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REVIEW

How Microalgae is Effective in Oxygen Deficiency Aggravated Diseases? A Comprehensive Review of Literature

Hengqing Cui[1,*], Yidan Su[1,*], Wei Wei[2,*], Fei Xu[3], Jie Gao[2], Wenjun Zhang[2]

[1]Department of Burns and Plastic Surgery, Shanghai Changzheng Hospital, Shanghai, 200003, People's Republic of China; [2]Changhai Clinical Research Unit, Shanghai Changhai Hospital, Naval Medical University, Shanghai, 200433, People's Republic of China; [3]Department of Plastic Surgery, Naval Medical Center, Naval Medical University, Shanghai, 200052, People's Republic of China

*These authors contributed equally to this work

Correspondence: Wenjun Zhang, Department of Burns and Plastic Surgery, Shanghai Changzheng Hospital, Shanghai, 200001, People's Republic of China, Tel +86 21 81885775, Fax +86 21 81886000, Email gift1013@163.com; Jie Gao, Changhai Clinical Research Unit, Shanghai Changhai Hospital, Naval Medical University, Shanghai, 200433, People's Republic of China, Tel +86 21 81871290, Fax +86 21 81871290, Email gaojiehighclea@163.com

Abstract: Hypoxia can aggravate the conditions of many oxygen-deficiency-aggravated diseases (ODAD), such as cancer, ischemic heart disease, and chronic wounds. Photosynthetic microalgae can alleviate the hepatotoxicity of the local microenvironment by producing oxygen. In addition, microalgae extracts have antitumor, anti-inflammatory, antibacterial, and antioxidant effects. These properties make them attractive candidates for developing methods to treat ODAD. Although researchers have exploited the advantages of microalgae and developed a variety of microalgae-based biomaterials to treat ODAD, a comprehensive review of this topic has not been presented previously. Therefore, in this review, we summarize the development and progress made in the field of developing microalgae-based biomaterials toward the treatment of ODAD. The challenges and prospects of this field are also discussed.

Keywords: chronic wounds, tumors, ischemic heart disease, hypoxia, oxygen generation

Introduction

Oxygen is a critical component of many pathological and physiological processes, such as endothelial cell proliferation, acute inflammation, fibroblast proliferation, and cancer cell metabolism.[1] However, under the conditions of an inadequate supply of oxygen (hypoxia), various oxygen-deficiency-aggravated diseases (ODAD) can be exacerbated, such as chronic wounds, solid tumors, and ischemic heart disease. Many chronic wounds present hypoxic conditions as there is a poor supply of oxygen to the wound bed.[2] Tissue oxygenation is a key factor that affects wound-healing processes. Acute hypoxia may stimulate neovascularization and accelerate wound healing, while chronic hypoxia is one of the predominant contributing factors in delayed wound healing, and this can be attributed to pathological repair and fibrosis.[3] A reconstituted oxygen supply can change this pathological process and accelerate wound healing. Hypoxia is frequently developed as a result of the imbalance between angiogenesis and tumor cell growth.[4,5] The hypoxic tumor microenvironment provides appropriate conditions for resisting various systemic anticancer treatments, such as radiotherapy,[6,7] immunotherapy,[8–10] and chemotherapy.[11,12] Therefore, tumor hypoxia is a significant obstacle to effective cancer treatment. It is being gradually accepted that effective tumor treatment requires alleviating the hypoxic tumor environment. Furthermore, ischemic heart disease is one of the most fatal diseases in the world and is caused by oxygen deficiency. The coronary arteries supply blood and oxygen to the heart muscle to maintain proper biological functions and cellular metabolism. However, a total blockage of blood flow to the heart results in the depletion of oxygen and adenosine triphosphate, which eventually results in myocardial infarction.[13] Hence, meeting the oxygen requirements for metabolism during myocardial infarction may attenuate the destructive effect caused by hypoxia.[14] Therefore, an effective approach for the treatment of ODAD involves mitigating hypoxia.

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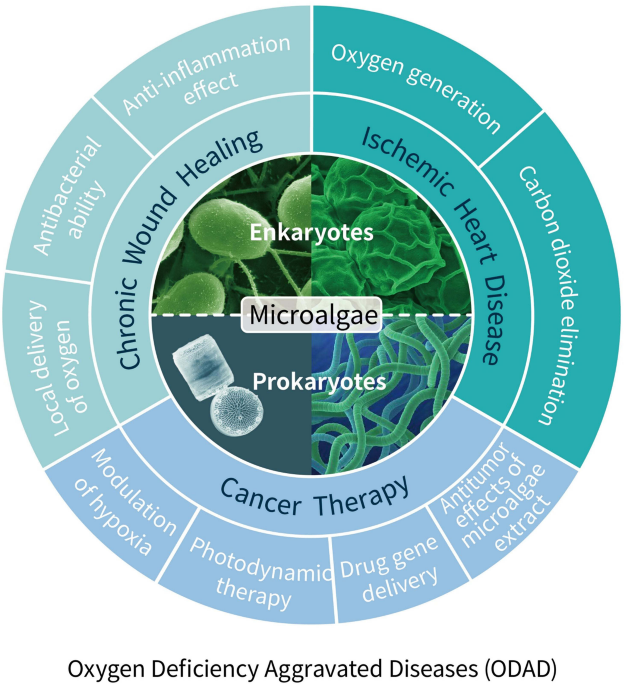

Figure 1 Schematic illustration of the microalgae-based materials used to treat oxygen deficiency aggravated diseases (ODAD).

Microalgae are a diverse group of unicellular prokaryotic and eukaryotic organisms that are widespread in nature, and can be used for mitigating hypoxia.[15] Microalgae are approximately 2–10 μm in size and are composed of lipids, proteins, nucleic acids, and carbohydrates. Unlike many other microorganisms, they are also considered excellent sources of various bioactive compounds, such as antioxidants, vitamins, and minerals.[16] All these factors make them suitable for introduction into functional foods and health supplements.[17,18] Most microalgae contain phytochemicals that help in the continuous generation of oxygen during photosynthesis. Thus, microalgae are considered oxygen generators.[15,19] They have excellent biocompatibility and bioactivity and do not exhibit significantly high aggressive behavior toward mammalian cells (except known species of toxic microalgae). Thus, microalgae have broad potential for use in the biomedical field.

Microalgae are gradually favored by researchers because of their natural abundance, low cost, and good biocompatibility when compared with traditional drugs. In recent years, the microalgae research field has grown, and reviews in this field have been published.[15,20] Some of these reviews focus on the field of tumor treatment, but there is no existing review of other hypoxic diseases like ischemic heart disease and wound healing. In this review, we summarize the current progress made in customized microalgae-based biomaterials that can be used to develop therapeutics to treat ODAD (Figure 1). Information on different microalgal genera and their unique properties are presented, and relevant examples from the literature are discussed in detail. Finally, the limitations and prospects in the field of developing microalgae-related biohybrid systems are discussed.

The Basic Concept of Microalgae with Clinical Significance

Microalgae are primarily autotrophic photosynthetic single-celled microorganisms that are generally classified into two categories: eukaryotes (ie, *Chlorella vulgaris*) and prokaryotes (ie, cyanobacteria).[21] They have several biomedical applications and have anticancer,[22,23] anti-inflammatory,[20,24] target therapy,[25] anti-obesity,[26] cargo delivery,[25,27] wound healing,[28,29] and other properties.

Eukaryote Microalgae

Chlamydomonas Reinhardtii

Chlamydomonas reinhardtii (*C. reinhardtii*) is a type of spherical freshwater unicellular green microalgae with two flagella, which impart them with their active locomotion properties. These microalgae can swim at a high speed of 100 μm s^{-1} by harvesting energy from the surrounding environment.[27,30] *C. reinhardtii* is negatively charged due to the presence of cell-wall-dispersed hydroxy-proline-containing glycoproteins. Therefore, these algae could attach to positively charged functionalized materials or cells by exploiting electrostatic interactions.[31] *C. reinhardtii* also has oxygen-generated photosynthetic activity. These features make them suitable for use as self-propelled microswimmers for providing oxygen, and to realize the targeted delivery of specific therapeutics. Yasa et al designed microalgae-powered biohybrid microswimmers to realize the targeted delivery of cancer therapy agents (such as dextran) by exploiting the non-covalent electrostatic interactions between *C. reinhardtii* and polyelectrolyte-functionalized magnetic polystyrene (PS) particles (diameter: 1 μm).[27] This biohybrid algal microswimmer had efficient 3D motility under the influence of a uniform magnetic field that helped deliver drugs to mammalian cells. The reported results presented an effective method to address the challenge posed by conventional biohybrid delivery systems without active motility and steerability.[32] Excellent drug delivery ability (to SK-BR-3 cells) was also achieved. In addition to developing materials that can be used for cancer therapy, a biohybrid microswimmer was developed by linking antibiotic molecules with *C. reinhardtii* via a photocleavable covalent linker to act as a microrobot against both gram-positive and gram-negative bacteria.[33] A UV-light-triggered covalent linker was used that did not function via electrostatic interactions to realize the release of the controlled antibiotic at the bacterial target site. As one of the most studied microalgae for genetic engineering, *C. reinhardtii* is widely used as an algal recombinant expression platform for biomedical applications.[34] A novel approach using transgenic *C. reinhardtii* was developed to produce oxygen and proangiogenic growth factors such as human vascular endothelial growth factor A (hVEGF-165) to promote wound healing in biomedical settings.[35] The study identified the optimal combination of *C. reinhardtii* and protein expression elements to produce recombination proteins in a high-efficiency model. Results from an in vitro angiogenesis tube-formation assay revealed that transgenic *C. reinhardtii* has the potential to effectively heal wounds.

