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REVIEW

Photosynthetic biomaterials: applications of photosynthesis in algae as oxygenerator in biomedical therapies

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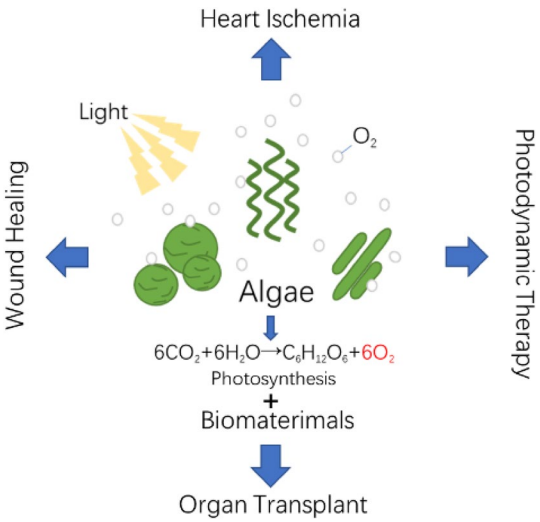
Abstract

For most organisms, molecular oxygen is indispensable for normal physiological metabolism; in humans, prolonged hypoxia in tissues can induce many diseases, exemplified by cardiovascular disease, chronic wounds, and tissue necrosis. Therefore, the oxygen in our environment is vital for life. As a main source of oxygen in the natural world that transforms light energy into chemical energy and oxygen, photosynthesis has been widely studied in scientific research and used in production of food, fuel, and medicine. In recent years, photosynthesis has become more closely involved in biomedicine and has been widely used in photodynamic therapy, tissue regeneration, transplantation, and in treatment of specific diseases. This review summarizes innovative applications of photosynthesis in biomedical research and highlights the theory and implications of clinical treatment for specific diseases.

Graphic abstract



Keywords Biomaterials · Photosynthesis · Hypoxia · Myocardial infarction · Photodynamic therapy · Tissue engineering

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Introduction

Due to the emergence of oxygenic photosynthetic bacteria (cyanobacteria) on the primitive Earth, the composition of the atmosphere started to change, and more and more oxygen (O_2) accumulated [1]; today, O_2 supports almost all lives on our planet except for some anaerobic organisms [2], and the photosynthesis of some photosynthetic bacteria also played a crucial role in the process of Earth evolution [3, 4].

Now the principle of oxygenic photosynthesis has been clarified clearly. After a process of photoinduced charge separation, complex arrays of chlorophyll and accessory carotenoid pigments as well as matrix enzymes are engaged in the transport of exciton energy [5, 6]; the chromophores in the reaction centers use this energy to transform the carbon dioxide (CO_2) and water into glucose and O_2 [7, 8]. Photosynthesis thus provides a continuous way to harvest and convert light energy to chemical energy.

As we know, oxygen is a key molecule for cell metabolism and some physiological processes, such as wound healing [9–11] and tissue regeneration [12–14]. In myocardial infarction (MI), the blockage in the coronary artery caused by the amassing of plaque reduces blood flow to the heart and the consequent formation of a hypoxic environment in cardiac tissue injures heart muscles irreversibly [15, 16]. Since myocardial cells are non-regenerative cells, the heart muscle cannot repair itself after myocardial infarction; thus, many scholars have focused on the treatment of myocardial infarction with stem cells [17–19]. Whether transplanting stem cells to heart tissue or using stem-cell patches to treat MI, oxygen is essential to improve the efficiency of vascularization among the affected tissues [20–22]. It is worth noting that hypoxia may also occur in the process of tissue regeneration; in particular, poor angiogenesis can result in cell death in heart tissue [23, 24]. For this reason, clinical transplants of engineered tissue remain a difficult challenge [25, 26]. The proliferation and migration of cells in wounds are strongly dependent on oxygen diffusion and cytokine secretion by special cells [27–29]. However, in diabetics with an altered wound microenvironment, exposure to high glucose levels disturbs hypoxia-inducible factor-1α (HIF-1α) stability via the effects of glucose on rapid hydroxylation and degradation of HIF-1 α after translation [30–32]. This change results in cells in wounds of diabetic patients failing to increase levels of vascular endothelial growth factor (VEGF) in response to soft tissue ischemia, which leads to damaged angiogenesis and delayed wound healing [33–36]. In practice, hyperbaric oxygen (HBO) and topical gaseous oxygen (TGO) therapies have been applied in some cases of chronic wound treatment, but the therapies have had only limited success because of only limited penetration of oxygen to the tissues [37–41]. A few cancer therapies, for example, radiotherapy (RT) and photodynamic therapy (PDT), also require oxygen to enhance efficacy [42–44]. PDT employs a light-activated photosensitizer to deliver energy to oxygen and then generates highly reactive singlet oxygen, which destroys tumor tissue by inducing cellular necrosis, apoptosis, acute inflammation, and attraction of leukocytes to the targeted tumors [45–47]. There are some oxygen-replenishing strategies for such therapies, including catalyzing endogenous H_2O_2 with organic or inorganic catalysts [48–50], water splitting [51–53], oxygen transport [54, 55], and respiratory inhibitors [56]. However, oxygen supplementation is usually insufficient for effective tumor therapy [57, 58].

Recent advances in the development of algal strains designed for biofuel production have facilitated the application of photosynthesis for sustainable development in energy, agriculture, food production, and biomaterials for drug delivery, biosensors, and heavy-metal adsorbents [59–61]. In addition, there is intense research effort on applications of photosynthesis in biomedicine; algae are used as the oxygen source in these studies, which benefit from the fact that algae are unicellular organisms that produce oxygen persistently [6, 62, 63]. A systematic review of the photosynthesis applications thus far developed for biomedical therapy, including their effects on disease recovery, is badly needed. This review describes the applications of photosynthesis for regeneration medicine and photodynamic cancer therapy developed thus far, and it highlights the problems of combining biomedicine with photosynthesis. The review concludes with a discussion of the future prospects for this innovative therapeutic approach.

A living oxygenerator for regeneration of myocardial cells

At present, myocardial infarction is the most common coronary artery disease, and one that results in death and disability, afflicting millions of people across the world [15, 64]. The past several decades of research and innovation have brought a huge improvement in the clinical methods used to treat formerly devastating cardiac illnesses. Building on these achievements, many therapies promoting cardiac tissue regeneration and angiogenesis have generated exciting results in preclinical models and early clinical trials [65–67].

Thicker artificial cardiac tissues

Tissue engineering has been applied to clinical treatment of several tissue necrotic diseases. Ishida O and his colleagues found that adipose-derived stem cell sheet transplants could cure heart failure in a porcine model [68–70]. However, before developing thicker cell sheets

or cell-dense 3D tissues, we first need to address the problem of the ischemic environment, which makes it difficult to generate thicker tissues [71]. The thickness limitation of 3D tissues without vascular networks is approximately 40–80 μm, and hypoxia and undernutrition of thicker multilayered cell sheet-tissues can cause tissue damage [72]. Therefore, Haraguchi et al. developed a method to improve O_2 delivery through creating thicker cardiac tissues with the alga *Chlorococcum littorale*. Five or ten rat cardiac cell sheets were cultivated with *C. littorale* in a chamber with M199-based medium under light, as shown in Fig. 1a. The photosynthetic activities of the algae increased the dissolved oxygen concentration in the medium (Fig. 1b) [73]. The authors also observed that, in the presence of the algae, the multilayered tissues showed decreased glucose consumption and lactate production, and that the tissues were in good histological condition (Fig. S1), with lower ammonia and creatine kinase (CK) concentrations in the culture medium [73]. In summary, culture conditions of the thicker tissues were improved by the co-cultivation with algae, resulting in the creation of 160-μm thick cardiac tissues [73]. This innovative artificial tissue is essentially a small ecosystem where the metabolic products (CO_2, ammonia) from mammalian cells can be reused by photosynthetic algae to produce O_2 that can be used by mammalian cells. This system can decrease the cell death rate of engineering tissues and promote the application of this technique to estimate the efficacy and cytotoxicity of candidate drugs in vitro.

