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REVIEW

Photosynthetic Bacteria: Light-Responsive Biomaterials for Anti-Tumor Photodynamic Therapy

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Abstract: Photodynamic therapy (PDT) is a promising noninvasive tumor treatment modality that relies on generating reactive oxygen species (ROS) and requires an adequate oxygen supply to the target tissue. However, hypoxia is a common feature of solid tumors and profoundly restricts the anti-tumor efficacy of PDT. In recent years, scholars have focused on exploring nanomaterial-based strategies for oxygen supplementation and integrating non-oxygen-consuming treatment approaches to overcome the hypoxic limitations of PDT. Some scholars have harnessed the photosynthetic oxygen production of cyanobacteria under light irradiation to overcome tumor hypoxia and engineered them as carriers of photosensitizers instead of inorganic nanomaterials, resulting in photosynthetic bacteria (PSB) attracting significant attention. Recent studies have shown that light-triggered PSB can exhibit additional properties, such as photosynthetic hydrogen production, ROS generation, and photothermal conversion, facilitating their use as promising light-responsive biomaterials for enhancing the anti-tumor efficacy of PDT. Therefore, understanding PSB can provide new insights and ideas for future research. This review mainly introduces the characteristics of PSB and recent research on light-triggered PSB in anti-tumor PDT to enrich our knowledge in this area. Finally, the challenges and prospects of using PSB to enhance the anti-tumor efficacy of PDT were also discussed.

Keywords: photosynthetic bacteria, PDT, hypoxia, cyanobacteria, purple bacteria, PTT

Introduction

Photodynamic therapy (PDT) is a non-invasive treatment modality based on the cytotoxic effects of reactive oxygen species (ROS). Its mechanism for ROS generation involves transferring energy from light to certain chemicals known as photosensitizers that can undergo photochemical reactions.[1] Many scholars believe that PDT is a promising approach for tumor treatment due to its unique advantages. First, the essential components of PDT are photosensitizers, light, and oxygen (O_2). These components are not individually toxic unless combined to trigger photochemical reactions that damage the target tissue or cells.[2] Second, photosensitizers accumulate in tumor tissues, which helps confine the treatment area and minimizes damage to surrounding healthy tissues. When exposed to localized light, the photocytotoxic effects of photosensitizers directly damage the organelles of tumor cells (eg, mitochondria, lysosomes, endoplasmic reticulum, and Golgi apparatus), resulting in tumor cell death. PDT also destroys vascular structures and blocks blood vessels in tumor tissues, resulting in significant anti-tumor effects. In addition, PDT can activate the immune system to inhibit tumor metastasis and recurrence.[3] Third, advanced endoscopic and fiberoptic light delivery techniques allow PDT to treat hard-to-reach hollow surgical structures (eg, the digestive tract, bronchus, and body cavity). PDT can also be employed for deep-seated and large tumors (>1 cm in size) under the guidance of computed tomography (CT) or ultrasound imaging.[4] Fourth, PDT can be repeated as necessary, and importantly, tumor cells do not develop drug resistance during repeated PDT. It is well known that the production levels of ROS are crucial for PDT efficacy, which depends on sufficient O_2 levels in the target tissues. However, O_2 concentration in solid tumor tissues is only 7–28 mmHg

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(1–4%), compared to 40–60 mmHg (5–8%) in normal tissues.[5,6] The primary reasons solid tumors often experience hypoxia are uncontrolled cell proliferation and abnormal blood vessel formation, which lead to low O_2 levels and inadequate supply and diffusion of O_2. Hypoxia in tumor tissues significantly limits the effectiveness of PDT, and the oxygen-consuming nature of PDT further exacerbates the hypoxic condition, promoting the proliferation and metastasis of residual tumor cells.[7] Although PDT has received clinical approval from the USA Food and Drug Administration (FDA), its clinical application in tumor treatment has been sluggish over the past few decades, and its effectiveness has not received full affirmation and acceptance.[8,9] Scholars initially attempted to enhance blood oxygen content and improve tumor blood circulation using hyperbaric oxygen therapy (HBOT), anticoagulant drugs, and warm water baths.[10–14] However, these methods have achieved only limited success due to incomplete vascular systems in tumor tissues and the presence of hypoxic areas distant from blood vessels.[15] As a result, scholars are actively seeking efficient and practical methods to increase O2 levels in tumor tissues or integrate non-oxygen-consuming treatments to overcome the challenges posed by hypoxia in PDT.