Chlorella

Chlorella is a well-known oxygen-producing photosynthetic green alga that is commonly used in photodynamic therapy (PDT) as it has good photosynthetic activity and the ability to continuously produce oxygen.[36] Additionally, it has been widely reported that *Chlorella* can enhance antitumor immune effects and generate a systemic antitumor immune response that is caused by *Chlorella*-released immunostimulatory substances such as mannan and β-glucan.[36,37] It has been widely reported that extracts and fractions of *Chlorella* have immunoregulatory and cancer prevention properties.[38] The anticancer properties of *Chlorella* were investigated in vitro and in vivo using human non-small-cell lung-cancer cell lines and a subcutaneous xenograft tumor model.[39] It was reported that the oral administration of *Chlorella* efficiently inhibited the growth of the xenograft tumor model in a dose-dependent manner. In addition, extracts obtained from *Chlorella vulgaris* exert antitumoral and antiproliferative effects on numerous cancer cell lines, such as HepG-2, HCT-116, and MCF-7.[40] In an in vivo study of the therapeutic effects exerted by an extract of *Chlorella vulgaris* on hepatocellular carcinoma (HCC), the algae was fed directly to HCC-induced rats and tumor markers, including TGF-β, M2-PK, OV-6, and AFP, were monitored.[41] After 12 weeks of treatment, the extent of oval cell formation and the expression levels of M2-PK, OV-6, AFP, and TGF-β were significantly reduced compared to those of the control group.

Chlorella has also been used in combination with PDT techniques to improve the local tumor-killing effect.[42] The dual oxygen-producing and immune-activating effects of *Chlorella* simultaneously boost the antitumor immune response and immune memory effect. The results from various animal experiments revealed that *Chlorella* efficiently enhances the systemic effect of PDT. In another work, perfluorocarbon (PFC) was used as an oxygen enricher to dissolve the O_2 generated by *Chlorella* and subsequently release it into the surrounding environment to maintain a proper oxygen level for PDT.[36] Destroyed *Chlorella* further acts as an adjuvant to recruit antigen-presenting cells (APCs) and generate PDT-related immune responses. Using a combination of oxygen production methods and amplified antitumor response, they

developed an effective way to supply enough oxygen to fully exert the efficacy of PDT and ultimately strengthen the tumor-killing ability. They adopted a simple and efficient strategy that can be used for improving the survival of advanced-stage cancer patients. However, the mononuclear phagocyte system in the liver and spleen captures most of the *Chlorella* following intravenous injection. It is estimated that approximately 2% of the administered drugs reach the tumors,[43] which greatly limits the clinical application of the drugs.[44] To overcome this problem, *Chlorella vulgaris* was engineered by coating it with a red blood cell membrane (RBCM) to reduce its uptake by the mononuclear phagocyte system and reduce system clearance.[45] RBCM-coated microalgae can reach the tumor sites efficiently and remarkably increase the blood oxygen saturation level in the tumor region 2 h after their intravenous injection. This biohybrid system could be used to develop novel technologies to attenuate macrophage-mediated phagocytosis of microalgae and induce photosynthesis to minimize tumor-tissue hypoxia and realize thorough tumor ablation.

In addition to cancer treatment, *Chlorella* provides antibacterial and antioxidant functionality, and can mediate metabolism. It was recently shown that extracts of *Chlorella* had very high antibacterial activity against six bacteria and four fungal strains.[46] The antibacterial activity was stronger than the antibacterial activity of other cyanobacteria and microalgal species. Furthermore, an extract obtained from *Chlorella* was investigated for preventing dental caries following the PDT technique.[47] It has been reported that *Chlorella* is rich in antioxidant agents and thus, is an effective supplemental treatment for oxidative-stress-related diseases such as chronic obstructive pulmonary disease caused by chronic cigarette smoking. The administration of *Chlorella* over six weeks significantly impeded the progression of smoking-related diseases and, in some cases, prevented death.[48] Recently, it was reported that polysaccharides from *Chlorella* could be used to reduce body weight, address glucose tolerance impairment, and treat dyslipidemia in obese C57BL/6 mice fed with a high-fat diet.[49] The changes in serum biochemistry of gut bacteria were studied using a high-throughput sequencing technique. Clinical trials have also confirmed that *Chlorella* and its extracts can regulate hyperlipidemia and hyperglycemia and improve liver function.[50] A double-blind placebo-controlled randomized clinical trial showed that the mean weight reduction achieved in the *Chlorella* group was higher than that of the placebo group. Serum glucose and the concentration of liver enzymes decreased significantly after 8 weeks of oral administration in seventy patients suffering from nonalcoholic fatty liver disease. These findings indicate that *Chlorella* could be considered an adjunctive treatment for patients suffering from metabolism-related disorders.

Prokaryotes Microalgae

Cyanobacteria, sometimes called blue–green algae, are prokaryotes devoid of assembled flagella. They swim directly toward light sources (phototaxis), respond to other environmental signals, and produce oxygen by photosynthesis.[51] Thus, they are natural microswimmers that can be used to carry therapeutic cargos.

Spirulina Platensis

Spirulina platensis (*S. platensis*) is a helical microalga, which contains several injectable therapeutic ingredients, such as polysaccharides, carotenoids, and phycocyanin. These algae also have a high loading efficiency as a result of the presence of aqueous pores structure on their cell membrane. Several instructive studies have been performed using *S. platensis* as microrobots to navigate inaccessible areas of the body, such as major organs. Therefore, such algae could be used to develop smart strategies for minimally invasive therapeutic techniques.[52,53] However, some critical challenges highlighted by laboratory and clinical usage need to be addressed. Efforts have been made in recent years to address the controlled release at the target site, robust spatiotemporal navigation, biosafety, and biodegradation in a physiological environment. The biodegradation and reversible dehydration/rehydration processes of *Spirulina* cells were used to fabricate a magnetic microswimmer for the gastrointestinal delivery of molecular agents such as TGF-β1.[54] Fe_3O_4-coated *S. platensis* move directionally under the influence of an external magnetic field toward target sites in different biofluids. Molecular agents were released based on the degradation of *S. platensis* and the principles of concentration diffusion. The results provided insights for realizing imaging-guided therapy exploiting the structural and functional features of *S. platensis*. For example, a magnetic microrobot was developed by combining core–shell-structured Pd@Au nanoparticles with *S. platensis*.[55] This biohybrid microrobot was an efficient platform for targeted delivery, controlled

drug release, and chemo-photothermal therapy, which can be monitored in real-time using computed tomography or magnetic resonance imaging techniques in the presence of contrast agents such as Au or Fe_3O_4 nanoparticles.

Because *S. platensis* has the highest protein content among all microalgae, it is commonly used as a protein resource in the food industry and as a food supplement in protein-deficient countries.[56] Phycocyanin is a light-harvesting pigment-binding protein in *S. platensis*. It is also an excellent natural edible pigment, food additive, cosmetic colorant, and fluorophore that is widely used in various fields.[57]

Diatoms

Diatoms are unicellular microorganisms found in both freshwater and seawater, and are characterized as a type of microalgae that builds a solid silica shell around its membrane to protect itself from environmental stress. There are tens of thousands of known diatom species, each characterized by the microstructure of their outer silica shell. The porous structure of diatoms makes them a candidate for loading and delivering drugs and genes. The genes of diatoms can be readily manipulated using genetic engineering methods. Diatom silica microparticles loaded with mesalamine and prednisone were developed for treating gastrointestinal disease therapy.[58] This study primarily explored the low biological toxicity and high-concentration drug loading performance of diatoms. The in vitro drug-release and cytotoxicity results showed that the diatoms were suitable drug carriers. A novel nanohybrid material fabricated by combining diatoms and graphene oxide was shown to be especially suitable for the selective delivery of pH-sensitive drugs to the intestine, and also for local chemotherapy requiring the release of drugs under acidic conditions.[59] Diatoms can be used for both drug and gene delivery as they have porous structures and modifiable surfaces. An innovative diatom platform modified with functional groups was developed to deliver small interfering ribonucleic acid (siRNA).[60] They also explored the biological toxicity of the hybrid system and the efficiency of transmitting siRNA into human epidermoid cancerous cells to silence genes. Their findings confirmed that diatoms are effective for use in the field of gene transmission. Biosilica-based materials have been used to repair bones as they have high stability and biocompatibility.[61] For example, β-tricalcium phosphate and diatoms were used to promote bone-tissue repair. Both biological silica and polyphosphate can improve the mineralization of osteoblasts and increase the expression of bone morphogenetic protein-2 and alkaline phosphatase in these cells.[62] Diatoms coated with chitosan can stop local bleeding as they have excellent fluid absorption ability and exert suitable hemostatic influence.[63] Calcium was added to the diatom column to develop an innovative, efficient, and biocompatible calcium-doped biological silica system, which can also strengthen the coagulation pathway, promote coagulation, and rapidly control bleeding.[64]

This characteristics and biological applications of commonly used microalgae discussed here are summarized in Table 1. Microalgae have been widely used in the field of biomedicine because of their desirable functionality.