Treating myocardial infarction directly

Oxygen resupply can rescue the myocardium from acute ischemia and yield durable improvements in cardiac function during and after induction of ischemia. Cohen et al. recently described the first instance of treatment of cardiac ischemia using photosynthetic microbes as oxygen sources. In this study, the cyanobacterium *Synechococcus elongatus* (*S. elongatus*) was injected into the ischemic region after ligation of the left anterior descending coronary artery in

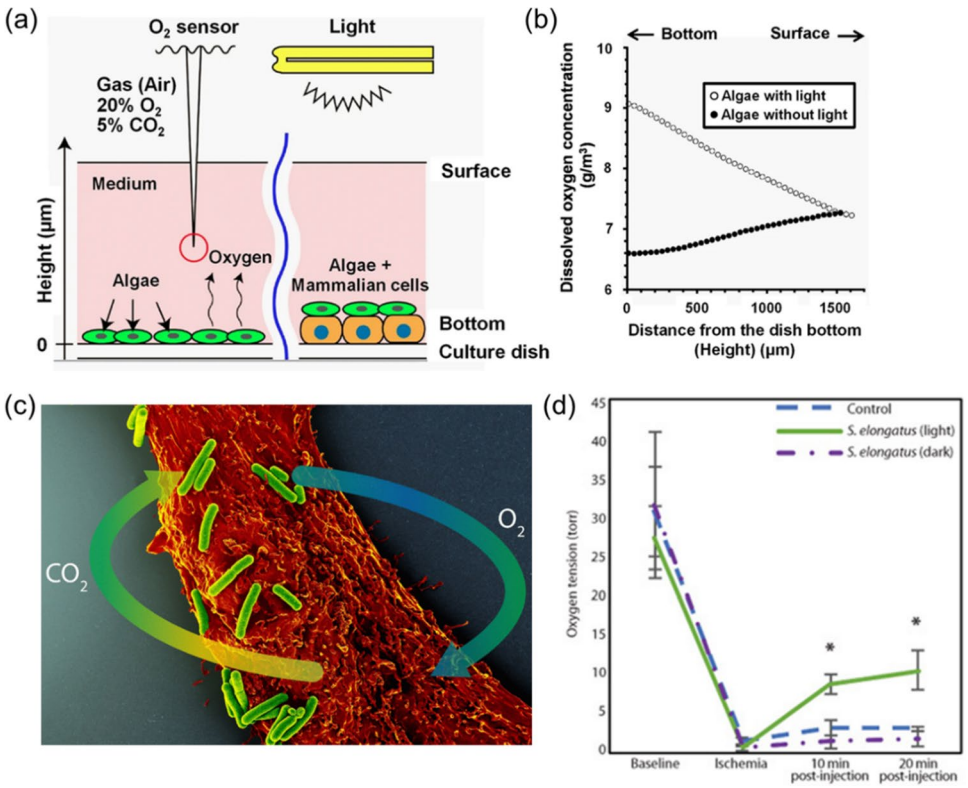

Fig. 1 The oxygen produced by photosynthesis promote MI treatment and myocardial tissue engineering. **a** The schematic illustration of the system for oxygen concentration measurement. **b** Representative oxygen concentration profiles plotted against the height from the bottom of the dish used for culturing the algae in an M199-based culture medium with/without light at 30 °C. **c** Schematic illustration of photosynthetic therapy, which comes out from false-colored scanning electron micrograph of multiple *S. elongatus* cyanobacteria (green) with a single rat cardiomyocyte (red). **d** Phosphorescent probe technology was used to quantify tissue oxygenation at baseline, time of ischemia, and 10 and 20 min after therapy. Oxygen tension was significantly higher in the S. elongatus (light)–treated group compared with controls and *S. elongatus* (dark) groups at 10 (group-time interaction, $P=0.004$) and 20 (group-time interaction, $P=0.003$) min after injection. **a**, **b** reproduced with permission from Ref. [73], and **c**, **d** reproduced with permission from Ref. [74]

rats, as shown in Fig. 1c [74]. Under light, rats with cyanobacteria exhibited significantly improved myocardial O_2 levels within 10 min (Fig. 1d), including recovery of cellular metabolic activity and enhanced cardiac function compared to saline or dark controls [74]. Using a rat ischemia–reperfusion model, Cohen and his colleagues also demonstrated that photosynthetic treatment, which was only restricted to the time of open-heart surgery, yields durable long-term benefits in cardiac function for four weeks after ischemic injury [74]. Although there was concern about the possibility that the injected cyanobacteria could induce a pathogenic reaction, serial flow cytometry of serum, immunohistochemistry, and histological analyses of cardiac tissue demonstrated that cyanobacterial therapy was nontoxic and nonpathogenic; in addition, most of the injected cyanobacteria were cleared by 24 h after injection [74]. Therefore, this method shows clinical potential for development of MI therapy that utilizes optic fibers and minimally invasive surgery instead of thoracotomy.

Photosynthesis-boosted photodynamic therapy

PDT has been receiving increasing attention as an important approach for cancer treatment [45, 75]. Many compounds can be used as photosensitizers in PDT with low systemic toxicity and excellent biocompatibility [76, 77]. Under laser activation, photosensitizers can transform oxygen into reactive oxygen species (ROS) to kill tumor cells; thus, PDT can be used as a controllable method to eliminate tumors in the body. Some types of photosensitizers extracted from plants, such as chlorophyll and its derivatives, have been at the forefront of current research [78]. Porphyrin derivatives also have been widely employed for cancer treatment and imaging because of their powerful phototherapeutic effects and excellent imaging capabilities [79–81]. In addition to the effective photosensitizers derived from plants utilized in anticancer therapy, some researchers have improved the therapeutic effects of PDT by combining PDT with oxygenic photosynthesis in algae or cyanobacteria and even thylakoid membrane in plant. Because the tumor microenvironment (TME) is often characterized by extreme hypoxia (pO_2 values ≤ 2.5 mmHg), acidic pH, and vascular abnormalities [82–84], the effects of oxygen-dependent PDT are severely limited by the hypoxic conditions and rapid oxygen consumption in cancerous tissues [85, 86].

Photodynamic therapy with algae as a source of oxygen

In order to alter the hypoxic microenvironment in tumors, Zhou et al. used *Chlorella* and calcium alginate to construct an autotrophic light-triggered green affording-oxygen engine