Currently, most of the photosensitizers approved for clinical anti-tumor PDT are second-generation compounds, such as Porfimer sodium salt (Photofrin®), 5-aminolevulinic acid (ALA, Levulan®), Methyl aminolevulinate(MAL, Metvix®), and Tetrasulfonic aluminum phthalocyanine (APkS4, Photosens®), etc. These photosensitizers have improved biochemical properties compared to the first-generation (hematoporphyrin derivatives, HpD).[16] However, they still face inherent limitations, such as poor water solubility and stability, shallow penetration depth of excitation light, photodamage, and poor tumor targeting. To overcome these limitations, scholars are developing third-generation photosensitizers by combining the second-generation compounds with specific components (eg, antibodies, carbohydrates, peptides, and amino acids) or encapsulating them in carrier systems.[17,18] For instance, combining photosensitizers with nanomaterials (NPs) can significantly enhance the tumor-targeting ability. Scholars have realized that NPs can also serve as delivery systems for O_2/catalytic agents to effectively enhance O_2 levels in hypoxic areas of tumor tissues or integrate non-oxygen -consuming treatments to improve the anti-tumor efficiency of PDT. To address these aims, scholars often develop NP-based carrier systems that involve complex design and modification,[19] which can increase research duration and funding requirements. Recently, some researchers have utilized photosynthesis by chlorophyll-containing microorganisms to generate O_2 within tumor tissues to overcome tumor hypoxia, suggesting that these photosynthetic microorganisms can serve as light-triggered oxygen-supplied systems.[20] Among these, photosynthetic bacteria (PSB), a specific group of prokaryotic autotrophic organisms with an original photo-energy synthesis system, have attracted attention in alleviating tissue hypoxia due to their unique properties in photosynthetic oxygen production. In addition to rescuing ischemic myocardium and chronic wounds, PSB have been employed as a light-triggered oxygen supplier to enhance the efficacy of anti-tumor PDT. Notably, light-triggered PSB also exhibit the properties of hydrogen production, ROS generation, and photothermal conversion, indicating that they can provide additional therapeutic benefits in tumor tissue, such as hydrogen therapy, photosensitizing effect, and photothermal therapy (PTT). PSB can serve as light-responsive biomaterials in anti-tumor PDT for increasing O_2 levels in tumor tissues and integrating non-oxygen-consuming treatments. Compared to inorganic NPs, PSB have several advantages, such as easy modification, high biocompatibility, low toxicity, convenient cultivation, and rapid reproduction.[21] Therefore, gaining a deeper understanding of PSB characteristics is essential for utilizing them better in anti-tumor PDT in the future. Therefore, gaining a deeper understanding of PSB characteristics is essential for utilizing them better in anti-tumor PDT in the future. This review will mainly introduce the characteristics of PSB and recent research on light-triggered PSB in anti-tumor PDT, and the challenges and prospects of PSB as light-responsive biomaterials for anti-tumor PDT also will be discussed.

NPs and Anti-Tumor PDT

In recent years, scholars have developed various NP-based strategies for oxygen supplementation and have integrated non-oxygen-consuming treatment approaches to overcome the hypoxic limitations of PDT. Hemoglobin (Hb), an O_2 carrier, can be encapsulated within NPs for transport to tumor tissues. In addition, NPs made from perfluorocarbons or metal-organic frameworks and other NPs encapsulated within red blood cell membranes can efficiently deliver O_2 to tumor tissues.[7,22,23] NPs can also carry catalytic agents (eg, catalase, manganese dioxide, and nano-enzymes) to decompose endogenous hydrogen peroxide (H_2O_2) into O_2 and water (H_2O) or carry carbon nitride (C3N4) to

decompose water to produce O_2 and hydrogen (H_2), leading to O_2 generation within tumor tissues, hydrogen-induced redox stress, and subsequent cell damage.[15] Specific photosensitizers (eg, indocyanine green, ICG) and nanomaterials (eg, Gold NPs) can convert light photon energy into heat under near-infrared (NIR) laser irradiation, allowing the combination of PDT and photothermal therapy (PTT) in tumor treatment. PTT does not require O_2, while its thermal effect can destroy tumor tissue and improve blood circulation to enhance O_2 levels in hypoxic tumor tissues.[24,25] As a result, the anti-tumor efficacy of synergistic PDT/PTT is better than that of PDT or PTT alone.[26] Currently, various types of NPs have been designed as drug-delivery systems for transporting photosensitizers and other therapeutic agents to tumor tissues. This strategy can reverse hypoxic conditions and enable the combination of PDT with other therapeutic methods, such as PTT, gas therapy, chemotherapy, and immunotherapy. The design and development of NPs are based on the enhanced permeability and retention (EPR) effect in tumor tissues. However, NPs will face the influence of various factors in vivo, such as tumor heterogeneity, poor blood perfusion, abnormal vascular endothelial function, and their physicochemical properties. There is a controversial debate regarding the effectiveness of NPs in improving drug delivery to tumors and enhancing therapeutic efficacy in clinical practice.[27–30] To increase tumor accumulation and retention, NPs require more complex design and modification with tumor-targeting ligands,[31] which may affect their size, physicochemical properties, synthesis yield, biosafety, biodegradability, immunogenicity, and clinical translation. In contrast, the properties of PSB facilitate the integration of oxygen supplementation and multimodal treatments without the need for complex design and modifications. Therefore, the first step is to understand the characteristics of PSB.