Treatment of Oxygen Deficiency Aggravated Diseases

Cancer Treatment

Modulation of Tumor Hypoxia

Because cancer is a leading threat to human health, continuous efforts are being made to cure this common disease. The radiotherapy technique is widely used for cancer therapy (pre- and post-surgery) and is based on the cell-killing effect of ionizing radiation. Approximately 50% of patients with tumors must receive radiotherapy during their course of treatment. The hypoxic environment around most locally advanced solid tumors significantly reduces the effect of radiotherapy.[65] This has been exploited in recent years to realize selective therapy and has been smartly used as a therapeutic target.[9] Many studies aimed to minimize tumor hypoxia and increase the sensitivity of the tumor cells to radiotherapy. There are several ways to alleviate the hypoxic tumor microenvironment, and these methods are classified into in situ oxygen generation and increasing the amount of oxygen delivered to the tumor.[66] As microalgae are natural oxygen generators, they have been used for in situ oxygen generation to minimize tumor hypoxia. A biohybrid microalgae system was developed to modulate the hypoxic environment and increase the sensitivity of tumors to radiotherapy.[67] Algae@SiO_2 was intravenously injected into a breast-cancer animal model, and silica was used as a biomimetic mineralization shell to improve the biocompatibility of the system. When irradiated by a 650 nm laser, chlorophyll II in the microalgae produces oxygen and change the hypoxic environment to

Table 1 Characteristics of Commonly Used Microalgae and Their Medical Applications

	Species	Remarks	Medical Application	References
Eukaryotes	*Chlamydomonas reinhardtii*	Negatively charged Self-powered	Drug delivery; anticancer/antibacterial agent Microrobots	[27,31]
	Chlamydomonas reinhardtii	Used in genetic engineering and oxygen production	Recombinant protein expression platform Wound healing	[34,35]
	Chlorella	Contains immunostimulatory substances	Anticancer agent	[39–41]
	Chlorella	Photosynthetic and oxygen-producing activities	Photodynamic therapy	[36,42,45]
	Chlorella	Antibacterial activity	Antimicrobial agent	[46,47]
	Chlorella	Antioxidant	Treatment of chronic obstructive pulmonary disease	[48]
	Chlorella	Mediates metabolism	Weight loss Mediates blood glucose Liver function improvement	[49,50]
Prokaryotes	*Spirulina platensis*	High loading efficiency	Drug delivery	[52,53]
	Spirulina platensis	Biodegradable Reversible dehydration/rehydration processes	Imaging-guided therapy	[54,55]
	Spirulina platensis	Contains high protein content	Preparation of healthcare products	[56,57]
	Diatom	High surface area	Drug delivery	[58,59]
	Diatom	Covered by reactive silanol (Si-OH) groups	Gene delivery	[60]
	Diatom	Highly stable and biocompatible	Tissue engineering	[62]
	Diatom	Fluid absorption Promotes hemostasis	Hemorrhage control	[63,64]

Abbreviation: PDT, photodynamic therapy.

a normoxic one. Under these conditions, reactive oxygen species (ROS) are released. Following laser irradiation, a beam of X-rays was used to treat 4T1 tumor-bearing mice. The results revealed that this novel biohybrid algae-based system had satisfactory biosafety and oxygen-generation ability. The system can be used to tune the hypoxic conditions in vitro and in vivo. ROS produced by chlorophyll can exert adjuvant effects on breast-cancer therapy. Calcium-phosphate-engineered photosynthetic microalgae[68] and RBCM-coated algae[45] could be used for modulating hypoxia and cancer therapy. The former study used the autofluorescence and photoacoustic imaging properties of microalgae to monitor the accumulation of functional materials at the tumor site, study the efficiency of tumor therapy, and visualize the therapy process. In the first study of its kind, RBCs were used to fabricate a near-infrared-triggered RBC microcarrier functionalized with a hypoxia probe and PDT photosensitizer (Rose Bengal).[65] This functional material was used to overcome biological barriers to modulate the hypoxic environment in a solid tumor, which subsequently increased the efficiency of PDT. Another study selected biological materials (ie, RBCM) instead of inorganic materials (such as silica or calcium phosphate) to coat microalgae to protect them from clearance by the mononuclear phagocyte system and overcome biological barriers to increase the accumulation of microalgae in tumors.[45] The delivery efficiency of RBCM–algae was higher than the efficiency of other systems reported previously.[43] Only 2% of the total injection of microalgae could reach the tumor sites when previously developed systems were used. The researchers studied the antitumor effect of the system using breast-cancer and ovarian-tumor models, and showed that both the intra-tumoral and intravenous-injection therapy methods are effective for delivering RBCM–algae to the tumor sites. Thus, there are synergistic effects of combining oxygen-generation methods with radiotherapy and PDT treatments (Figure 2).

In addition to the challenge of oxygen production, it is difficult to maintain the local oxygen concentration for a prolonged period of time. Therefore, various methods have been developed toward achieving sustained oxygen release. For example, PFC was used to collect oxygen produced by algae,[36] which was subsequently released to overcome the hypoxic condition in a tumor. The tumor-killing effect can be improved using this method, and was attributed to oxygen enrichment around the photosensitizer. The amount of oxygen stored in PFC is much higher than the amount of oxygen consumed during PDT (Figure 3).

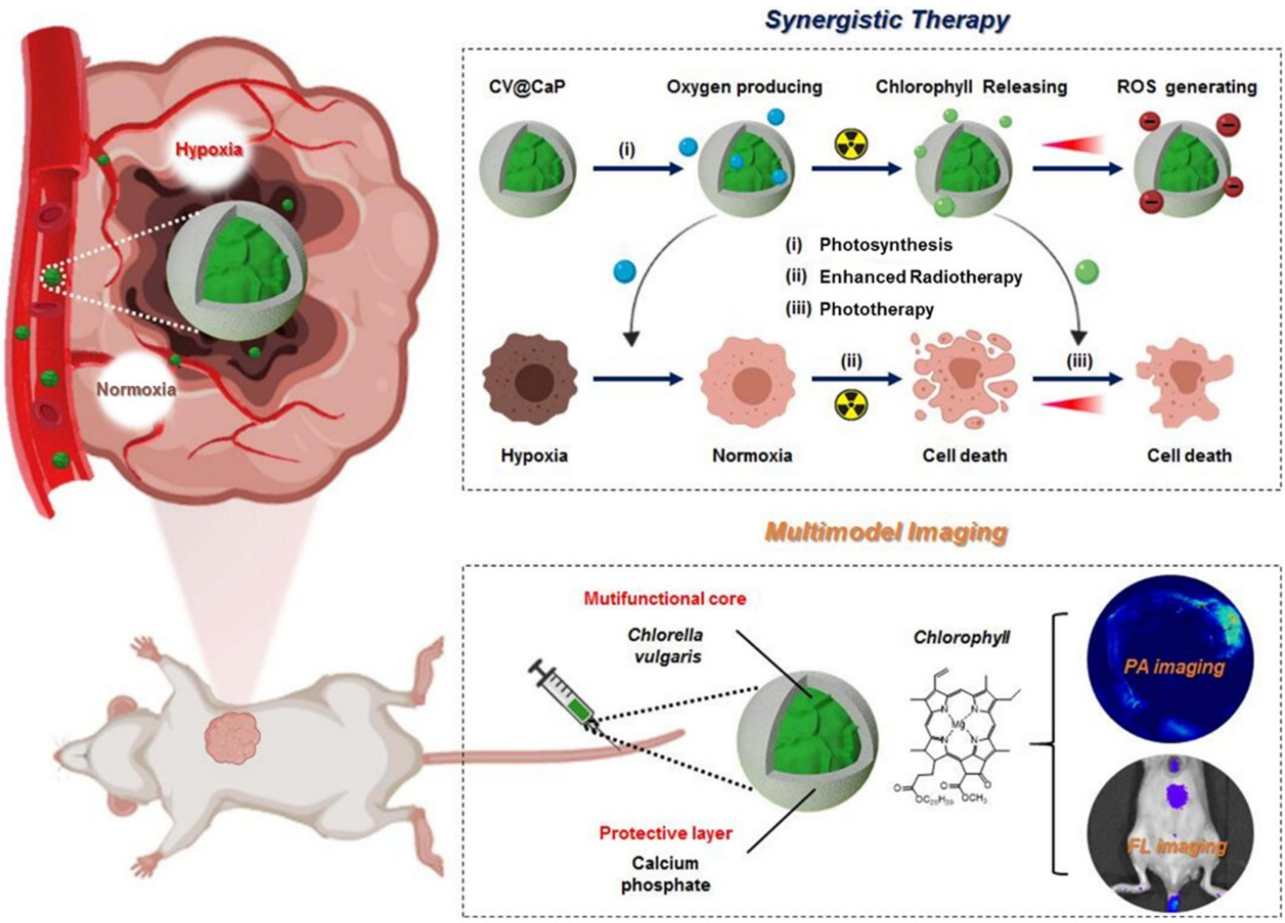

Figure 2 Schematic illustration of the synergistic therapeutic effect of calcium phosphate-engineered photosynthetic microalgae. The oxygen produced by *Chlorella vulgaris* can alleviate the local hypoxic conditions in tumors. Normoxia can increase the effect of radiotherapy, and chlorophyll released from *Chlorella vulgaris* can produce reactive oxygen species under the action of laser irradiation. This can synergistically induce the death of tumor cells. Reproduced from Zhong D, Li W, Hua S, et al. Calcium phosphate engineered photosynthetic microalgae to combat hypoxic-tumor by in-situ modulating hypoxiaand cascade radio-phototherapy. Theranostics. 2021;11(8):3580–3594. Copyright (2021), Ivyspring. Creative Commons Attribution License (https://creativecommons.org/licenses/by/4.0/).[68]

These data illustrate that alleviating the hypoxic environment in solid tumors can increase the efficacy of radiotherapy and PDT. Other materials can be used to coat microalgae to fabricate new biomaterials that prevent their rapid removal from the body and deliver further functionality to treatment targets. Recent studies have primarily focused on improving the biocompatibility of microalgae and exploiting the characteristics of microalgae for developing therapeutic methods.

