endogenous H₂O₂ into highly toxic hydroxyl radicals to induce apoptosis. The MnO₂ in EMD NSs could also react with H₂O₂ in the TME to produce a large amount of O₂, alleviating tumor hypoxia while overcoming hypoxia-induced chemoresistance. After genetic modification, *E. coli*, *Shewanella oneidensis*, and *Spirulina platensis* could produce oxygen to improve the hypoxic TEM. Interestingly, these oxygen shuttles could also rely on oxygen targeting accurately reach tumors, greatly inhibiting tumor growth.

3. Conclusions and perspectives

The development of live microorganism-based oxygen shuttles have facilitated the rapid development of novel advanced bioactive materials for high-performance hypoxic tumor therapy. In this review, we summarize the recent advances in innovative live microorganism-based oxygen shuttles for the treatment of hypoxic tumors. Photosynthetic microorganism-based oxygen shuttles possessed inherent advantages in cancer treatment over traditional oxygen shuttles. The controlled and continuous oxygen produced by photosynthetic microorganisms in response to light could increase the oxygen concentration at the tumor site and reverse the immunosuppressive TME, thus greatly improving the therapeutic effect of oxygen-dependent treatment modalities. Thus, oxygen shuttles constructed by photosynthetic microorganisms showed excellent oxygen encapsulation rate and loading capacity compared to conventional oxygen shuttles. However, Cyanobacteria and *Chlorella* were mostly administered through *i.v.*, the low tumor targeting ability of photosynthetic microorganisms would lead to insufficient oxygen production. Genetically engineered bacteria were also developed for oxygen production. However, it should be noted that although these engineered bacteria greatly improved their tumor accumulation, some inherent disadvantages of engineered bacteria such as the instability of gene expression and the introduction of resistance genes. Although many

attenuated live bacteria have been developed, such as *Salmonella* and *E. coli*, their residual toxicity has still been a concerned even after the removal of toxin genes. It should be further noted that Cyanobacteria and *Chlorella* are superior to engineered bacteria in biocompatibility. Although Microalgae have been used in the treatment of various diseases such as cardiovascular diseases, brain diseases, human wound healing, and gut-related diseases, it still needs more studies to assess their safety and therapeutic efficacy before clinical applications. In addition, we discussed in detail how oxygen production increased the therapeutic efficacy in hypoxic tumors. Notably, the novel oxygen shuttle has made significant progress in the treatment of hypoxic tumors, but there are still numerous challenges involved in the clinical translation of bacteria.

Bacterial virulence remains a prominent obstacle to the application of bacterial therapies in clinic, and even attenuated species may have some adverse effects in a dose-dependent manner. Furthermore, it is likely that most administered bacteria will be cleared by the mesh endothelial system before colonization in tumor site, thereby affecting therapeutic efficacy. With the rapid development of synthetic biology, an increasing number of targeted and controlled biological loads have been developed to transport drugs and imaging agents. Bacteria can be genetically engineered to reduce their inherent virulence without affecting tumor targeting, thereby increasing maximum tolerance. In addition, transgenic bacterial strains that respond to various stimuli (such as chemicals, temperature, light, osmolarity, and pH) can be generated which ensures a controlled release of cargo after sensing specific environmental signals. Stimulus response strategies further increase the in-situ accumulation of bacteria and minimize diffusion to normal tissues. In addition, bacterial surface modification of therapeutic agents, nanoparticles, liposomes, and micelles can enhance their targeted aggregation, and the biofilm surface modification of the nanoparticles improves their biocompatibility and targeting. Similarly, bacterial toxicity and immunogenicity can be mitigated by wrapping cells with highly biocompatible nanomaterials or biomimics, which prevent them from being rapidly cleared by the immune system. What is more noteworthy is that the related bacteria in the intestinal microbiome are expected to be linked to the tumor treatment. Thus, attenuated or nontoxic probiotic strains can be developed to replace existing pathogens. As naturally avirulent strains, *L. lactis* and *L. casei* are widely used in the food industry and commonly regarded as beneficial strains for maintaining microbe balance in the intestine. They are facultatively anaerobic and can replace pathogenic *Salmonella* to serve as magic bullets targeting tumor hypoxia.

The instability of gene-engineered bacteria also contributes to their poor therapeutic efficacy. Bacteria possess a large genetic toolbox to enable rapid and simple modifications while it is also a primary drawback that hinders their application in clinical practice. Bacteria are prone to lose genes in repeat passage or in response to a complicated growth environment. In addition, after foreign gene editing, it is likely to affect their inherent biofunction, such as oxygen concentration-sensing. Therefore, to ensure the biosafety and stability of engineered live bacterial drugs, the following basic problems must be considered in the design: (1) avoid introducing resistance genes; (2) do not use plasmid-based gene editing systems as they are easy to lose and cause horizontal gene transfer, permanently integrate the gene circuit into the genome.

The oxygen production efficiency of microorganisms is highly important in the treatment of hypoxic tumors in vivo. Thus, how to accurately monitor the efficiency of oxygen production by microorganisms in vivo has been regarded as another big challenge. Due to the complicated biological environment of the human body, it is necessary to explore innovative methods to track bacterial biodistribution and their oxygen production capacity in vivo. Synthetic biology and imaging techniques can be used to monitor the survival and oxygen production of bacteria in vivo [121,122]. The oxygenation effect of tumors in vivo can be investigated by combined photoacoustic (PA) and B-mode ultrasound (US) imaging using oxygen saturation mode (sO₂). Reliably, many probes have been developed for gas detection, such as a wide variety of probes of

CO, NO and H₂S. We believe these advanced O₂ tracking techniques would accelerate their clinical applications of oxygen shuttles.

Declaration of competing interest

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.

Data availability

No data was used for the research described in the article.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (32271420, 21977024, and 31971304), the Beijing-Tianjin-Hebei Basic Research Cooperation Project (19JCZDJC64100), Cross-Disciplinary Project of Hebei University (DXK201916). One Hundred Talent Project of Hebei Province (E2018100002). Science Fund for Creative Research Groups of Nature Science Foundation of Hebei Province (B2021201038), Natural Science Foundation of Hebei Province (B2020201091), Guangdong Basic and Applied Basic Research Foundation (2021B1515120065).