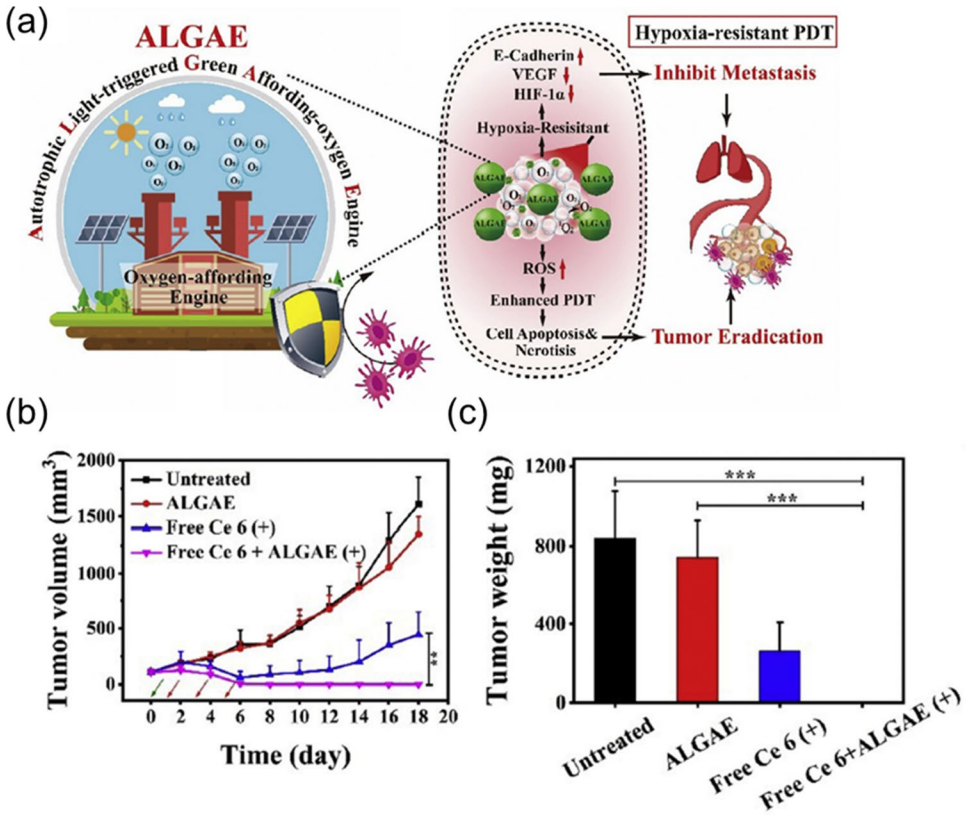

Fig. 2 Schematic diagram and treatment effect of the hypoxia-resistant PDT induced by the ALGAE system. **a** The excellent oxygen generation triggered by ALGAE was found to inhibit tumor metastasis and induce tumor eradication. **b** Tumor growth curves ($n=5$). Black curve: untreated. Red curve: implanted ALGAE. Blue curve: normal PDT treatment. Purple curve: PDT treatment with ALGAE ($^{**}p<0.01$). **c** Tumor weights at the end point of the experiment with different treatments ($n=5$, $^{***}p<0.001$). Reproduced with permission from Ref. [87]

(ALGAE) (see Fig. 2a) to serve as a controllable and inexhaustible oxygen generator with good biocompatibility and degradability. The ALGAE system is activated by the same wavelength as PDT—635 nm irradiation for Chlorin e6 (Ce 6) and can function for at least 10 d after implantation [87]. The researchers found that ALGAE can dramatically mitigate tumor hypoxia, downregulate HIF-1α expression, enhance ROS generation, and elevate PDT cytotoxicity for a long period, and successfully eradicate tumors and prevent tumor metastasis, as shown in Fig. 2b and 2c [87]. Another key feature is that ALGAE can be metabolized completely and safely by the body [87].

Chlorella has also been used as an oxygenator for PDT therapy to treat breast cancer. In one study, *Chlorella* cells were enfolded with gold nanorods (AuNRs) in a rapid-gelling, injectable BSA-PEG–based hydrogel to form a depot system, "Chlorella AuNRs BSA-Gel" (Fig. 3a) [88], in which *Chlorella* generates oxygen through photosynthesis under 660-nm light and AuNRs mildly elevate tissue temperature (41–42 °C) around the tumor in response to a 808-nm near-infrared laser. This study demonstrated that this system expanded tumor vasculature and then facilitated the delivery of doxorubicin (DOX) and oxygen to hypoxic tumors of mice [88]. Chlorella AuNRs BSA-Gel plus DOX dramatically suppressed 4 T1 breast cancer cell-xenografted tumors in BALB/C mice (Fig. 3b and 3c). The study also confirmed that Chlorella AuNRs BSA-Gel has low clinical toxicity and high biodegradability [88].

A recent report has demonstrated that magnetic engineered cyanobacterium—*Spirulina platensis*—can be utilized for tumor-targeted imaging and therapy. In an innovative study, Zhong et al. created a photosynthetic biohybrid nanoswimmers (PBNs) system fabricated with superparamagnetic magnetite (Fe_3O_4 nanoparticles, NPs) that can be attracted to a magnet via a dip-coating process; Fig. 4a shows that *S. platensis* remains active within PBNs [89]. These PBNs can be guided precisely to a tumor after intravenous injection and generate oxygen photosynthetically as an in situ oxygenator, thus improving the effectiveness of radiotherapy (RT) [89]. Furthermore, RT-treated PBNs released the cyanobacterial chlorophyll into the tissues, thus adding photosensitizer capabilities that can produce cytotoxic ROS under laser irradiation to achieve the benefits of PDT (Fig. 4b and 4c) [89]. Because of the autofluorescence and 680 nm absorbance peak of the abundant chlorophyll in *S. platensis*, these cyanobacteria have also

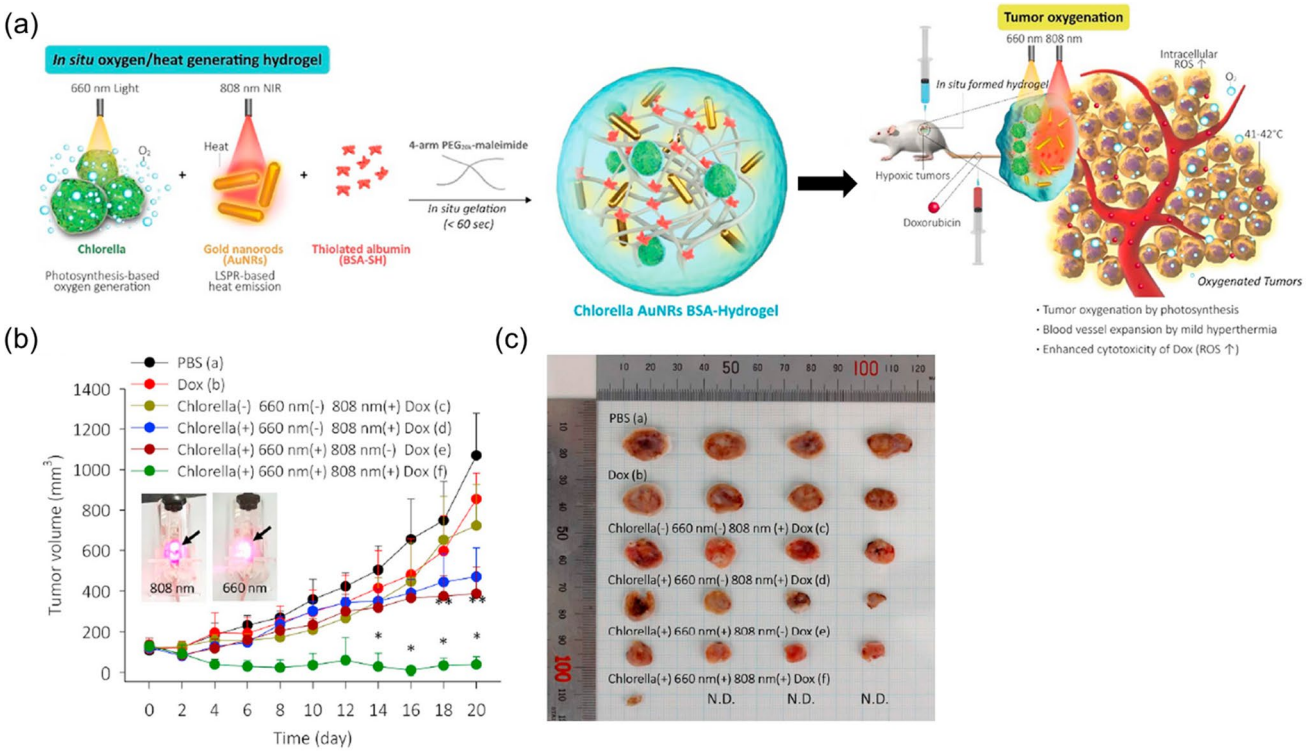

Fig. 3 Schematic diagram and treatment effect of PDT induced by the Chlorella AuNRs BSA-Hydrogel. **a** Scheme showing in situ rapid gelation of Chlorella AuNRs BSA-Gel that generates oxygen and mild heat based on photosynthesis and localized surface plasmon resonance (LSPR) induced by 660-nm and 808-nm laser illuminations and the strategy for overcoming hypoxia based on tumor oxygenation in conjunction with mild hyperthermia. **b** Profile of tumor volumes of 4 T1 tumor-bearing mice in different groups. **c** Photographs of 4 T1 tumors excised from mice of each group. Reproduced with permission from Ref. [88]