Microalgae Mediated Photodynamic Therapy

PDT is a common local-tumor therapy method that uses photosensitizers such as chlorin e6 (Ce6) or microalgae to convert light energy into singlet oxygen ($^1O_2$). Abnormal cells, such as cancer cells, tend to uptake photosensitizers. Focusing the light directly on cancer cells can limit the side effects faced by normal healthy cells. When cancer cells capture photosensitizers exposed to a specific wavelength of light, $^1O_2$ generated by the photosensitizers induces cancer-cell apoptosis. Hence, PDT has attracted immense attention in the field of cancer treatment as a minimally invasive technique, as it generates only a minor systemic response.[69] Because microalgae are good photosensitizers, they are suitable for use with PDT. For example, *S. platensis* was irradiated with lasers of varying energy densities to study the effect of PDT on head and neck squamous-cell carcinoma cell lines.[70] They reported that *S. platensis* was a safe and effective natural photosensitizer that could be used to treat several oral and hypopharyngeal cancer-cell lines with minimal side effects. They recommended an optimal photosensitizer concentration of 0.3 or 0.6 g/L, and irradiation using a 635 nm laser. The lack of in vitro experimental results to verify the in vivo data limits the applicability of the reported results. PDT alone cannot be used to effectively treat hypoxic tumors because of its oxygen-dependent functionality.[71,72]

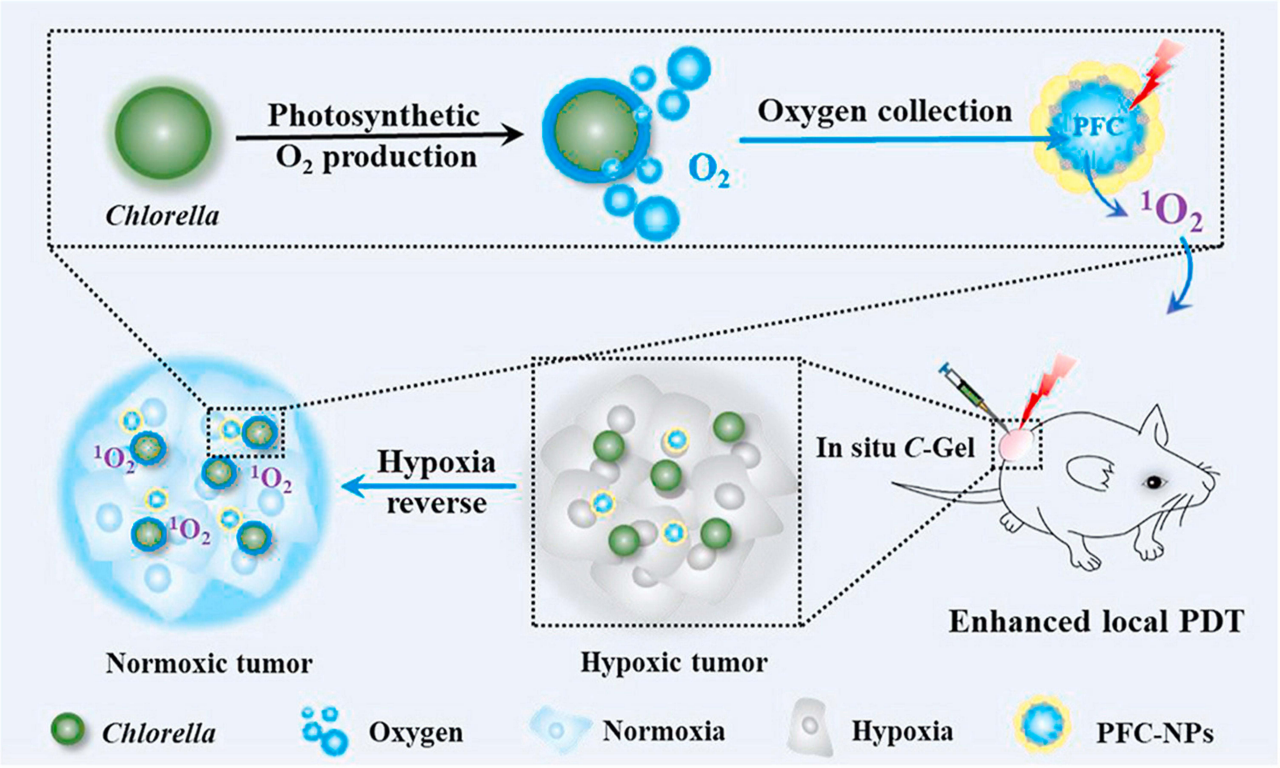

Figure 3 Schematic diagram of the PFC hybrid material. Oxygen generated by *Chlorella* can be collected by PFC to maintain a high concentration around the photosensitizer, which can continuously alleviate the hypoxic conditions of tumor tissues. The relief of tumor hypoxia can enhance the PDT effect mediated by singlet oxygen. *J Biomaterials. Feb 2021;269:120621*. Copyright (2020), Elsevier. Reproduced from Wang H, Guo Y, Wang C, et al. Light-controlled oxygen production and collection for sustainable photodynamic therapy in tumor hypoxia. 605Biomaterials. 2021;269:120621. doi:10.1016/j.biomaterials.2020.120621. Copyright 2021, with permission from Elsevier.[36]
Abbreviations: PFC, perfluorocarbon; PDT, photodynamic therapy.

To address this, an oxygen-releasing material for hypoxia-resistant PDT was developed, which generated three times the amount of oxygen produced by other systems, and hence, improved the tumor inhibition ability of PDT compared to conventional PDT.[73] Hybrid multifunctional diatom microalgae were developed by incorporating a chemical photosensitizer or photo-triggered CO-release molecule inside the microalgae to realize both drug delivery and PDT.[74] When irradiated by a laser, the material killed tumors via the cytotoxic effects of CO or $^1O_2$. This functional material integrates two different photosensitive materials into the microalgae and the antitumor properties occur via novel mechanisms that differ from the traditional mechanism where only $^1O_2$ is involved in the generation of the antitumor effect.

Microalgae can produce oxygen and act as a photosensitizer, which are the two core factors of PDT-based treatment. Hence, numerous researchers have used microalgae to treat tumors. However, PDT is currently only an auxiliary tumor treatment. Researchers are studying methods of combining traditional cancer treatments, such as radiotherapy or chemotherapy, with PDT to comprehensively improve the treatment effect and prolong the life expectancy of patients. Although further research on the microalgae-mediated PDT method is required to enable clinical application of the method, this new treatment platform offer promise for improved tumor treatments.

Drug and Gene Delivery Using Microalgae

Chemotherapy is a drug-treatment method that uses powerful chemicals to kill fast-growing cells in the human body. Chemotherapy is most often used to treat cancer as cancer cells grow and multiply more quickly than most healthy cells in the body. As these drugs travel throughout the body, they can also affect rapidly growing healthy cells, resulting in unpleasant side effects. Many chemotherapy-related side effects are associated with the drug dosage.[75] Efficient anticancer therapeutics should selectively kill cancerous cells, leaving the healthy cells unaffected. Therefore, some researchers have changed the method of drug delivery to reduce the dose of systemic drugs. Methods for delivering a sufficient

concentration of the drug at the site of action are required. The ability of microalgae to use the energy in the surrounding environment to move freely makes them a promising drug carrier in the field of tumor treatment.

Diatoms were used to design a bioinspired hybrid multifunctional drug-delivery system to deliver chemotherapeutic agents to the tumor sites.[74] Vitamin B_{12} was linked to the outer surface of the diatom as an adaptor to specifically bind to colorectal cancer cells. These novel materials can target and recognize tumor cells and slowly release chemotherapeutic drugs following laser activation. In this way, the dose of oral drugs can be minimized to reduce the side effects related to high drug concentrations. The use of organic solvents and the formation of covalent cross-links often result in cytotoxicity, which significantly hinders the in vivo application of many materials. Delalat et al developed a genetic method to transform diatoms into microalgae characterized by high GB1 expression levels.[76] GB1 is an immunoglobulin-G-binding domain of protein G that can help drug carriers to bind to cancer cells. A chemotherapy drug was encapsulated inside the microalgae by cationic micelles and liposomes. The developed biomaterials can specifically target tumor cells and slowly release antitumor drugs to kill tumors. A highlight of this study was the fabrication of genetically engineered microalgae expressing the GB1 fusion protein, which can target and recognize tumor cells through molecules on the surface of diatoms, and effectively deliver chemotherapeutic drugs. This method could be used to avoid biological toxicity attributable to the formation of covalent crosslinks. Under these conditions, the biocompatibility of the drug carriers is improved. In addition to the exploitation of the autologous expression of targeted molecules, the electrostatic adsorption between materials and algae can be used to connect carriers and drugs. Previous studies designed medical biohybrid microswimmers exploiting the electrostatic adsorption effect to prepare noncovalently formed biohybrid systems for cargo delivery (Figure 4). Microalgae coated with a thin and soft layer of chitosan-based polyelectrolyte solution achieved a high manufacturing yield of 90%,[77] which is significantly higher than that achieved in other studies. They reported the generation of electrostatic interactions between microalgae-based hybrid systems and negatively charged cells such as SK-RB-3, enabling the hybrid systems to be adsorbed on the cell surface to realize drug delivery. However, we believe that the adsorption is nonspecific. The movement of microalgae in different biological fluids is guided by the action of an external magnetic field,[27] which could improve the accuracy of algae-targeted drug delivery.

The biocompatibility and degradability of microalgae make them suitable candidates for drug and gene delivery systems. Researchers are primarily focusing on reducing the biological toxicity and improving the targeting of drug-delivery systems. These works have opened a new pathway to realize the delivery of tumor drugs.