References

- [1] V. Bhandari, C. Hoey, L.Y. Liu, E. Lalonde, J. Ray, J. Livingstone, R. Lesurf, Y.J. Shiah, T. Vujcic, X.Y. Huang, S.M.G. Espirito, L.E. Heisler, F. Yousef, V. Huang, T.N. Yamaguchi, C.Q. Yao, V.Y. Sabelnykova, M. Fraser, M.L.K. Chua, T.V. Kwast, S.K. Liu, P.C. Boutros, R.G. Bristow, Molecular landmarks of tumor hypoxia across cancer types, *Nat. Genet.* 51 (2019) 308–318.
- [2] C. Michiels, C. Tellier, O. Feron, Cycling hypoxia: a key feature of the tumor microenvironment, *Bba. Mol. Cell. Res.* 1866 (2016) 76–86.
- [3] Y. Fan, W.Z. Tu, M.W. Shen, X.M. Chen, Y.S. Ning, J.J. Li, T.F. Chen, H. Wang, F.F. Yin, Y. Liu, X.Y. Shi, Targeted tumor hypoxia dual-mode CT/MR imaging and enhanced radiation therapy using dendrimer-based nanosensitizers, *Adv. Funct. Mater.* 30 (2020), 1909285.
- [4] M. Gao, C. Liang, X.J. Song, Q. Chen, Q.T. Jin, C. Wang, Z. Liu, Erythrocyte-membrane-enveloped perfluorocarbon as nanoscale artificial red blood cells to relieve tumor hypoxia and enhance cancer radiotherapy, *Adv. Mater.* 29 (2017), 1701429.
- [5] X.Y. Luo, J. Cao, J.M. Yu, D.Q. Dai, W. Jiang, Y.H. Feng, Y. Hu, Regulating acidosis and relieving hypoxia by platelet membrane-coated nanoparticle for enhancing tumor chemotherapy, *Front. Biotechnol.* 12 (2022), 885105.
- [6] Y.H. Zhang, H.F. Liu, X.Y. Dai, H. Li, X.H. Zhou, S.Z. Chen, J.C. Zhang, X.J. Liang, Z.H. Li, Cyanobacteria-based near-infrared light-excited self-supplying oxygen system for enhanced photodynamic therapy of hypoxic tumors, *Nano Res.* 14 (2021) 667–673.
- [7] W.W. Zhu, Z.L. Dong, T.T. Fu, J.J. Liu, Q. Chen, Y.G. Li, R. Zhu, L.G. Xu, Z. Liu, Modulation of hypoxia in solid tumor microenvironment with MnO₂ nanoparticles to enhance photodynamic therapy, *Adv. Funct. Mater.* 26 (2016) 5490–5498.
- [8] Y.Y. Yang, X. Liu, W. Ma, Q. Xu, G. Chen, Y.F. Wang, H.H. Xiao, N. Li, X.J. Liang, M. Yu, Z.Q. Yu, Light-activatable liposomes for repetitive on-demand drug release and immunopotential in hypoxic tumor therapy, *Biomaterials* 265 (2021), 120456.
- [9] J.M. Henk, P.B. Kunklerdagger, C.W. Smith, Radiotherapy and hyperbaric oxygen in head and neck cancer final report of first controlled clinical trial, *Lancet* 310 (1977) 101–103.
- [10] K. Ogawa, K. Kohshi, S. Ishiuchi, M. Matsushita, N. Yoshimi, S. Murayama, Old but new methods in radiation oncology: hyperbaric oxygen therapy, *Int. J. Clin. Oncol.* 18 (2013) 364–370.
- [11] S. Rockwell, C.G. Irvin, M. Kelley, C.S. Hughes, H. Yabuki, E. Porter, J.J. Fischer, Effects of hyperbaric oxygen and a perfluoroethylbromide emulsion on the radiation responses of tumors and normal tissues in rodents, *Inr. J. Radiation. Oncolog. Bml. Phys.* 22 (1992) 81–93.
- [12] H.A.S. van den Brenk, D. Jamieson, Brain damage and paralysis in animals exposed to high pressure oxygen-pharmacological and biochemical observations, *Biochem. Pharmacol.* 13 (1964) 165–182.
- [13] L. Yu, Z.J. Wang, Z.M. Mo, B.H. Zou, Y.Y. Yang, R. Sun, W. Ma, M. Yu, S.J. Zhang, Z.Q. Yu, Synergistic delivery of triptolide and Ce6 with light-activatable liposomes for efficient hepatocellular carcinoma therapy, *Acta Pharm. Sin. B* 11 (7) (2021) 2004–2015.
- [14] D.D. Wang, H.H. Wu, W.Q. Lim, S.Z.F. Phua, P.P. Xu, Q.W. Chen, Zhen Guo, Y.L. Zhao, A mesoporous nanoenzyme derived from metal-organic frameworks with endogenous oxygen generation to alleviate tumor hypoxia for significantly enhanced photodynamic therapy, *Adv. Mater.* 31 (2019), 1901893.