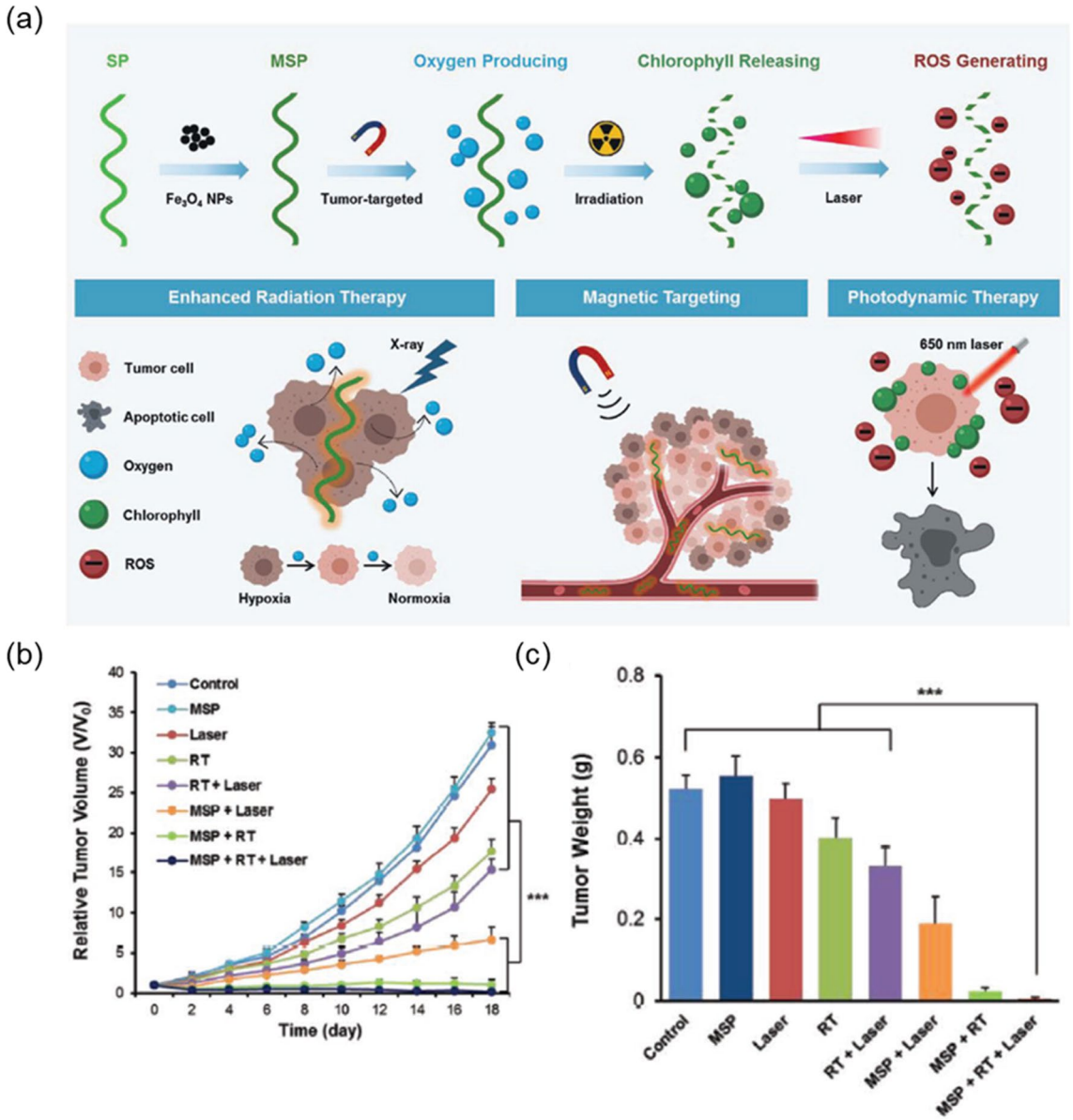

Fig. 4 Schematic diagram and treatment effect of PDT induce by PBNs. **a** The schematic illustration for the mechanism integrating magnetic-targeting properties with synergistic radiotherapy/photodynamic therapy. **b** Tumor growth curves of mice after different treatments. **c** The tumor weights at 18 d in different groups ($n=5$ per group). Reproduced with permission from Ref. [89]

been used by themselves as a safe, targeted drug-delivery system and for fluorescence imaging-guided chemotherapy in treating lung metastases of breast cancer [90]. Therefore, PBNs can also be used as theranostic agents for fluorescence (FL) or photoacoustic (PA) imaging and, because of the Fe_3O_4 NPs in PBNs, as contrast agents for magnetic resonance (MR) imaging [89]. By coating the alga *Chlorella vulgaris* with low-cytotoxicity magnetite NPs, this team created an experimental algal system with a red blood cell membrane cloaking, called red blood cell membrane (RBCM) -Algae (Fig. 5a) which showed high photosynthesis activity under red light (660-nm light-emitting diode light) and produced 12.1 mg/L of dissolved oxygen per hour, and increased O_2 in tumor tissues far more than the native algae without the RBCM modifications [91]. With its low immunogenicity, it showed low cytotoxicity even at high concentrations of 5×10^7 cells/mL. Clonogenic assay and immunofluorescence staining of γ-H2AX demonstrated that the improved oxygen supply released from the RBCM-Algae induced more DNA damage to sensitize cancer cells to radiation [91]. After a series of experiments confirming that RBCM-Algae could sensitize tumor cells to radiation, the researchers showed that the efficacy of RT and PDT in mice inoculated with 4T1 breast