Antitumor Effects of Microalgal Extracts

Microalgae produce specific enzymes to survive in various harsh conditions throughout their period of evolution. In addition to microalgae, numerous microalgal extracts or components, such as bioactive molecules, cell walls, or microalgae-derived nanoparticles, have interesting properties, especially antitumor functionality.[48,50,78] Although the anticancer mechanism associated with microalgae extracts is complex, it can be generalized into cancer-cell killing and immune-modulation effects.[15]

Direct Cancer-Cell Killing Effect

Several types of biomolecules extracted and purified from microalgae provide effective anti-proliferative effects. For example, microalgal extracts such as polyunsaturated fatty acids, polysaccharides, peptides, carotenoids, and some other bioactive products showed excellent antimetastatic properties in both in vitro and in vivo experiments.[78] The properties of these compounds are similar to those of chemotherapy drugs. The anticancer activities of these materials were evaluated using several cancer cell lines, including lung, prostate, stomach, breast, and pancreatic cancer cell lines via in vitro cell-growth-inhibition assays, apoptotic cell-death assays, and colony-forming assays.[79] In in vivo experiments, mice bearing PC3 prostate cancer cells were used to observe the antimetastatic effect. The extracts from microalgae inhibited the colony-forming ability of a variety of tumor cell lines and killed suspended cancer cells. In addition, extracts from heterotrophic cultures of *Galdieria sulphuraria* were shown to inhibit the growth of adenocarcinoma A549 cells through the induction of cell apoptosis.[80] However, the composition of the extract was not determined, and the antitumor mechanism of the extract was not explored in detail. The antitumor effect of an extract from *Chlorella sorokiniana* on A549 non-small-cell lung cancer cells was studied in vitro and in vivo (subcutaneous xenografts).[39] This

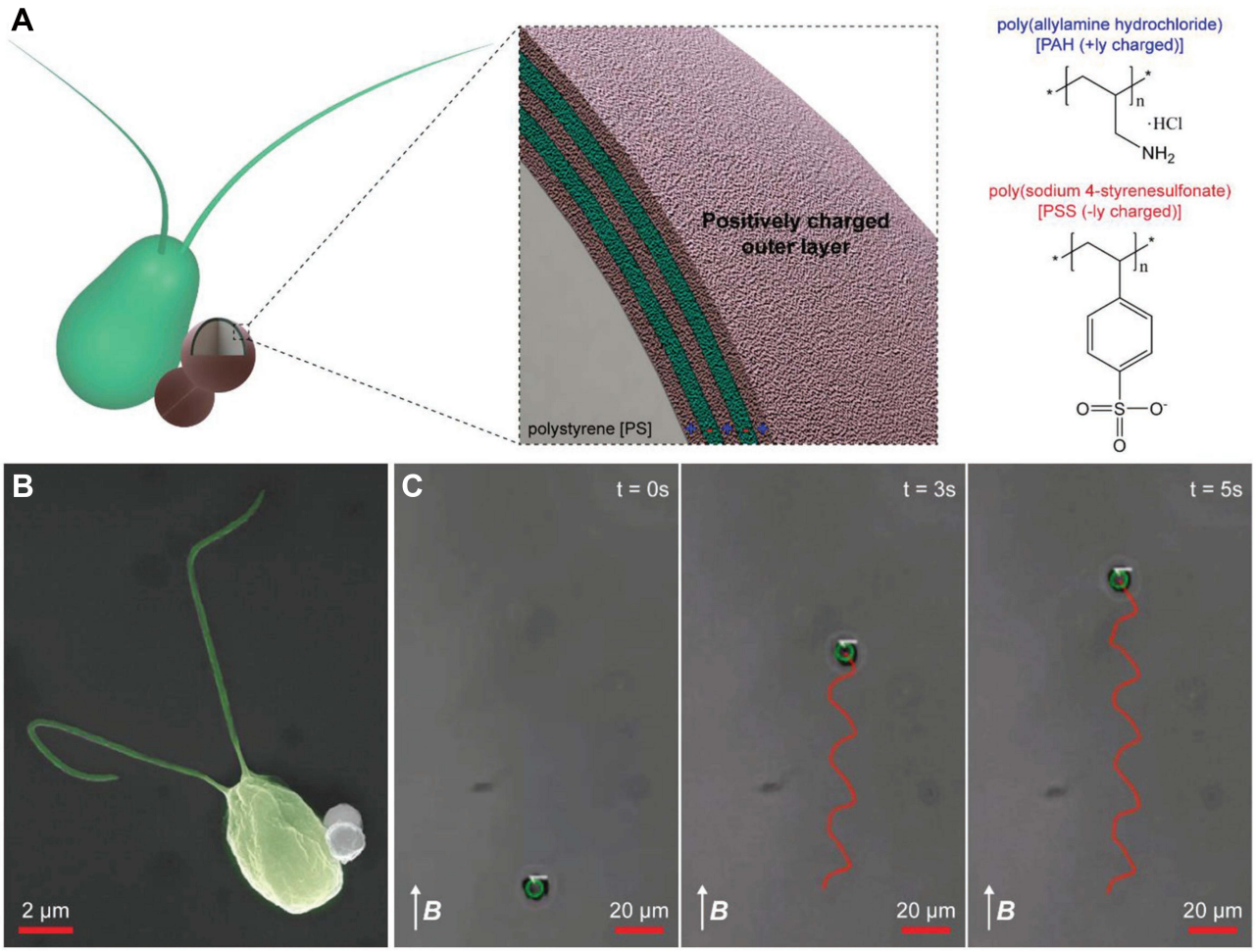

Figure 4 Overview of *C. reinhardtii*-powered microswimmers for drug delivery. (**A**) Microalgae were connected to positively charged functional particles via electrostatic interactions. (**B**) Scanning electron microscopy (SEM) image of the hybrid microswimmer system. (**C**) Trajectory of the microswimmer system under the influence of a uniform magnetic field (26 mT). The red line indicated the propulsion trajectories of an algal microswimmer. Scale bars: 20 μm. Reproduced from Yasa O, Erkoc P, Alapan Y, Sitti M. Microalga-powered microswimmers toward active cargo delivery. Adv Mater. 2018;30(45):e1804130. Copyright (2018), John Wiley and Sons.[27]

extract was shown to be a potential tumor therapeutic agent as it induced apoptosis in non-small-cell lung cancer cell lines by downregulating Bcl-2, XIAP. The anticancer activity of extracts from *Chloromonas* was studied using cervical, melanoma, and breast cancer cells.[81] Extracts from several kinds of diatoms (*S. marinoi, A. carterae, T. rotula, T. issuecica, A. tamarense, D. salina, C. affinis*, and *S. japonicum*) were screened for anticancer activity.[82] They reported 100% blockage of the leukemia cancer (U-937) cell line in the sub-G1 phase of the cell cycle using a purified *S. marinoi* extract (48 h of treatment). Minimal cell-killing effect was observed for the normal MePR-2B cells in the control group. The *S. marinoi* extract was purified using silica gel chromatography and high-performance liquid chromatography techniques to obtain pure 1-monoarachidonoylglycerol (MAG). Subsequently, pure MAG was isolated from *S. marinoi* for cytotoxicity studies and mechanism evaluation. The MAG purified from diatoms had antiproliferative and proapoptotic effects by inducing selective cell death in cancer cells. Purification of the extracts enabled the active components to be identified.

Microalgal-Extract-Mediated Photodynamic Therapy

In addition to the direct toxic effect on tumor cells discussed above, microalgae are phototrophic organisms containing several natural photosensitizers, including β-carotene,[83] astaxanthin,[84] phycoerythrin,[85] and tetrapyrrole.[85] These components can absorb light energy and transform the energy to cell-killing ability.[15] The effect of phycoerythrin on the cell cycle was evaluated using the stomach cancer cell line SGC-7901.[85] When activated by a 496 nm laser, a cancer-cell-killing effect

was observed due to the induction of apoptosis. Semi-purified extracts of several microalgae were used as photosensitizers to study their role in tumor treatment.[86] Several extracts, when irradiated with blue or red light (or both), had significant cancer-cell-killing ability in a dose-dependent manner. In addition, the extracts activated by both blue and red light showed higher cell toxicity than those activated by a single light source. However, microalgal extracts directly used for PDT of tumor cells are limited by their low efficiency. The current focus is on improving the efficiency of extract-mediated tumor treatment processes. Researchers are aiming to combine extracts with other chemical materials to overcome the inherent drawbacks. Electrospraying and microemulsion techniques were used to encapsulate microalgae extracts to enable their controlled release.[87] Another study developed a type of Ce6-modified β-carotene-bound albumin nanoparticle to treat breast cancer.[83] The β-carotene was used as a natural physical cross-linker to combine albumin molecules with Ce6 to improve the efficiency of PDT. Furthermore, polypyrrole nanoparticles were synthesized using astaxanthin-conjugated bovine serum albumin polymer as the stabilizing agent, where the astaxanthin functioned as a photosensitizer to provide an anticancer effect.[84] This customized material showed significantly high cytotoxic effects on the breast-cancer cell model MBA-MD -231 when irradiated with a continuous laser beam (808 nm), and side effects were not observed for normal cells. In addition, the material acts as a photographic developer in image-guided phototherapy. Studies using microalgae to exert antitumor effects through the above mechanisms are summarized in Table 2.

Microalgal-Extract-Mediated Immunomodulation

In addition to the cancer-cell-killing effects (comparable to those of chemotherapeutic drugs), microalgal extracts have immunomodulation effects. They play important roles in the immune-stimulation process by activating immune cells such as dendritic cells (DCs), natural killer cells, and T lymphocytes.[88] Previous studies[89,90] extracted sulfated polysaccharides from *Tribonema sp*. to study the immunological effects of the systems on RAW264.7 murine macrophage cells. The concentrations of interleukin 6, interleukin 10, and tumor necrosis factor α were determined following the stimulation by polysaccharides. Polysaccharides from microalgae *Parachlorella kessleri* HY1 biomass were purified and isolated, and the immunomodulation effect of the purified extracts on melanoma-bearing C57Bl/6 mice was studied.[91] The polysaccharides could elicit immune responses by stimulating innate and adaptive immunity. The data revealed that polysaccharides isolated from *Parachlorella kessleri* could function as nonspecific immune stimulators that played an auxiliary role in the tumor immunotherapy process.