- [15] L.Z. Feng, O. Betzer, D.L. Tao, T. Sadan, R. Popovtzer, Z. Liu, Oxygen nanoshuttles for tumor oxygenation and enhanced cancer treatment, *CCS Chem* 1 (2019) 239–250.
- [16] M. Gao, C. Liang, X.J. Song, Q. Chen, Q.T. Jin, C. Wang, Z. Liu, Erythrocyte-membrane-enveloped perfluorocarbon as nanoscale artificial red blood cells to relieve tumor hypoxia and enhance cancer radiotherapy, *Adv. Mater.* 29 (2017), 1701429.
- [17] C. Zhang, W.H. Chen, L.H. Liu, W.X. Qiu, W.Y. Yu, X.Z. Zhang, An O₂ self-supplementing and reactive-oxygen-species-circulating amplified nanoplatform via H₂O/H₂O₂ splitting for tumor imaging and photodynamic therapy, *Adv. Funct. Mater.* 27 (2017), 1700626.
- [18] X.C. Cai, Z.X. Xie, B.B. Ding, S. Shao, S. Liang, M.L. Pang, J. Lin, Monodispersed copper(I)-based nano metal-organic framework as a biodegradable drug carrier with enhanced photodynamic therapy efficacy, *Adv. Sci.* 6 (2019), 1900848.
- [19] Y.H. Cheng, H. Cheng, C.X. Jiang, X.F. Qiu, K.K. Wang, W. Huan, A.H. Yuan, J.H. Wu, Y.Q. Hu, Perfluorocarbon nanoparticles enhance reactive oxygen levels and tumor growth inhibition in photodynamic therapy, *Nat. Commun.* 6 (2015) 8785.
- [20] Z.K. Chen, L.L. Liu, R.J. Liang, Z.Y. Luo, H.M. He, Z.H. Wu, H. Tian, M.B. Zheng, Y.F. Ma, L.T. Cai, Bioinspired hybrid protein oxygen nanocarrier amplified photodynamic therapy for eliciting anti-tumor immunity and abscopal effect, *ACS Nano* 12 (2018) 8633–8645.
- [21] S.T. Gao, P.L. Zheng, Z.H. Li, X.C. Feng, W.X. Yan, S.Z. Chen, W.S. Guo, D.D. Liu, X.J. Yang, S.X. Wang, X.J. Liang, J.C. Zhang, Biomimetic O₂-evolving metal-organic framework nanoplatform for highly efficient photodynamic therapy against hypoxic tumor, *Biomaterials* 178 (2018) 83e94.
- [22] W. Jiang, Q. Li, L. Xiao, J.X. Dou, Y. Liu, W.H. Yu, Y.C. Ma, X.Q. Li, Y.Z. You, Z.T. Tong, H. Liu, H. Liang, L.G. Lu, X.D. Xu, Y.D. Yao, G.Q. Zhang, Y.C. Wang, J. Wang, Hierarchical multiplexing nanodroplets for imaging guided cancer radiotherapy via DNA damage enhancement and concomitant DNA repair prevention, *ACS Nano* 12 (2018) 5684–5698.
- [23] W.T. Zhang, S.H. Li, X.N. Liu, C.Y. Yang, N. Hu, L.N. Dou, B.X. Zhao, Q.Y. Zhang, Y.R. Suo, J.L. Wang, Oxygen-generating MnO₂ nanodots-anchored versatile nanoplatform for combined chemo-photodynamic therapy in hypoxic cancer, *Adv. Funct. Mater.* 28 (2018), 1706375.
- [24] H.S. Hao, M. Yu, Y.F. Yi, S.J. Sun, X.Y. Huang, C.Y. Huang, Y.Q. Liu, W.X. Huang, J.Q. Wang, J. Zhao, M.Y. Wu, Mesoporous calcium peroxide-ignited NO generation for amplifying photothermal immunotherapy of breast cancer, *Chem. Eng. J.* 437 (2022), 135371.
- [25] Q.Y. Liu, L.Y. Shi, Y. Liao, X.S. Cao, X.Q. Liu, Y.X. Yu, Z.F. Wang, X.H. Lu, J.W. Wang, Ultrathin-FeOOH-coated MnO₂ sonosensitizers with boosted reactive oxygen species yield and remodeled tumor microenvironment for efficient cancer therapy, *Adv. Sci.* 9 (2022), 2200005.
- [26] G.V. Enriquez, A. Arroyo, M. Grijalva, R.I.A. Zafra, J. Camacho, Molecular and cellular effects of hydrogen peroxide on human lung cancer cells: potential therapeutic implications, *Oxid. Med. Cell. Longev.* (2016), 1908164.
- [27] M.X. Wang, F. Zhang, C.Q. Wang, N. Yin, Y.T. Wang, G.X. Qin, Q.L. Xu, J.H. Gong, H.Z. Liu, X.R. Duan, Target-binding accelerated response for sensitive detection of basal H₂O₂ in tumor cells and tissues via a dual-functional fluorescence probe, *Anal. Chem.* 94 (2022) 5962–5969.
- [28] D.D. Zhang, W. Wei, Y. Liu, Y.P. Pu, S.Q. Liu, Dual imaging of poly (ADP-ribose) polymerase-1 and endogenous H₂O₂ for the diagnosis of cancer cells using silver-coated gold nanorods, *Anal. Chem.* 93 (2021) 16248–16256.
- [29] G. Chen, Y.Y. Yang, Q. Xu, M.G. Ling, H.M. Lin, W. Ma, R. Sun, Y.C. Xu, X.Q. Liu, N. Li, Z.Q. Yu, M. Yu, Self-amplification of tumor oxidative stress with degradable metallic complexes for synergistic cascade tumor therapy, *Nano Lett.* 20 (11) (2020) 8141–8150.