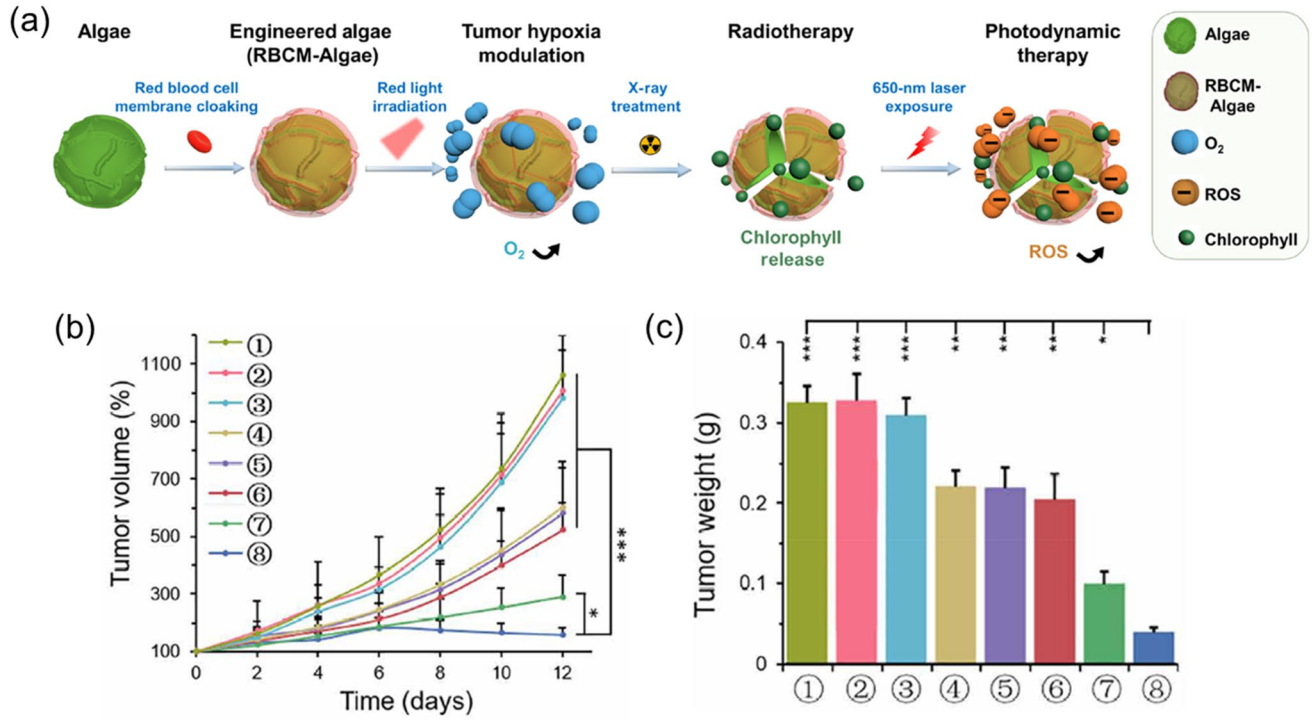

Fig. 5 Schematic diagram and treatment effect of PDT induced by RBCM-Algae biosystem. **a** Illustrative description of engineered processes and treatments. **b** Average tumor growth curves of all the groups. **c** The weight of the tumors collected from the 4 T1 tumor–bearing mice of each group (day 12). 1, control; 2, laser alone; 3, RBCM-Algae alone; 4, x-ray irradiation (RT) alone; 5, RT + laser; 6, RBCM-Algae + laser; 7, RBCM-Algae + RT; 8, RBCM-Algae + RT + laser. Reproduced with permission from Ref. [91]

cancer cells (1×10^6 cells) can be enhanced by RBCM-Algae via intravenous injection (Fig. 5b and 5c). They also clarified the molecular mechanism underlying this process, showing that RBCM-Algae decreased expression of HIF-1α and VEGF, and increased ROS production, thus resulting in reduced proliferation and increased apoptosis rates of tumor cells [91].

The cyanobacterium *Synechococcus 7942* has also been used to enhance the therapeutic efficacy of PDT. With specific chemical binding between terminal amine groups on the outer membrane of *Synechococcus* and carboxy groups of human serum albumin/indocyanine green (HSA/ICG) with amide bonds, the bacteria were adhered to ICG-encapsulated HSA nanoparticles (HSA/ICG NPs) to eventually form the S/HSA/ICG system. HSA/ICG NPs were produced by assembling HSA and ICG through intermolecular disulfide conjugations, as shown in Fig. 6a and 6b [92]. These NPs were then injected into tumor-bearing mice, demonstrating that S/HSA/ICG could remarkably ameliorate tumor hypoxia and enhance PDT effects by continuous photosynthesis, through which it could produce oxygen under 660 nm laser irradiation and evoke systemic antitumor immune responses by inducing immunogenic cell death (ICD) (Fig. 6c) [92]. *Synechococcus* enhanced the accumulation of ICG in tumors, thereby more effectively targeting and penetrating tumor tissue, with enhanced therapeutic effects (Fig. S2) [92].

Photodynamic therapy with thylakoid membranes as a source of oxygen

In addition to use of cyanobacteria and microalgae as oxygen-generators for PDT, investigators have also extracted thylakoid membranes from plants and combined them with synthetic nanoparticles to form an efficient O_2 generation system in vivo [93]. This photosynthetic leaf-inspired abiotic/biotic nano-thylakoid (PLANT) system can normalize the tumor microenvironment and enhance the therapeutic effects of anti-angiogenesis therapy and photodynamic therapy. In this system, the photosynthetic molecules in thylakoids play a major role in producing oxygen under the 660-nm light irradiation, with rates of O_2 production exceeding those of traditional O_2 generation materials such as CaO_2 or MnO_2 [93]. However, compared with the materials containing microalgae, the persistence of O_2 production in PLANT should be reconsidered.

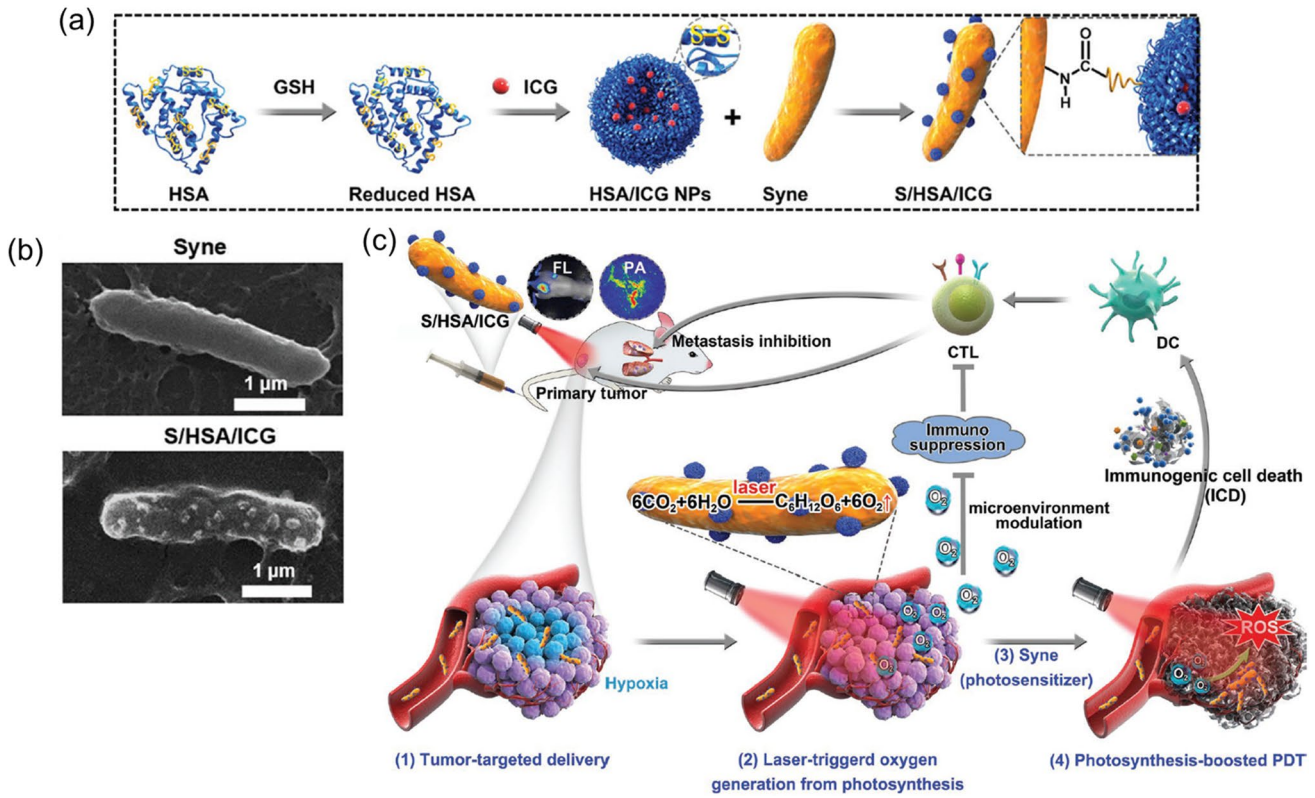

Fig. 6 Fabrication of S/HAS/ICG and mechanism of S/HAS/ICG improving the effect of PDT. **a** Preparation procedure of S/HSA/ICG. Synthesized S/HSA/ICG were attached to Syne through amide bonds. **b** Scanning electron micrograph of Syne (up) and S/HSA/ICG (down). **c** Schematic illustration of nano-photosensitizer (HSA/ICG) conjugated Syne as an in situ photocatalyzed oxygen generation system for metastatic tumor immunogenic PDT. Reproduced with permission from Ref. [92]