DCs are a type of APCs that provide antigens to T cells. These are referred to as "professional" APCs. Most DCs in the human body are in an immature state and express low levels of costimulatory and adhesion factors. Sulfolipids can activate the immune system through the activation of DCs, and can thus be used as vaccine adjuvants. Manzo et al reported a novel sulfolipid named β-SQDG18 that induces the maturation of human DCs, which was used as an adjuvant to immunize mice against ovalbumin.[92] The immune response induced by ovalbumin /β-SQDG18 was similar to that induced by traditional adjuvants such as complete Freund's adjuvant or titerMax.

The immunomodulation process is mostly used during adjuvant therapy for tumor treatment and has recently attracted the attention of researchers. The immunomodulation process includes all the processes involved with the modification/ regulation of the immune response that can be studied to develop therapeutic processes. In the era of comprehensive tumor treatment, immune regulation is expected to play an increasingly important role.

Chronic Wound Healing

Chronic wound healing is a challenging clinical problem worldwide. Tumors, exposure to radiation, diabetes, trauma, and local pressure all contribute to the formation of chronic wounds.[93] More than 6.5 million people globally develop chronic wounds every year, costing the medical system over 25 billion USD per year.[29,94] Chronic wounds seriously affect the quality of life of patients, and the related systemic infection can be life threatening.

The process of wound healing is complex and dynamic and can be divided into four stages: hemostasis, inflammation, proliferation, and matrix remodeling.[95] Excessive inflammation, infection, hypoxia, and the development of numerous other factors are observed in these stages, which can potentially result in poor healing. However, these factors can be manipulated to potentially accelerate the process of wound healing. Some researchers have used microalgae to promote the healing of chronic wounds as they provide anti-inflammatory, oxygen-producing, and antibacterial functions.

Table 2 Summary of Research Conducted Using Microalgae for Cancer Therapy

No.	Microalgae	Therapeutic Mechanism	Cell Lines	Animal Model	Remarks	Reference
1	*Chlorella vulgaris*	Hypoxia alleviation Radiotherapy sensitization	4T1	Breast cancer	ROS and oxygen produced by chlorophyll have adjuvant effect	[67]
2	*Chlorella vulgaris*	Hypoxia alleviation Cascade radio-phototherapy	4T1	Breast cancer	Artificial mineral shells effectively deliver material to tumor sites	[68]
3	*Chlorella vulgaris*	Hypoxia alleviation Radiotherapy sensitization PDT effect	4T1	Breast cancer	RBCM-coated microalgae reduce system clearance	[45]
4	*Chlorella vulgaris*	Singlet oxygen Hypoxia alleviation	CT26	Colon cancer	Perfluorocarbon used to collect oxygen	[36]
5	*Spirulina platensis*	PDT effect	CAL-27, FaDu	None	Novel, safe, and effective natural photosensitizer for cancer PDT	[70]
6	*Chlorella pyrenoidosa*	Hypoxia alleviation PDT effect	4T1	Breast cancer	Produced oxygen to relieve hypoxia	[72]
7	Diatom	Drug delivery Singlet oxygen	HCT-116	None	Multifunctional diatoms achieve combined drug delivery with PDT	[74]
8	Diatom	Target delivery of chemotherapy drug	SH-SY5Y	Neuroblastoma	Autologous expression of target molecules	[76]
9	*Chlamydomonas reinhardtii*	Drug delivery	SK-RB-3	None	Microalgae coated with thin and soft chitosan	[77]
10	*Canadian marine microalgal*	Induce apoptotic cell death	A549, H460, MCF7, MNNG, PC3, DU145, BxPC3, N87	Prostate cancer	Antimetastatic activity tested for several cancer cells	[79]
11	*Galdieria sulphuraria*	None	A549	Lung cancer	Antitumor mechanism not explored in detail	[80]
12	*Chlorella sorokiniana*	Induce apoptosis by downregulating Bcl-2, XIAP	A549	Lung cancer	Mitochondrial-mediated apoptosis demonstrated	[39]
13	*Skeletonema marinoi*	1-monoarachidonoylglycerol induce selective cell death in cancer cells	U-937	None	Purified bioactive compounds from diatoms and mechanism proposed	[82]
14	*Red algae*	PDT induced cancer cell apoptosis	SGC-7901	None	PDT effect of R-phycoerythrin in gastric cancer cell line	[85]
15	*Chlorella, Scenedesmus, Chlamydomonas, Nannochloropsis, Tetraselmis, Polystichum braunii*	PDT effect generated by extract from several microalgae	A549, LNCap, MCF7, MDA-MB 435	None	PDT effect of various microalgae extracts on different tumor cells	[86]
16	*Chlorella*	β-carotene functioned as a natural physical cross-linker	4T1	Breast cancer	β-carotene combined albumin molecules with Ce6 to increase PDT efficiency	[83]

(*Continued*)

Table 2 (Continued).

No.	Microalgae	Therapeutic Mechanism	Cell Lines	Animal Model	Remarks	Reference
17	*Chlorella*	Astaxanthin functioned as a photosensitizer	MDA-MB-231	None	Astaxanthin functioned as a photosensitizer to help kill cancer cells	[84]

Abbreviations: ROS, reactive oxygen species; RBCM, red blood cell membrane; PDT, photodynamic therapy.

Oxygen Delivery by Microalgae

Oxygen plays an important role in all stages of wound healing.[96] Chronic wounds tend to transform into delayed-healing wounds when the partial pressure of oxygen becomes lower than the hypoxia threshold. Therefore, oxygen therapy, including topical oxygen therapy[97,98] and hyperbaric oxygen therapy,[2,99,100] have been used to promote wound healing under both basic and clinical research conditions. However, the application of these oxygen-based treatment methods is limited as they have low oxygen-delivery efficiency. The conditions of local hypoxia can be temporarily alleviated under conditions of topical oxygen therapy. The original hypoxic conditions are re-established within several minutes of treatment.[101] As hyperbaric oxygen therapy can only be performed in hospitals, it greatly limits the application of this method for treating chronic wounds. Therefore, some researchers have focused on maintaining the desired oxygen concentration for a prolonged time and improving the efficiency of oxygen transmission.

A patch was developed with a material similar to that used for wound dressings that contained gel beads coated with *Synechococcus elongatus (S. elongatus)* PCC7942 to promote chronic wound healing in patients with diabetes.[28] The aim was to develop an oxygen-therapy treatment that could be used in the absence of medical equipment. This novel patch can generate dissolved oxygen (≤240 μM) when illuminated with light. Oxygen produced (during in vitro experiments) by these novel materials efficiently modulated the hypoxic conditions of cells under high-glucose culture conditions and promoted neovascularization when irradiated with light. In addition, it promoted the survival of the skin flap in large-skin -defect animal models. The mechanism by which the new dressing promoted wound healing was related to the nonhealing wound being converted into an acute wound-healing phenotype following the process of gene expression detection. The research team designed a convenient oxygenic patch to promote the healing of chronic wounds, which is considered a feasible design idea (Figure 5). Hopfner designed a biological scaffold to relieve the hypoxic conditions using the tissue-engineering process.[102] The scaffold provides a platform for *C. reinhardtii* to survive and proliferate, and has a strong photosynthetic capacity to release oxygen in the presence of light.

In addition to oxygen, growth factors also play an important role in wound healing. Biological sutures that simultaneously deliver oxygen and recombinant growth factors locally to promote wound healing were demonstrated.[34] Using the recombinant protein expression and oxygen generation ability of *C. reinhardtii*, the suture promoted cell migration and proliferation in vitro. However, the ability of the material to promote wound healing in vivo needs to be further evaluated. Chavez et al further studied the ability of photosynthetic gene-based therapeutic materials to promote wound healing in vivo by performing a series of studies.[103,104] In a study from 2014 by the same group,[104] they synthesized a biomaterial based on *C. reinhardtii* to modulate the hypoxic conditions in the wound bed. The activation of the immune system and survival ability of microalgae were also evaluated. In 2016, they modified *C. reinhardtii* using genetic engineering technology to produce oxygen and recombinant protein,[103] using an idea similar to that of Centeno-Cerdas et al.[105] They studied the ability of the material to promote wound healing by conducting cell proliferation, migration, and tubule formation experiments in vitro, and also used zebrafish to study angiogenesis using the *C.-reinhardtii*-based hybrid material. In addition, fully immunocompetent mice were used to develop a full-skin-defect mouse model to evaluate the biocompatibility and wound healing promotion ability of this novel material. The genetically modified microalgae were seeded in a dermal scaffold, which could survive for more than seven days in the host to continuously generate oxygen and recombinant protein.