- [30] J. Shen, H.Z. Yu, Y.M. Shu, M. Ma, H.R. Chen, A robust ROS generation strategy for enhanced chemodynamic/photodynamic therapy via H₂O₂/O₂ self-Supply and Ca²⁺ overloading, *Adv. Funct. Mater.* 31 (2021), 2106106.
- [31] K. Yang, S.L. Qi, X.Y. Yu, B. Bai, X.Y. Zhang, Z.W. Mao, F.H. Huang, G.C. Yu, A hybrid supramolecular polymeric nanomedicine for cascade-amplified synergistic cancer therapy, *Angew. Chem. Int. Ed.* 61 (2022), e202203786.
- [32] G. Wang, J.Y. Gao, Y.K. Fu, Z.H. Ren, J. Huang, X. Li, G.R. Han, Implantable composite fibres with self-supplied H₂O₂ for localized chemodynamic therapy, *Chem. Eng. J.* 388 (2020), 124211.
- [33] H.M. Liu, R. Cheng, X.H. Dong, S. Zhu, R.Y. Zhou, L. Yan, C.Y. Zhang, Q. Wang, Z.J. Gu, Y.L. Zhao, BiO_{2-x} nanosheets as radiosensitizers with catalase-like activity for hypoxia alleviation and enhancement of the radiotherapy of tumors, *Inorg. Chem.* 59 (2020) 3482–3493.
- [34] B.L. Xu, Y. Cui, W.W. Wang, S.S. Li, C.L. Lyu, S. Wang, W.E. Bao, H.Y. Wang, M. Qin, Z. Liu, W. Wei, H.Y. Liu, Immunomodulation-enhanced nanozyme-based tumor catalytic therapy, *Adv. Mater.* 32 (2020), 2003563.
- [35] D.M. Zhu, H. Chen, C.Y. Huang, G.X. Li, X. Wang, W. Jiang, K.L. Fan, H₂O₂ self-producing single-atom nanozyme hydrogels as light-controlled oxidative stress amplifier for enhanced synergistic therapy by transforming “cold” tumors, *Adv. Funct. Mater.* 32 (2022), 2110268.
- [36] Y.J. Sang, F.F. Cao, W. Li, L. Zhang, Y.W. You, Q.Q. Deng, K. Dong, J.S. Ren, X.G. Qu, Bioinspired construction of a nanozyme-based H₂O₂ homeostasis disruptor for intensive chemodynamic therapy, *J. Am. Chem. Soc.* 142 (2020) 5177–5183.
- [37] S.T. Gao, Y. Jin, K. Ge, Z.H. Li, H.F. Liu, X.Y. Dai, Y.H. Zhang, S.Z. Chen, X.J. Liang, J.C. Zhang, Self-supply of O₂ and H₂O₂ by a nanocatalytic medicine to enhance combined chemo/chemodynamic therapy, *Adv. Sci.* 6 (2019), 1902137.
- [38] H. Kobayashi, P.L. Choyke, Super enhanced permeability and retention (SUPR) effects in tumors following near infrared photoimmunotherapy, *Nanoscale* 8 (2016) 12504–12509.
- [39] J. Fang, R. Islam, W. Islam, H.Z. Yin, V. Subr, T. Etrych, K. Ulbrich, H. Maeda, Augmentation of EPR effect and efficacy of anticancer nanomedicine by carbon monoxide generating agents, *Pharmaceutics* 11 (2019) 343.
- [40] D. Huang, L.N. Sun, L. Huang, Y.Z. Chen, Nanodrug delivery systems modulate tumor vessels to increase the enhanced permeability and retention effect, *J. Personalized Med.* 11 (2021) 124.
- [41] Q. Chen, L.Z. Feng, J.J. Liu, W.W. Zhu, Z.L. Dong, Y.F. Wu, Z. Liu, Intelligent albumin-MnO₂ nanoparticles as pH-/H₂O₂-responsive dissociable nanocarriers to modulate tumor hypoxia for effective combination therapy, *Adv. Mater.* 28 (2016) 7129–7136.
- [42] Y. Zhong, T. Su, Q.X. Shi, Y.R. Feng, Z. Tao, Q.X. Huang, L. Li, L.Q. Hu, S.F. Li, H. Tan, S. Liu, H. Yang, Co-administration of iRGD enhances tumor-targeted delivery and anti-tumor effects of paclitaxel-enclosed PLGA nanoparticles for colorectal cancer treatment, *Int. J. Nanomed.* 14 (2019) 8543–8560.
- [43] L.H. Dang, C. Bettgeowda, D.L. Huso, K.W. Kinzler, B. Vogelstein, Combination bacteriolytic therapy for the treatment of experimental tumors, *Proc. Natl. Acad. Sci. USA* 98 (2001) 15155–15160.
- [44] C. Zu, J.S. Wang, Tumor-colonizing bacteria: a potential tumor targeting therapy, *Crit. Rev. Microbiol.* 40 (2014) 225–235.
- [45] Z.M. Geng, Z.P. Cao, R. Liu, K. Liu, J.Y. Liu, W.H. Tan, Aptamer-assisted tumor localization of bacteria for enhanced biotherapy, *Nat. Commun.* 12 (2021) 6584.
- [46] W.F. Chen, C.T. He, N. Qiao, Z.F. Guo, S.L. Hu, Y.S. Song, H.R. Wang, Z.R. Zhang, B.W. Ke, X. Sun, Dual drugs decorated bacteria irradiate deep hypoxic tumor and arouse strong immune responses, *Biomaterials* 286 (2022), 121582.
- [47] P.L. Zheng, M. Fan, H.F. Liu, Y.H. Zhang, X.Y. Dai, H. Li, X.H. Zhou, S.Q. Hu, X.J. Yang, Y. Jin, N. Yu, S.T. Guo, J.C. Zhang, X.J. Liang, K. Cheng, Z.H. Li, Self-propelled and near-infrared-phototoxic photosynthetic bacteria as photothermal agents for hypoxia-targeted cancer therapy, *ACS Nano* 15 (2021) 1100–1110.