Compared with traditional photodynamic therapy

The abovementioned PDTs are attractive methods for efficient cancer treatment, in that the living biomaterial-based therapy inhibits tumor growth with high biosafety in vivo. Research to date has also shown that the use of algae or cyanobacteria for PDT is increasing and is emerging as a proven technique. Compared with traditional PDT, these algae-based methods produce a better tumor microenvironment to enhance the therapeutic effects of PDT. When exposed to light, algae are superior to traditional photosensitizers, as some algae not only produce oxygen, but also generate ROS. Due to their ROS production, algae have the potential for use as an antibacterial drug. Nevertheless, more clinical studies are still needed to confirm long-term toxicity and immunocompatibility of the various species of microalgae before employing in widespread clinical application. Zhong D and colleagues demonstrated that at least one cyanobacterium, *S. platensis*, is also a safe and biodegradable carrier for targeted delivery and imaging-guided therapy for cancer metastasis [90].

Photosynthetic biomaterials for tissue engineering

The past several decades have seen the emergence of an effort called tissue engineering and regenerative medicine where scientists apply tools from various fields, such as polymer materials, 3D bioprinting and stem cells, to construct biological substitutes that can mimic tissues or organs for treatment and research purposes.

Algae-based biomaterials as skin substitution

Several researchers are working on developing manufacturing of advanced biomaterials for tissue engineering. Hopfner U, Schenck TL, and Chávez MN created biomaterials combined with photosynthetic microalgae. All of these researchers aim to address hypoxia in the engineered tissues, which is the key to improving clinical outcomes of artificial tissue. Hopfner U first built a collagen-based scaffold on which the microalgae *Chlamydomonas reinhardtii* could be co-cultured with fibroblasts (see Fig. 7a). By measuring the

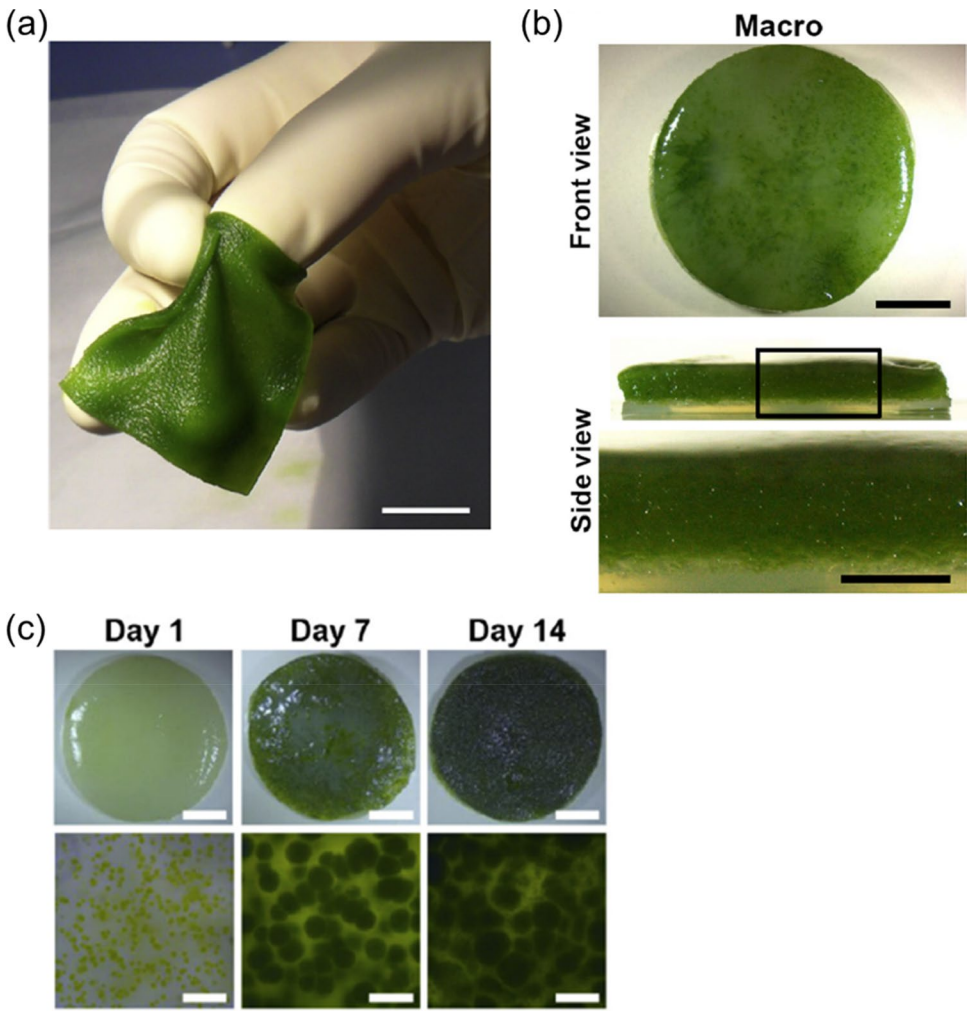

Fig. 7 The scaffolds contain with microalgae. **a** *C. reinhardtii* algae were seeded at a high cell density (2.5×10^7 cells ml^{-1}) in a collagen-based scaffold (5 × 10 cm). **b** Fibrin containing *C. reinhardtii* was incorporated in a collagen scaffold and incubated in TAPS medium. **c** Encapsulated transgenic algae proliferated in the scaffold increasing the green color of the scaffold. **a** Reproduced with permission from Ref. [94], **b** Reproduced with permission from Ref. [95], and **c** Reproduced with permission from Ref. [96]

chlorophyll content of the scaffold at different times, Hopfner U and colleagues showed that *C. reinhardtii* proliferated in these conditions, creating clusters of photosynthetic cells in the inner cavities of the scaffold [94]. After combining with microalgae, the scaffold produced oxygen quickly under light stimulation, reaching a peak of 14% oxygen after a 2-h light exposure [94]. After putting the photosynthetic scaffold with fibroblasts into a hypoxic incubator and exposing the system to light, the cells could be kept alive; levels of the hypoxia marker HIF-1α were significantly decreased as oxygen production increased [94]. Hopfner U's works were the crucial initial step in the application of photosynthesis to tissue engineering biomaterials.

Next, Schenck TL investigated the functioning of the autotrophic tissue in vivo. This time Schenck TL chose a biocompatible hydrogel to build the scaffold as the carrier for *C. reinhardtii*; they also added fibrin to keep the algal cells in place and to decrease any innate immune response to the algae (see Fig. 7b) [95]. After five days of post-implantation in athymic nude mice, the scaffold algae were metabolically active and reproducing. The presence of *C. reinhardtii* did not induce expression of 40 cytokines related to recruitment of immunoactive cells or to immune responses; however, two other inflammation-related compounds, C5a and CCL12, were increased in the algae-mammalian chimeric tissues [95]. In order to further investigate the systemic immune response, the researchers injected microalgae into transgenic zebrafish larvae in which macrophages expressed green fluorescent protein (GFP); these experiments showed no differences compared to the control group, and the number of macrophages infiltrating the area injected with *C. reinhardtii* was dramatically lower than the control group injected with *E. coli* [95]. These data from two different in vivo models demonstrated that microalgae do not cause major inflammation.