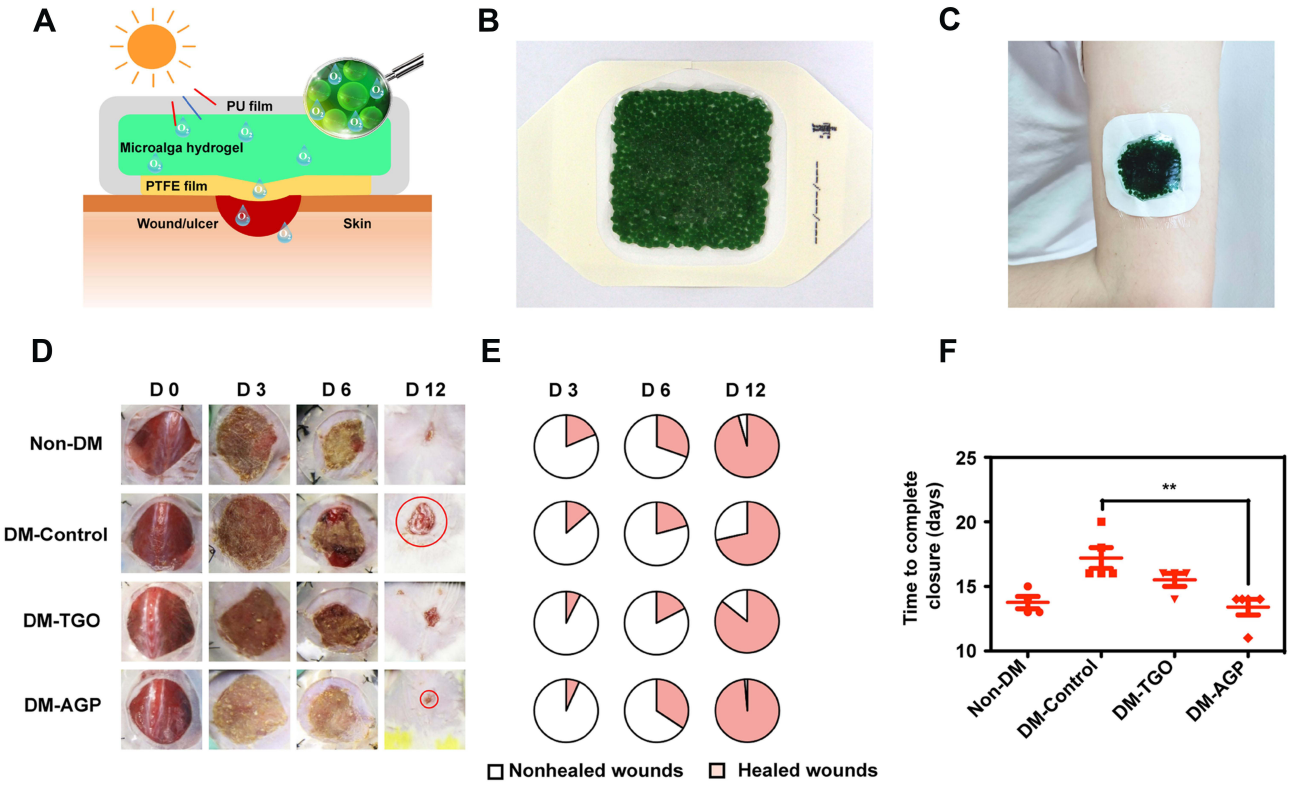

Figure 5 Microalgae-gel patch for chronic wound healing. (**A**) Schematic illustration of the microalgae-gel patch for promoting chronic wound healing via the process of light-triggered oxygen production. (**B**) Image of the microalgae-gel patch. (**C**) Application of microalgae-gel patches. (**D**) Images of the wound healing process in different groups. Red circles mark the wound areas in the diabetic mouse (DM)-control and DM-alga-gel patch (AGP) groups on day 12. (**E**) Schematic diagram of the wound healing proportion. (**F**) Summary of wound healing time. $^{**}P < 0.01$. The two groups are compared with one-way Analysis of Variance (ANOVA). From Chen H, Cheng Y, Tian J, et al. Dissolved oxygen from microalgae-gel patch promotes chronic wound healing in diabetes. Sci Adv. 2020;6(20):eaba4311. © The Authors, some rights reserved; exclusive licensee AAAS. Distributed under a CCBY-NC 4.0 license https://creativecommons.org/licenses/by/4.0/". Reprinted with permission from AAAS.[28]

The body of literature reveals that in situ oxygen delivery by algae to modulate local hypoxia is effective. With the introduction of transgenic technology, it has been observed that algae can synthesize biological factors while producing oxygen to promote wound healing. The chance of survival of microalgae and their oxygen maintenance ability at the wound bed can be effectively improved by combining the algae with suitable chemical materials. The reported results describe a platform for the application of microalgae in the field of chronic wound healing.

Antibacterial Ability of Microalgae

Wound infection significantly delays wound healing. Most chronic wounds are accompanied by bacterial infections resulting from a range of factors, including bacterial colonization and local infection. The presence of bacteria on the wound bed can result in a local continuous inflammatory reaction, and affect the extent of collagen deposition and the process of re-epithelialization, resulting in delayed wound healing.[106] Therefore, the strategy of using antibacterial biomaterials to promote wound healing has also been widely used to treat chronic wounds.[107,108]

An oxygen-producing biomaterial was developed by coating *S. platensis* with a natural polymer (carboxymethyl chitosan), which adhered to *Staphylococcus-aureus*-infected wounds, and produced oxygen to improve the antibacterial effect during wound healing.[109] When irradiated with a laser (650 nm), the novel material can release chlorophyll as a natural photosensitizer to generate bacteria-killing ROS. The rate of wound healing in the irradiated material group was higher than that observed for the control group. A recent report presented a bioactive hydrogel using microalgae to promote the process of healing infected wounds.[110] Unlike the previous study,[109] berberine was loaded onto the hybrid system to interfere with the quorum-sensing process and hinder the formation of bacterial biofilms. When irradiated by a laser, this system generates oxygen and ROS to achieve synergistic bactericidal and antivirulence activity. In addition to

alleviating the hypoxic conditions in the wound bed and promoting vascularization and cell migration, the produced oxygen reduces biofilm resistance and improves its sensitivity to antibiotics.

Antibacterial Activity of Algal Extracts

Algae and algae extracts are considered to be effective antibacterial agents. Although the pharmacological mechanism associated with some drugs is not clearly understood, it has been reported that some functional groups have effective antibacterial activity.

Polysaccharides are a major source of food and an important form of energy for most living organisms. The antibacterial mechanism associated with polysaccharides is potentially related to the binding of glycoprotein receptors on the surface of polysaccharides to the compounds in the bacterial cell wall, plasma membrane, and deoxyribonucleic acid (DNA). The formation of the receptor–ligand complex results in increased plasma membrane permeability, protein leakage, and bacterial DNA binding, which eventually results in bacterial death.[111,112] Kadam et al were the first to report that laminarin-rich extracts from *Ascophyllum nodosum* and *Laminaria hyperborea* have antimicrobial activity.[113] In addition, polysaccharides extracted from *Sargassum swartzii* effectively inhibit the growth of both Gram-positive and Gram-negative bacteria.[114]

A fatty acid is a carboxylic acid consisting of a hydrocarbon chain and a terminal carboxyl group. Fatty acids from microalgae usually contain 14 to 24 carbon atoms, and can be classified as saturated fatty acids, monounsaturated fatty acids, or polyunsaturated fatty acids. It has been reported that free algal fatty acids can be used to inhibit electron transport and normal oxidative phosphorylation processes occurring in the bacterial cell membrane.[111,115] A study of the antibacterial properties of extracts obtained from several types of microalgae showed that several compounds in the extracts, including phenols, terpenes, acetogenins, indoles, fatty acids, and volatile halogenated hydrocarbons, have antibacterial properties.[116]

Phlorotannins are usually found in brown algae and account for approximately 1–5% of the dry matter of brown algae. The antibacterial properties of phloroglucinol are attributed to the inhibition of the oxidative phosphorylation process and the ability of phloroglucinol to bind to bacterial proteins (such as enzymes) and cell membranes, which results in cell lysis. The OH group and phenolic aromatic rings in phlorotannins bind to the -NH group of bacterial protein, exploiting hydrogen bonding and hydrophobic interactions.[111] Wei et al extracted low-molecular-weight phlorotannins from *Sargassum* to test their killing ability using *Vibrio parahaemolyticus*.[117] The results revealed that the compound had a significantly inhibitory effect on *Vibrio parahaemolyticus*, and the minimum inhibitory concentration was 900 μg/mL. This compound could be used to develop antibiotics for use in various fields and to maintain food safety standards. In another study, a natural antibiotic was extracted from Arame (*Eisenia bicyclis*), which had high antibacterial activity against methicillin-resistant staphylococcus aureus, a minimum inhibitory concentration of 32 μg/mL.[118]

The oxygen production and ROS killing effect have not been observed for microalgal extracts. Hence, the bactericidal ability of these compounds is lower than that of microalgae. Although some researchers have reported the antibacterial activity of extract systems by conducting in vitro studies, few researchers have used the developed system for in vivo wound treatment. A combination of biomaterials can be used to address the existing challenges in the field and increase the efficiency of antibacterial therapies.

Anti-Inflammatory Effect of Microalgae

Inflammation plays an important role in the pathological and physiological healing of wounds. The hypoxic microenvironment of chronic wounds further promotes the progression of inflammation.[119] Reducing the inflammatory response of wounds is an effective treatment strategy.[120,121] Microalgae and their extracts contain a variety of bioactive components with anti-inflammatory and antioxidant properties.[122,123] For example, a microalgae-based wound dressing was developed to promote wound healing by exploiting its anti-inflammatory, antioxidant, and antimicrobial properties.[124] In the case of chronic wounds, a wound dressing that can fight inflammation, sterilize the wound, and minimize local hypoxia is ideal for promoting wound healing. Paradoxically, although ROS produced by algae under conditions of laser irradiation can kill bacteria, their presence is not conducive to wound healing.[125] Most researchers

have not conducted in-depth studies on this aspect of ROS. Microalgae can be combined with materials to form multifunctional biomaterials, which can be used to develop new treatment methods for the treatment of chronic wounds.