- [48] Z.J. Yang, Y.J. Zhu, Z.L. Dong, Y. Hao, C.J. Wang, Q.G. Li, Y.M. Wu, L.Z. Feng, Z. Liu, Engineering bioluminescent bacteria to boost photodynamic therapy and systemic anti-tumor immunity for synergistic cancer treatment, *Biomaterials* 281 (2022), 121332.
- [49] T. Yin, Z.Y. Diao, N.T. Blum, L. Qiu, A.Q. Ma, P. Huang, Engineering bacteria and bionic bacterial derivatives with nanoparticles for cancer therapy, *Small* 18 (2022), 2104643.
- [50] J.H. Fritz, S.E. Girardin, C. Fitting, C. Werts, D.M. Lecreux, M. Caroff, J.M. Cavailon, D.J. Philpott, M.A. Conquy, Synergistic stimulation of human monocytes and dendritic cells by Toll-like receptor 4 and NOD1- and NOD2-activating agonists, *Eur. J. Immunol.* 35 (2005) 2459–2470.
- [51] X.H. Huang, J.M. Pan, F.N. Xu, B.F. Shao, Y. Wang, X. Guo, S.B. Zhou, Bacteria-based cancer immunotherapy, *Adv. Sci.* 8 (2021), 2003572.
- [52] B.C. Wei, J.M. Pan, R.T. Yuan, B.F. Shao, Y. Wang, X. Guo, S.B. Zhou, Polarization of tumor-associated macrophages by nanoparticle-loaded *Escherichia coli* combined with immunogenic cell death for cancer immunotherapy, *Nano Lett.* 21 (2021) 4231–4240.
- [53] Z. Jing, S.Q. Wang, K.Y. Xu, Q. Tang, W.J. Li, W. Zheng, H.B. Shi, K.L. Su, Y.T. Liu, Z.Y. Hong, A potent micron neoantigen tumor vaccine GP-neoantigen induces robust antitumor activity in multiple tumor models, *Adv. Sci.* 9 (2022), 2201496.
- [54] R.M. Soo, J. Hemp, D.H. Parks, W.W. Fischer, P. Hugenholz, On the origins of oxygenic photosynthesis and aerobic respiration in Cyanobacteria, *Science* 355 (2017) 1436–1440.
- [55] E.M. Zhao, H.F. Liu, Y.R. Jia, T.S. Xiao, J.X. Li, G.Q. Zhou, J. Wang, X.H. Zhou, X.J. Liang, J.C. Zhang, Z.H. Li, Engineering a photosynthetic bacteria-incorporated hydrogel for infected wound healing, *Acta Biomater.* 140 (2022) 302–313.
- [56] C. Chen, T. Tang, Q.W. Shi, Z.D. Zhou, J.H. Fan, The potential and challenge of microalgae as promising future food sources, *Trends Food Sci. Technol.* 126 (2022) 99–112.
- [57] J.A. Liber, A.E. Bryson, G. Bonito, Z.Y. Du, Harvesting microalgae for food and energy products, *Small Methods* (2020), 2000349.
- [58] Y. Wang, Y.N. Xue, T. Zhang, Q.Q. Fang, M.Y. Jin, X.F. Wang, Z.C. Wang, Y.Y. Hu, W.Y. Zhao, D. Lou, W.Q. Tan, Photosynthetic biomaterials: applications of photosynthesis in algae as oxygenator in biomedical therapies, *Bio-Des. Manuf.* 4 (2021) 596–611.
- [59] A. Shahid, M. Khurshid, B. Aslam, S. Muzammi, H.M. Mehwish, M.S.R. Rajoka, H.F. Hayat, M.H. Sarfraz, M.H. Razaq, M.A. Nisar, M. Waseem, Cyanobacteria derived compounds: emerging drugs for cancer management, *J. Basic Microbiol.* (2021) 1–18.
- [60] M.R.O.B. Silva, G.M. Silva, A.L.F. Silva, L.R.A. Lima, R.P. Bezerra, D.A.V. Marques, Bioactive compounds of *arthrosira* spp. (*Spirulina*) with potential anticancer activities: a systematic review, *ACS Chem. Biol.* 16 (2021) 2057–2067.
- [61] J.E. Cohen, A.B. Goldstone, M.J. Paulsen, Y. Shudo, A.N. Steele, B.B. Edwards, J.B. Patel, J.W. MacArthur, M.S. Hopkins, C.E. Burnett, K.J. Jaatinen, A.D. Thakore, J.M. Farry, V.N. Truong, A.T. Bourdillon, L.M. Stapleton, A. Eskandari, A.S. Fairman, W. Hiesinger, T.V. Espivosa, W.L. Patrick, K. Ji, J.A. Shizuru, Y.J. Woo, An innovative biologic system for photon-powered myocardium in the ischemic heart, *Sci. Adv.* 3 (2017), e1603078.
- [62] D.N. Zhong, D.X. Zhang, W. Chen, J. He, C.J. Ren, X.C. Zhang, N. Kong, W. Tao, M. Zhou, Orally deliverable strategy based on microalgal biomass for intestinal disease treatment, *Sci. Adv.* 7 (2021), eabi9265.
- [63] M.L. Obaid, J.P. Camacho, M. Brenet, R.C. Orovicio, F. Carvajal, X. Martorell, C. Werner, V. Simón, J. Varas, W. Calderón, C.D. Guzmán, M.R. Bono, S.S. Martín, A.E. Zájizur, J.T. Egaña, A first in human trial implanting microalgae shows safety