Chávez MN improved photosynthetic biomaterials still further by creating a genetically modified strain of *C. reinhardtii* that synthesizes and secretes the human angiogenic growth factor VEGF into the culture medium at a rate of 1.4 ± 0.2 fg/cell (28.0 ± 4.38 ng/mL measured by enzyme linked immunosorbent assay, ELISA) [96]. Figure 7c shows these algae proliferating in the engineered scaffold. Next,

western blots confirmed that VEGF causes autophosphorylation of the VEGF-receptor 2 and activation of the VEGF signaling pathway; in addition, the viability and migration capacity of the endothelial cells increased in vitro [96]. Experiments further verified that the genetically modified algae could promote vascular ingrowth after three days of injection in zebrafish larvae, compared to the control and wild-type algae [96]. Eventually, the photosynthetic scaffolds combined with the VEGF transgenic algae markedly increased the number of CD31 positive endothelial progenitors and α-SMA positive angiogenesis in the wound bed area [96]. Following these promising methods, further strains could be designed to synthesize other therapeutic proteins such as antibiotics, enzymes, or immune-modulatory molecules, so that the wound area would be a more regenerative microenvironment. But research first needs to confirm that the proteins can be expressed in the algae efficiently through reasonable methods of genetic engineering. Further experiments are also needed to assess the therapeutic effects of photosynthetic scaffolds in repairing larger tissue defects or in animal models where healing capacity is compromised.

Algae-gel patch for wound healing

Recently, Chen H et al. invented an innovative patch dressing, "algae-gel patch" (AGP) (Fig. 8a and 8b), for treating chronic diabetic wounds. As mentioned earlier, oxygen is important for wound healing, including repair of chronic wounds in diabetics, via regulation of cell proliferation, migration, and angiogenesis. Therefore, Chen H et al. created an oxygen-producing patch by introducing living photosynthetic microalgae into a hydrogel [97]. The researchers first produced hydrogel beads, 1 mm in diameter, containing the active cyanobacteria *Synechococcus elongatus* (PCC7942), which consume added carbonates (COO_3^{2-} and HCO_3^-) to produce O_2 and CO_2 through respiration and photosynthesis

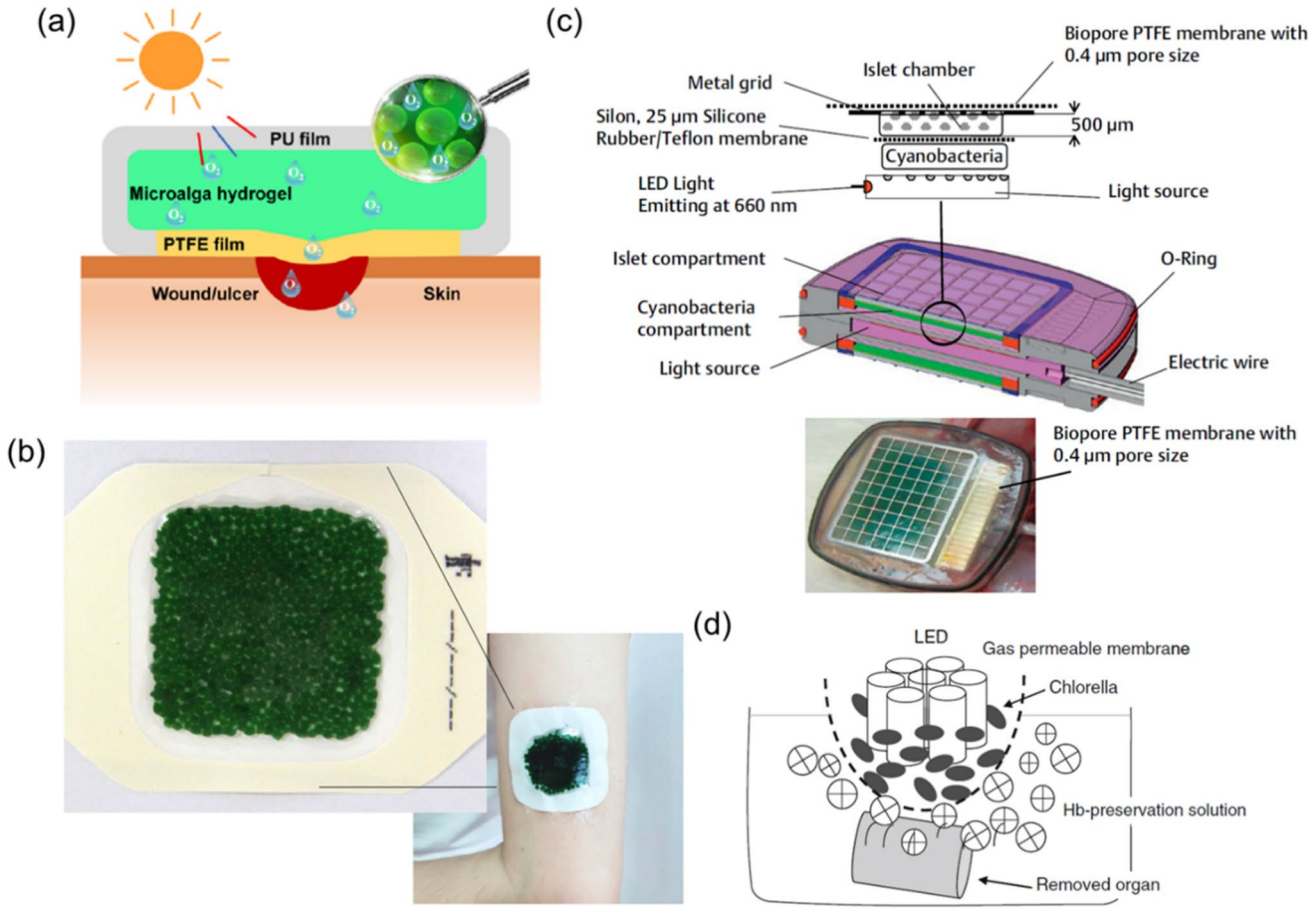

Fig. 8 The autotrophic devices and patch that all can produce oxygen. **a** Schematic view of the device. Inset: cross section of the device and detailed explanation (upper) and actual device withdrawn from an animal after implantation for seven days (device dimensions: 31 mm × 31 mm × 7 mm) (lower). **b** Illustration of the system for photosynthetic respiratory assistance of harvested organs. **c** Schematic illustration of microalga-hydrogel patch (AGP) preparation through polyurethane film and polytetrafluoroethylene membrane to perform the light response dissolved oxygen release for chronic wound. **d** Photographs of the AGP and its sticking on the arm. **a**, **b** reproduced with permission from Ref. [97], **c** reproduced with permission from Ref. [100], and **d** reproduced with permission from Ref. [102]

respectively [97]. The system was packaged using impermeable polyurethane film; hydrophilic polytetrafluoroethylene (PTFE) membrane with a 0.22-μm pore size was used as the AGP lining where it was affixed to the wound, to allow the bidirectional permeability of gases and water along with bacteria filtration performance (Fig. 8a) [97]. The researchers next performed a series of experiments, such as O_2 skin penetration test of the AGP, and wound healing and angiogenesis assays in vitro and in vivo, to compare the effects of this patch on healing of chronic diabetic wounds with that of topical gaseous oxygen (TGO) therapy. The AGP was shown to have more effective O_2 skin penetration than TGO treatment, along with increased fibroblast proliferation and angiogenesis in vivo. Fig. S3 shows the effects of AGP on skin flap regeneration. In summary, this patch dressing provides a promising approach for development of photosynthetic biomaterials in clinical application.