Ischemic Heart Disease

Cardiovascular disease (CVD) is a leading cause of human death worldwide. Approximately 17.9 million people die from CVD each year, accounting for 32% of global deaths.[126] Therefore, in the past few decades, researchers have been exploring treatment methods to alleviate conditions associated with myocardial ischemia and hypoxia and promote tissue regeneration and angiogenesis.[127,128] Researchers have studied several biological scaffolds for oxygen production, biological factors, and metabolic waste removal.[129] In recent years, algae have also been used to develop biomaterials that can be used for the treatment of ischemic heart disease as they exhibit photoautotrophy and genetic amenability. They are also candidates for the development of new treatment methods as they can be potentially used for the direct conversion of carbon dioxide to useful products.

Cohen et al used *S. elongatus* to fabricate an oxygen-producing biomaterial for the treatment of ischemic heart disease.[14] According to their hypothesis, during photosynthesis, *S. elongatus* can convert carbon dioxide into oxygen in the absence of blood and maintain the conditions for the survival of local cardiomyocytes. Treatment with the new materials (10 or 20 min after myocardial ischemia) could alleviate the hypoxic conditions in animal models, and the cardiac output increased by approximately 60% compared to the ischemic control. After 4 weeks of material application, the cardiac ejection fraction and end-systolic

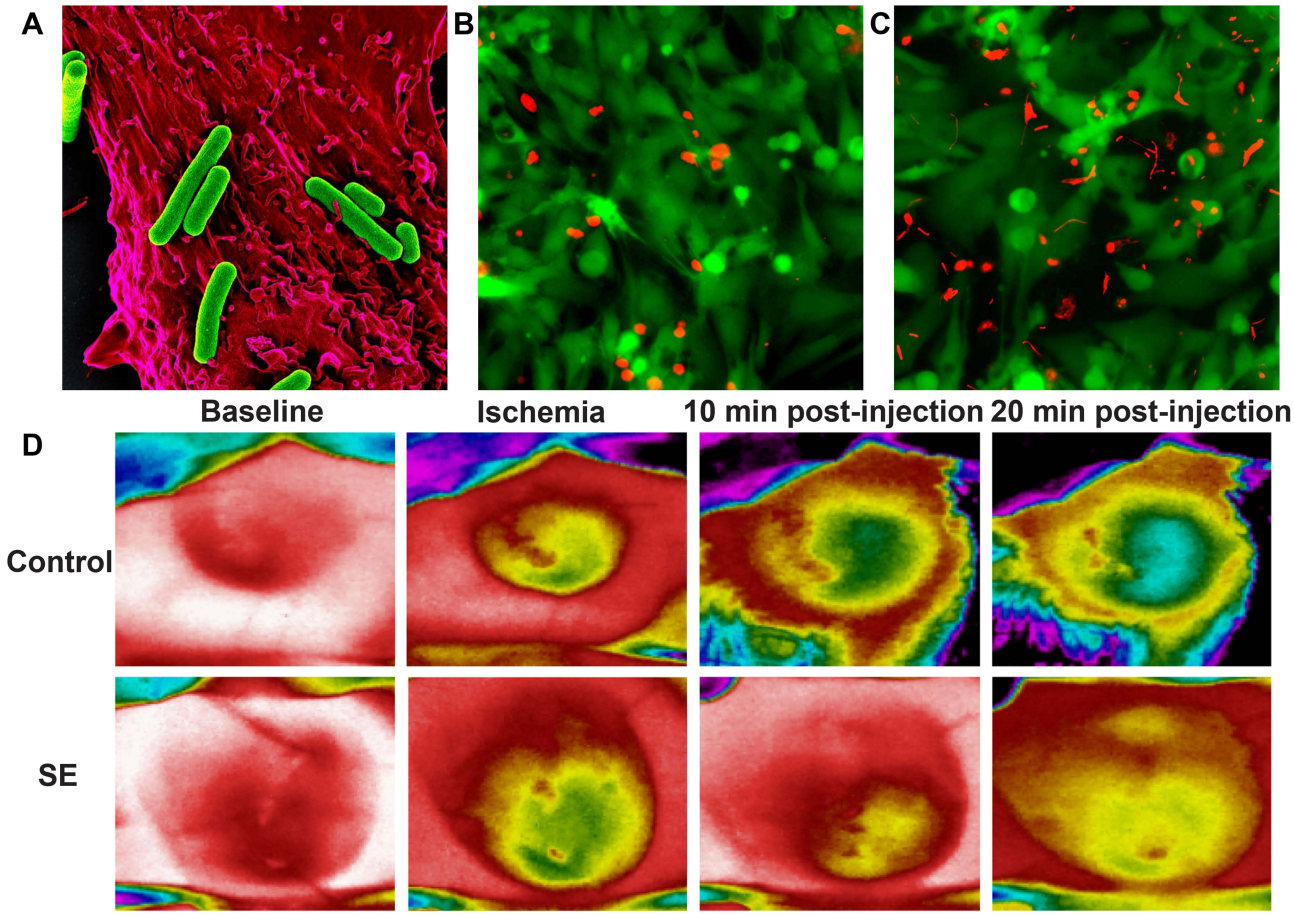

Figure 6 Application of microalgae in ischemic heart disease. (**A**) SEM image of cyanobacteria and cardiomyocytes. (**B** and **C**) Dead and live cell staining for cardiomyocytes. (**D**) Thermal images of rat hearts in different groups recorded before and after treatment. From Cohen JE, Goldstone AB, Paulsen MJ, et al. An innovative biologic system for photon-powered myocardium in the ischemic heart. Sci Adv.2017;3(6):e1603078. © The Authors, some rights reserved; exclusive licensee AAAS. Distributed under a CCBY-NC 4.0 license https://creativecommons.org/licenses/by/4.0/". Reprinted with permission from AAAS.[14]

volume significantly increased, as reflected by the results of the cardiac magnetic resonance analysis (Figure 6). Inspired by this work, Stapleton et al designed microgels containing alginate-cyanobacteria and calcium-ethylenediaminetetraacetic acid to produce oxygen using a T-junction microfluidic device.[130] The results of in vitro experiments revealed that microgel-coated cyanobacteria survived longer than those suspended in phosphate buffered saline. The novel hybrid materials significantly attenuated cardiomyocyte hypoxia and inhibited cardiomyocyte apoptosis. They conducted an in vivo experiment and used an ischemia–reperfusion mouse model to test the therapeutic effect of the new materials. After 4 weeks of cardiac ischemia–reperfusion, groups treated with microgel-coated cyanobacteria exhibited a significant level of improvement in the properties related to the ejection fraction. The echocardiography technique was used for analysis and the results were similar to those reported by Cohen et al[14]

Oxygen-producing microalgae can be used to develop a new strategy for treating ischemic heart disease. There are few reports on oxygen-producing microalgae in the literature, and the biological effects of these microalgae and their potential for clinical application need to be further studied. At present, rodents are primarily used to study the efficiency and properties of these materials. Large animal models should be used to further evaluate the functional effects and biosafety of the materials before they can be used in clinical settings. While tumors or wounds can be treated using non-invasive methods, invasive methods are used to treat the heart to activate the photosynthetic process in microalgae to produce oxygen. Thus, microalgae cannot be effectively used to impart first aid. Myocardial ischemia occurs via several complex pathological processes. The harm caused by blood flow occlusion cannot be addressed by solely addressing the problem of oxygen supply. The novel method of using microalgae to treat ischemic heart disease may provide a platform for the development of a new treatment strategy that can be used to treat ischemic heart disease.

The Future Prospectives

Microalgae that are present widely in nature are being successfully exploited to treat ODAD by exploiting their interesting characteristics. With the rapid development of biotechnology and chemical technology, microalgae-based biomaterials are being increasingly developed. In this paper, we reviewed the progress of microalgae-based biomaterials used for the treatment of ODAD. The evaluation of the literature revealed that the field of microalgal therapeutics is emerging.

Although microalgal materials have bright application prospects, some problems need to be addressed to realize the full potential of the materials. The immunogenicity of the materials, the viability of the materials in living bodies, the ability of effective accumulation at target sites, and methods to maintain the desired local oxygen concentrations should be studied to address current limitations and gaps in the knowledge. To address current limitations, some researchers have improved algae-based biomaterials to make them suitable for biological applications. For example, coating materials are used to help reduce the extent of immune response generated by microalgae. PFC could be used to maintain the effective oxygen concentration, and improve the targeting ability by molecular crosslinking to further improve the therapeutic effect of microalgae.

Future research should focus on improving the oxygen production efficiency of microalgae to further increase the local oxygen concentration at the wound site. The activation mode of microalgae should also be further studied. Microalgae are primarily used externally as internal organs cannot be irradiated. In addition to rodent-based in vivo research, research using large animal models should also be carried out to promote the clinical application of the materials.

Tumors, chronic wounds, and ischemic heart disease seriously threaten human life, and traditional treatment methods are limited. The use of microalgae-based biomaterials in the field of treating ODAD has proven effective, and this has opened up a new path for the treatment of ODAD. Microalgae-based biomaterials have good therapeutic potential, and may be used to develop new treatment strategies that can reform the landscape of ODAD therapeutics. Therefore, an in-depth understanding of microalgae-based biomaterial is required for developing more therapeutic biomaterials.

Abbreviations

APCs, antigen-presenting cells; Ce6, chlorin e6; CVD, cardiovascular disease; DCs, dendritic cells; DNA, deoxyribonucleic acid; HCC, hepatocellular carcinoma; MAG, 1-monoarachidonoylglycerol; ODAD, oxygen-deficiency-

aggravated diseases; PDT, photodynamic therapy; PFC, perfluorocarbon; RBCM, red blood cell membrane; ROS, reactive oxygen species; siRNA, small interfering ribonucleic acid.

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Disclosure

The authors declare no conflict of interest.

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