- of photosynthetic therapy for the effective treatment of full thickness skin wounds, *Front. Med.* 8 (2021), 772324.
- [64] M.F. Huo, L.Y. Wang, L.L. Zhang, C.Y. Wei, Y. Chen, J.L. Shi, Photosynthetic tumor oxygenation by photosensitizer-containing Cyanobacteria for enhanced photodynamic therapy, *Angew. Chem. Int. Ed.* 59 (2020) 1906–1913.
- [65] L.L. Liu, H.M. He, Z.Y. Luo, H.M. Zhou, R.J. Liang, H. Pan, Y.F. Ma, L.T. Cai, In situ photocatalyzed oxygen generation with photosynthetic bacteria to enable robust immunogenic photodynamic therapy in triple-negative breast cancer, *Adv. Funct. Mater.* 30 (2020), 1910176.
- [66] J.J. Yu, M. Liberton, P.F. Cliften, R.D. Head, J.M. Jacobs, R.D. Smith, D.W. Koppelaar, J.J. Brand, H.B. Pakrasi, *Synechococcus elongatus* UTEX 2973, a fast growing cyanobacterial chassis for biosynthesis using light and CO₂, *Sci. Rep.* 5 (2015) 8132.
- [67] T. Sun, Y.Y. Zhang, C.N. Zhang, H.J. Wang, H.Z. Pan, J. Liu, Z.X. Li, L. Chen, J. Chang, W.W. Zhang, Cyanobacteria-based bio-oxygen pump promoting hypoxia-resistant photodynamic therapy, *Front. Bioeng. Biotechnol.* 8 (2020) 237.
- [68] C. He, C.H. Dong, H. Hu, L.D. Yu, Y. Chen, Y.Q. Hao, Photosynthetic oxygen-self-generated 3D-printing microbial scaffold enhances osteosarcoma elimination and prompts bone regeneration, *Nano Today* 41 (2021), 101297.
- [69] C.C. Wang, P.R. Zhao, D.W. Jiang, G.L. Yang, Y.D. Xue, Z.G. Tang, M. Zhang, H. Wang, X.W. Jiang, Y.L. Wu, Y.Y. Liu, W.A. Zhang, W.B. Bu, In-situ catalytic reaction for solving the aggregation of hydrophobic photosensitizers in tumor, *ACS Appl. Mater. Interfaces* 12 (2020) 5624–5632.
- [70] Y. Chen, L.Z. Wang, J.L. Shi, Two-dimensional non-carbonaceous materials-enabled efficient photothermal cancer therapy, *Nano Today* 11 (2016) 292–308.
- [71] C.C. Xue, L. Sutrisno, M.H. Li, W. Zhu, Y. Fei, C.H. Liu, X. Wang, K.Y. Cai, Y. Hu, Z. Luo, Implantable multifunctional black phosphorus nanoformulation-deposited biodegradable scaffold for combinational photothermal/chemotherapy and wound healing, *Biomaterials* 269 (2021), 120623.
- [72] B.S. Li, Lai Cui, G.G. Zeng, D.L. Huang, L. Qin, M.M. Zhang, M. Cheng, X.G. Liu, H. Yi, C.Y. Zhou, F.L. Huang, S.Y. Liu, Y.K. Fu, Black phosphorus, a rising star 2D nanomaterial in the post-graphene era: synthesis, properties, modifications, and photocatalysis applications, *Small* 15 (2019), 1804565.
- [73] T. Chen, W.W. Zeng, C.J. Tie, M. Yu, H.S. Hao, Y. Deng, Q.Q. Li, H.R. Zheng, M.Y. Wu, L. Mei, Engineered gold/black phosphorus nanoplateforms with remodeling tumor microenvironment for sonoactivated catalytic tumor theranostics, *Bioact. Mater.* 10 (2022) 515–525.
- [74] F.G. Qi, P.H. Ji, Z.X. Chen, L.P. Wang, H.L. Yao, M.F. Huo, J.L. Shi, Photosynthetic Cyanobacteria-hybridized black phosphorus nanosheets for enhanced tumor photodynamic therapy, *Small* 17 (2021), 2102113.
- [75] M.R. Hamblin, Upconversion in photodynamic therapy: plumbing the depths, *Dalton Trans.* 47 (2018) 8571–8580.
- [76] J.H. Hu, J.L. Shi, Y.Q. Gao, W. Yang, P. Liu, Q.H. Liu, F. He, C.X. Wang, T. Li, R. Xie, J.X. Zhu, P.P. Yang, 808 nm near-infrared light-excited UCNPs@mSiO₂-Ce6-GPC3 nanocomposites for photodynamic therapy in liver cancer, *Int. J. Nanomed.* 14 (2019) 10009–10021.
- [77] J. Xu, L.G. Xu, C.Y. Wang, R. Yang, Q. Zhuang, X. Han, Z.L. Dong, W.W. Zhu, R. Peng, Z. Liu, Near-infrared-triggered photodynamic therapy with multitasking upconversion nanoparticles in combination with checkpoint blockade for immunotherapy of colorectal cancer, *ACS Nano* 11 (2017) 4463–4474.
- [78] Y. Li, J.L. Tang, D.X. Pan, L.D. Sun, C.Y. Chen, Y. Liu, Y.F. Wang, S. Shi, C.H. Yan, A versatile imaging and therapeutic platform based on dual-band luminescent lanthanide nanoparticles toward tumor metastasis inhibition, *ACS Nano* 10 (2016) 2766–2773.
- [79] X.Y. Zhang, Y.Y. Zhang, C.N. Zhang, C. Yang, R. Tian, T. Sun, W.W. Zhang, J. Chang, H.J. Wang, An injectable hydrogel co-loading with cyanobacteria and upconversion nanoparticles for enhanced photodynamic tumor therapy, *Colloids Surf., B* 201 (2021), 111640.
- [80] M.F. Huo, P.L. Liu, L.L. Zhang, C.Y. Wei, L.Y. Wang, Y. Chen, J.L. Shi, Upconversion nanoparticles hybridized Cyanobacterial cells for near-infrared mediated photosynthesis and enhanced photodynamic therapy, *Adv. Funct. Mater.* 31 (2021), 2010196.
- [81] M. Lismont, L. Dreesen, S. Wuttke, Metal-organic framework nanoparticles in photodynamic therapy: current status and perspectives, *Adv. Funct. Mater.* 27 (2017), 1606314.
- [82] M.Q. Chang, W. Feng, L. Ding, H.G. Zhang, C.H. Dong, Y. Chen, J.L. Shi, Persistent luminescence phosphor as in-vivo light source for tumoral cyanobacterial photosynthetic oxygenation and photodynamic therapy, *Bioact. Mater.* 10 (2022) 131–144.
- [83] S.T. Lu, W. Feng, C.H. Dong, X.R. Song, X. Gao, J.H. Guo, Y. Chen, Z.Q. Hu, Photosynthetic oxygenation-augmented sonodynamic nanotherapy of hypoxic tumors, *Adv. Healthc. Mater.* 11 (2022), 2102135.
- [84] C. Gilreath, M. Boerma, Z.Q. Qin, M.K. Hudson, S.Z. Wang, The hypoxic microenvironment of breast cancer cells promotes resistance in radiation therapy, *Front. Oncol.* 10 (2021), 629422.
- [85] L. Chan, P. Gao, W.H. Zhou, C.M. Mei, Y.Y. Huang, X.F. Yu, P. K. Chu, T.F. Chen, Sequentially triggered delivery system of black phosphorus quantum dots with surface charge switching ability for precise tumor radiosensitization, *ACS Nano* 12 (2018) 12401–12415.
- [86] X.H. Dong, R. Cheng, S. Zhu, H.M. Liu, R.Y. Zhou, C.Y. Zhang, K. Chen, L.Q. Mei, C.Y. Wang, C.J. Su, X.F. Liu, Z.J. Gu, Y.L. Zhao, A heterojunction structured WO_{2.9}-WSe₂ nanoradiosensitizer increases local tumor ablation and checkpoint blockade immunotherapy upon low radiation dose, *ACS Nano* 14 (2020) 400–416.
- [87] F. Gong, J.W. Chen, X. Han, J.Y. Zhao, M.Y. Wang, L.Z. Feng, Y.G. Li, Z. Liu, L. Cheng, Core-shell TaOx@MnO₂ nanoparticles as a nano-radiosensitizer for effective cancer radiotherapy, *J. Mater. Chem. B* 6 (2018) 2250–2257.