Autotrophic device for tissue transplants

At present, many diseases can be effectively cured through tissue transplants [98, 99]. During the transplant process, the supply of blood and nutrients is disrupted until revascularization occurs and sufficient oxygen is restored; both of these factors limit graft integrity and are indispensable for functioning and long-term survival of tissues. In 2014, a research group successfully developed a chamber system for transplantation of human pancreatic islets without immunosuppression to treat type I diabetes. This system consisted of a sandwich-like chamber, with immobilized photosynthesizing *Synechococcus lividus* mounted on the top of a flat LED that emitted red light at 660 nm with intensity of 8 μE/(m^2·s) (as shown in Fig. 8c) [100]. Islet cells kept alive in an alginate slab (500–1000 islet equivalents/cm^2) were set onto the photosynthetic slab separated by a gas-permeable silicone rubber/Teflon membrane, and the complete module was sealed with a microporous Teflon membrane (pore size: 0.4 μm) to prevent the contents from contact with host immune cells [100]. Upon illumination, the algae produced oxygen by photosynthesis, and the oxygen diffused via the silicone/Teflon membrane into the islet compartment [100]. Oxygen production from implanted encapsulated microorganisms was stable for 1 month [100]. After implantation of the device into diabetic rats, normoglycemia was achieved for 1 week [100]. Upon retrieval of the device, blood glucose levels returned to the diabetic state [100]. These experiments demonstrated that an implanted autotrophic device can provide oxygen to transplanted islets and thus maintain the viability and functionality of the islet. In earlier work, Bloch K tried a similar approach, but using the alga *Chlorella sorokiniana*, which he co-encapsulated and co-cultured with pancreatic islets in alginate, to produce oxygen for implantation of a bioartificial pancreas; this method also successfully induced a higher glucose-stimulated insulin response compared to normoxic perfusion [101].

Yamaoka I and his colleagues recently studied how *Chlorella* photosynthesis can be used to assist organ preservation before transplantation. This research team designed a supplementary respiration device consisting of one gas-permeable pouch and a suspension of *Chlorella*, which can produce oxygen under LED light (as shown in Fig. 8d) [102]. The results from in vivo experiments indicated that rats receiving transplanted pancreases preserved under photosynthetic respiratory assistance can survive over 1 week, longer than the rats with transplanted organs preserved in a cold environment for 30 min, which stayed alive for only 3–5 h. The device also promotes the recovery of pancreas after transplantation [102]. If similar methods are adopted to facilitate transplant of human organs, research will be needed to establish the rates of oxygen production needed from autotrophic devices to satisfy the requirements of whole organs.

Summary and perspective

As we have previously reviewed, many kinds of algae and cyanobacteria have been used to combine photosynthesis with biomedical therapies to test the effectiveness of these oxygenic photosynthetic organisms in MI treatment, photodynamic therapy, tissue regeneration, chronic wound management, and transplantation. All the research mentioned in this review demonstrated that photosynthetic microorganisms in scaffolds or other engineered systems can provide a constant oxygen supply. The longevity and photosynthetic effectiveness of algal and cyanobacterial cells seem superior to that of isolated plant chloroplasts or thylakoids. Therefore, the algae can maintain the effect of producing oxygen for a longer time. However, algae will in the end be digested by the animal or human host. Novel photosynthetic organism encapsulation technologies with better living parameters are needed to increase longevity of these systems in vivo. The potential of photosynthetic biomaterials for biomedical therapies has just begun to be discovered. In order to better meet clinical needs, pathological mechanisms of diseases should be understood clearly and identifying an appropriate photosynthetic organism from the broad biodiversity observed is required. We should consider algal features such as cell shape, size, and life cycle, as well as the absorption spectrum and intensity requirements for photosynthesis, according to the specific problems to be resolved.

The human body harbors many microorganisms, to form a symbiotic system. This natural human-microbial consortium suggests the possibility of generating viable endosymbiotic chimeric tissues, and of using photosynthetic microorganisms to build a symbiotic system to facilitate the survival

of mammalian cells for transplantation and to improve therapies for particular diseases. Recently, Williams KM et al. confirmed the safety of *Synechococcus elongatus* for development of cyanobacteria–mammalian symbiotic therapeutics through detecting the various immunological indicators in rats [103]. Another two studies, which generated a viable plant-vertebrate chimera [104] and synthetic chloroplast, respectively, demonstrated the possibility of creating a symbiotic system involving mammalian cells and algae [105]. Those studies showed no significant immune response against the photosynthetic symbiont; nevertheless, the immunogenicity and toxicity of the photosynthetic organisms remain the chief concerns about applying algae to clinical treatment today. We need to investigate the possible immune response of different individuals to such systems, along with the development of immunomodulatory drugs to improve immune tolerance to foreign organisms. Genetic engineering tools can also be exploited to modify gene expression in the algae, as in the protocol described in Chávez MN et al.'s research [96]. Apart from enhancing local release of other therapeutic molecules or cytokines, gene editing can potentially be used to change the immunogenicity of the algae. Overall, photosynthetic symbiosis represents a valuable and still underdeveloped strategy for creating novel engineered O_2-generating biomaterials and enhancing O_2-dependent therapies.

In conclusion, Table 1 summarizes all of the algae and cyanobacteria reviewed in this article, and their potential clinical applications. We can see that algae and cyanobacteria have been widely applied for PDT-related research and that this tool still attracts interest in other fields of biomedical research. Photosynthesis can also be utilized to eliminate the excess carbon dioxide produced by our body and to balance internal pH. The introduction of photosynthetic organisms as clinical tools will decrease the healthcare costs for treating chronic wounds and MI and meet current clinical needs for the stable oxygenation of hypoxic organs or tissues. Finally, the success of this approach requires close collaboration among basic scientists from different disciplines.

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Table 1 Summary of the applications and function of all species of algae and thylakoid membrane

Photosynthetic organism	Applications	Function	References
Synechococcus elongatus	Photon-powered myocardium	Supply oxygen for myocardium in the ischemic heart	[74]
	Microalgae-gel patch	Promote diabetic chronic wound healing	[97]
Synechococcus lividus	Implantable islet cell device	Supply oxygen for pancreatic islets	[100]
Chlorella sorokiniana	Bioartificial pancreas		[101]
Chlorococcum littorale	Cardiac cell-layered tissues	Improve the culture condition of the thicker tissues	[73]
Spirulina platensis	Biodegradable microalgae-based carriers (SP@DOX)	As natural drug carriers for targeted drug delivery and effective treatment on cancer metastasis	[90]
	Photosynthetic biohybrid nanoswimmers system (PBNs)	Utilized for tumor-targeted imaging and therapy and as oxygenerator	[89]
Chlorella vulgaris	Red blood cell membrane engineered algae (RBCM-Algae)	Modulate hypoxic and immunosuppressive microenvironment and improve production of ROS in tumor	[91]
	Autotrophic light-triggered green affording oxygen engine (ALGAE)		[87]
	Chlorella-gold nanorods hydrogels		[88]
Synechococcus 7942	S/HSA/ICG system		[92]
Chlamydomonas reinhardtii	Photosynthetic gene therapy for regeneration	Gene modified microalgae express VEGF and produce oxygen	[96]
	Photosynthetic tissues	Generate chimeric tissues comprised of algae and murine cell to overcome hypoxia	[95]
	Photosynthetic scaffolds	As an alternative source of oxygen delivery	[94]
Thylakoid membrane	Photosynthetic leaf-inspired abiotic/biotic Nanothylakoid (PLANT) system	Enhance the efficacy of phototherapy or antiangiogenesis therapy	[93]

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Declarations

Conflict of interest The authors declare that there is no conflict of interest.

Ethical approval This study does not contain any studies with human or animal subjects performed by any of the authors.

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