- [88] R. Chai, L.D. Yu, C.H. Dong, Y.P.C. Yin, S. Wang, Y. Chen, Q. Zhang, Oxygen-evolving photosynthetic cyanobacteria for 2D bismuthene radiosensitizer-enhanced cancer radiotherapy, *Bioact. Mater.* 17 (2022) 276–288.
- [89] J. Jiang, W.L. Wang, H.Z. Zheng, X. Chen, X. Liu, Q.Q. Xie, X.M. Cai, Z.L. Zhang, R.B. Li, Nano-enabled photosynthesis in tumors to activate lipid peroxidation for overcoming cancer resistances, *Biomaterials* 285 (2022), 121561.
- [90] M.J. Bae, H.S. Shin, O.H. Chai, J.G. Hanc, D.H. Shon, Inhibitory effect of unicellular green algae (*Chlorella vulgaris*) water extract on allergic immune response, *J. Sci. Food Agric.* 93 (2013) 3133–3136.
- [91] T. Bito, E. Okumura, M. Fujishima, F. Watanabe, Potential of *Chlorella* as a dietary supplement to promote human health, *Nutrients* 12 (2020) 2524.
- [92] P. Kubatka, A. Kapinova, P. Kruzliak, M. Kello, D. Vybohov, K. Kajo, M. Novak, M. Chripkova, M. Adamkov, M. Pec, J. Mojzis, B. Bojkova, M. Kassayova, N. Stollarov, D. Dobrota, Antineoplastic effects of *Chlorella pyrenoidosa* in the breast cancer model, *Nutrition* 31 (2015) 560–569.
- [93] M. Gouda, M.A. Tadda, Y.L. Zhao, F. Farmanullah, B.Q. Chu, X.L. Li, Y. He, Microalgae bioactive carbohydrates as a novel sustainable and eco-friendly source of prebiotics: emerging health functionality and recent technologies for extraction and detection, *Front. Nutr.* 9 (2022), 806692.
- [94] X.C. Wang, C.Y. Yang, Y.R. Yu, Y.J. Zhao, In situ 3D bioprinting living photosynthetic scaffolds for autotrophic wound healing, *Research* (2022), 9794745.
- [95] H.H. Chen, Y.F. Guo, Z.W. Zhang, W.X. Mao, C.Y. Shen, W. Xiong, Y.F. Yao, X.Z. Zhao, Y.Q. Hu, Z.G. Zou, J.H. Wu, Symbiotic algae-bacteria dressing for producing hydrogen to accelerate diabetic wound healing, *Nano Lett.* 22 (2022) 229–237.
- [96] C. Lee, K. Lim, S.S. Kim, L.X. Thien, E.S. Leeb, K.T. Ohc, H.G. Choid, Y.S. Yoon, *Chlorella*-gold nanorods hydrogels generating photosynthesis-derived oxygen and mild heat for the treatment of hypoxic breast cancer, *J. Contr. Release* 294 (2019) 77–90.
- [97] J.R. Lakkakula, P. Gujarathi, P. Pansare, S. Tripathi, A comprehensive review on alginate-based delivery systems for the delivery of chemotherapeutic agent: Doxorubicin, *Carbohydr. Polym.* 259 (2021), 117696.
- [98] X. Yan, F. Li, K.D. Hu, J.Z. Xue, X.F. Pan, T. He, L. Dong, X.Y. Wang, Y.D. Wu, Y.H. Song, W.P. Xu, Y. Lu, Nacre-mimic reinforced Ag@reduced graphene oxide-sodium alginate composite film for wound healing, *Sci. Rep.* 7 (2017), 13851.
- [99] T.J. Zhou, L. Xing, Y.T. Fan, P.F. Cui, H.L. Jiang, Light triggered oxygen-affording engines for repeated hypoxia-resistant photodynamic therapy, *J. Contr. Release* 307 (2019) 44–54.
- [100] Y. Qiao, F. Yang, T.T. Xie, Z. Du, D.N. Zhong, Y.C. Qi, Y.Y. Li, W.L. Li, Z.M. Lu, J.H. Rao, Y. Sun, M. Zhou, Engineered algae: a novel oxygen-generating system for effective treatment of hypoxic cancer, *Sci. Adv.* 6 (2020), eaba5996.
- [101] W.L. Li, D.N. Zhong, S.Y. Hua, Z. Du, M. Zhou, Biomimetic biohybrid-algae for tumor hypoxia modulation and cascade radio-photodynamic therapy, *ACS Appl. Mater. Interfaces* 12 (40) (2020) 44541–44553.
- [102] D.N. Zhong, W.L. Li, S.Y. Hua, Y.C. Qi, T.T. Xie, Y. Qiao, M. Zhou, Calcium phosphate engineered photosynthetic microalgae to combat hypoxic-tumor by in-situ modulating hypoxia and cascade radio-phototherapy, *Theranostics* 11 (2021) 3580–3594.
- [103] X.Y. Ji, J. Wang, Y. Kang, L. Mei, Z.G. Su, S.M. Wang, G.H. Ma, J.J. Shi, S.P. Zhang, Enhanced solar energy harvest and electron transfer through intra- and inter-molecular dual-channel in chlorosome-mimicking supramolecular self-assemblies, *ACS Catal.* 8 (2018) 10732–10745.
- [104] X.Y. Ji, Y. Kang, T.J. Fan, Q.Q. Xiong, S.P. Zhang, W. Tao, H. Zhang, An antimonene/Cp^{*}Rh(phen)Cl/black phosphorus hybrid nanosheet-based Z-scheme artificial photosynthesis for enhanced photo/bio-catalytic CO₂ reduction, *J. Mater. Chem.* 8 (2020) 323–333.
- [105] M.T. Ou, C.C. Lin, Y. Wan, Y.T. Lu, W.Y. Wang, Z.M. Li, W.W. Zeng, X.W. Zeng, X.Y. Ji, L. Mei, Heterojunction engineered bioactive chlorella for cascade promoted cancer therapy, *J. Contr. Release* 345 (2022) 755–769.
- [106] W.F. Chen, Y. Wang, M. Qin, X.D. Zhang, Z.R. Zhang, X. Sun, Z. Gu, Bacteria-driven hypoxia targeting for combined biotherapy and photothermal therapy, *ACS Nano* 12 (2018) 5995–6005.
- [107] J.X. Fan, M.T. Niu, Y.T. Qin, Y.X. Sun, X.Z. Zhang, Progress of engineered bacteria for tumor therapy, *Adv. Drug Deliv. Rev.* 185 (2022), 114296.
- [108] S. Naganandhini, Z. John Kennedy, M. Uyttendaele, D. Balachandrar, Persistence of pathogenic and non-pathogenic *Escherichia coli* strains in various tropical agricultural soils of India, *PLoS One* 10 (2015), e0130038.
- [109] F.I. Lugo, J.V. Estrada, C.A. Alvis, J.O. López, M.C.M. Horcasitas, Developing strategies to increase plasmid DNA production in *Escherichia coli* DH5 α using batch culture, *J. Biotechnol.* 233 (2016) 66–73.
- [110] X.Y. Deng, W.B. Yang, Z.W. Shao, Y.L. Zhao, Genetically modified bacteria for targeted phototherapy of tumor, *Biomaterials* 272 (2021), 120809.
- [111] C.Y. Huang, F.B. Wang, L. Liu, W. Jiang, W. Liu, W. Ma, H. Zhao, Hypoxic tumor radiosensitization using engineered probiotics, *Adv. Healthc. Mater.* 10 (2021), 2002207.
- [112] S.J. Ding, Z.M. Liu, C.Y. Huang, N. Zeng, W. Jiang, Q. Li, Novel engineered bacterium/black phosphorus quantum dot hybrid system for hypoxic tumor targeting and efficient photodynamic therapy, *ACS Appl. Mater. Interfaces* 13 (2021) 10564–10573.
- [113] S.Q. Wang, L. Shi, S.J. Yu, H.W. Pang, M.Q. Qiu, G. Song, D. Fu, B.W. Hu, X.X. Wang, Effect of *Shewanella oneidensis* MR-1 on U(VI) sequestration by montmorillonite, *J. Environ. Radioact.* 242 (2022), 106798.
- [114] Q.W. Chen, J.W. Wang, X.N. Wang, J.X. Fan, X.H. Liu, B. Li, Z.Y. Han, S.X. Cheng, X.Z. Zhang, Intervening tumor progression by coupling bacteria respiration with tumor metabolism, *Angew. Chem., Int. Ed.* 59 (2020) 21562–21570.

- [115] W.T. Li, X.L. Zhou, S.K. Liu, J.L. Zhou, H. Ding, S.L. Gai, R.M. Li, L. Zhong, H.J. Jiang, P.P. Yang, Biodegradable nanocatalyst with self-supplying Fenton-like ions and H₂O₂ for catalytic cascade-amplified tumor therapy, *ACS Appl. Mater. Interfaces* 13 (2021), 50760-50773.
- [116] J.X. Fan, M.Y. Peng, H. Wang, H.R. Zheng, Z.L. Liu, C.X. Li, X.N. Wang, X.H. Liu, S.X. Cheng, X.Z. Zhang, Engineered bacterial bioreactor for tumor therapy via Fenton-like reaction with localized H₂O₂ generation, *Adv. Mater.* 31 (2019), 1808278.
- [117] D.N. Zhong, W.L. Li, Y.C. Qi, J. He, M. Zhou, Photosynthetic biohybrid nanoswimmers system to alleviate tumor hypoxia for FL/PA/MR imaging-guided enhanced radio-photodynamic synergetic therapy, *Adv. Funct. Mater.* 30 (2020), 1910395.
- [118] J.B. Pan, Y.Q. Wang, H.Y. Pan, C. Zhang, X.G. Zhang, Y.Y. Fu, X.J. Zhang, C.S. Yu, S.K. Sun, X.P. Yan, Mimicking drug-substrate interaction: a smart bioinspired technology for the fabrication of theranostic nanoprobe, *Adv. Funct. Mater.* 27 (2017), 11603440.
- [119] O. Felfoul, M. Mohammadi, S. Taherkhani, D. Lanaue, Y.Z. Xu, D. Loghin, S. Essa, S. Jancik, D. Houle, M. Lafleur, L. Gaboury, M. Tabrizian, N. Kaou, M. Atkin, T. Vuong, G. Batist, N. Beauchemin, D. Radzioch, S. Martel, Magneto-aerotactic bacteria deliver drug-containing nanoliposomes to tumor hypoxic regions, *Nat. Nanotechnol.* 11 (2016) 941-947.
- [120] Y.W. Bao, X.W. Hua, J. Zeng, F.G. Wu, Bacterial template synthesis of multifunctional nanospindles for glutathione detection and enhanced cancer-specific chemo-chemodynamic therapy, *Research*, 2020, 9301215.
- [121] W. Ma, Q.L. Chen, W.G. Xu, M. Yu, Y.Y. Yang, B.H. Zou, Y.S. Zhang, J.X. Ding, Z.Q. Yu, Self-targeting visualizable hyaluronate nanogel for synchronized intracellular release of doxorubicin and cisplatin in combating multidrug-resistant breast cancer, *Nano Res.* 14 (3) (2021) 846-857.
- [122] S.L. Qi, H.Y. Zhang, X.Y. Zhang, X.Y. Yu, Y.J. Wang, Q.F. Meng, K. Yang, B. Bai, R. Tian, S.J. Zhu, L. Rao, F.H. Huang, G.C. Yu, Supramolecular engineering of cell membrane vesicles for cancer immunotherapy, *Sci. Bull.* 67 (2022) 1898-1909.