Characteristics of PSB

PSB are Gram-negative facultative anaerobic bacteria that cannot form spores. Along with the general characteristics of facultative anaerobes, one of their most distinctive features is their ability to use light for photosynthesis. PSB exhibits two main types of photosynthesis based on different molecular mechanisms: oxygenic and anoxygenic.[32] Cyanobacteria, namely blue-green algae, are oxygenic PSB as they perform oxygenic photosynthesis. The dominant groups of anoxygenic PSB include purple phototrophic bacteria (PPSB, sulfur, and non-sulfur phototrophs) and green sulfur bacteria (GSB) that perform anoxygenic photosynthesis. In addition, PSB possesses other unique properties worth noting.

Hypoxia Chemotaxis

PSB are Gram-negative facultative anaerobes that are sensitive to the O_2 content in the surrounding environment and tend to move toward the hypoxic zone to survive in anaerobic conditions.[33] Tumor tissues have unique hypoxic microenvironments that attract them to target and move toward the hypoxic regions to colonize.

Phototaxis

PSB have photoreceptors that enable them to perceive specific light stimulation (eg, direction, intensity, and wavelength), allowing them to move towards or away from the light sources. This behavior is known as phototaxis, which helps PSB capture the appropriate light for photosynthesis or escape harmful light sources. Flagellated anoxygenic PSB (eg, PPSB) have flagella, and light signals can drive the flagellar motor to start flagellar rotation and forward the cell.[34] PPSB exhibit positive phototaxis in response to far-red light but moves away from visible light.[35] In contrast, cyanobacteria lack flagella but have type IV pili. Their IV pili complexes receive signals from photoreceptors to enable particular pili to move towards or flee from light sources.[36–38] In addition, a single spherical cyanobacteria cell can act as a microlens to focus incoming light onto the membrane at the back of the cell, facilitating direct and accurate sensing of the light direction.[39] Cyanobacteria exhibit positive phototaxis in response to red and green light while escaping from ultraviolet (UV), blue, and high-intensity light.[37]

Photosynthesis and Photosynthetic Oxygen Production

Photosynthesis involves the conversion of solar energy into chemical energy, which is essential for the growth and metabolic processes of PSB. Although the molecular mechanisms of photosynthesis in oxygenic and anoxygenic PSB differ, the fundamental principles of energy transduction are similar. Cyanobacteria are the only PSB with the ability to produce O_2 through photosynthesis by their two types of reaction centers (RC): photosystem I (PSI) and photosystem II

(PSII).[40,41] Both PSI and PSII are intrinsic protein complexes located in the thylakoid membranes. They consist of a chlorophyll-rich core complex and a chlorophyll-binding peripheral antenna system.[42–44] The peripheral antenna system, known as light-harvesting complex I (LHCI) in PSI and light-harvesting complex II (LHCII) in PSII, is responsible for absorbing the external light energy.[45] In addition to LHCII, the phycobilisome (PBS) attaches to the surface as an extramembrane light-harvesting antenna. PBS can absorb light between 450 and 650 nm, and even beyond 700 nm in some cases. PBS complements the absorption spectrum of chlorophylls in PSII, leading to more efficient capture of sunlight and energy transfer to the core complex of PSII.[46] PSII is a water-oxidizing enzyme that can utilize harvested energy to perform photocatalytic water oxidation to produce O_2 in the catalytic core oxygen-evolving complex (OEC), which consists of a tetramanganese-calcium cluster Mn_4O_5Ca.[47] Oxygenic photosynthesis requires synergy between PSI and PSII, which provides the properties of photosynthetic oxygen production under light irradiation in cyanobacteria (see Figure 1).

In contrast, anoxygenic PSB have only a single type of RC located within the photosynthetic membrane for conducting anoxygenic photosynthesis. For example, GSB only have type I RC (PSI), while PPSB only have type II RC (PSII-like photosystem).[48,49] Anoxygenic PSB also have light-harvesting complexes (LHC), known as LHI and LHII in PPSB or chlorosomes in GSB.[50,51] LH1 surrounds the RC to form the core of the photosynthetic complex, while LH2 spreads in the periphery of the RC in most PPSB. In addition to chlorosomes, GSB have another antenna complex called the Fenna-Matthews-Olson (FMO) protein.[52] Notably, anoxygenic PSB possess bacteriochlorophylls (BChls) instead of chlorophyll. As the major chromophores of LHC and RC, BChls have light-energy conversion functions. However, the maximum absorbance peak of BChls is located in the near-infrared region,[53] which limits the photosynthetic efficiency. Carotenoids act as accessory pigments to absorb the blue-green light and transfer energy to the BChls for expanding the captured light wavelength range, which is beneficial for more light energy transfer from the LHC to the RC.[54,55] The RC of anoxygenic PSB can convert sunlight into chemical energy but cannot oxidize water. Therefore, anoxygenic PSB do not have the properties of photosynthetic oxygen production.[49]

Photosynthetic Hydrogen Production

Most oxygenic and anoxygenic PSB contain nitrogenase or hydrogenase, which enables them to produce H_2 through different physiological mechanisms. Cyanobacteria produce H_2 through water biophotolysis, which requires the participation of PSI and PSII[56] (see Figure 1). In addition to O_2, PSII generates hydrogen protons (H+) and electrons through

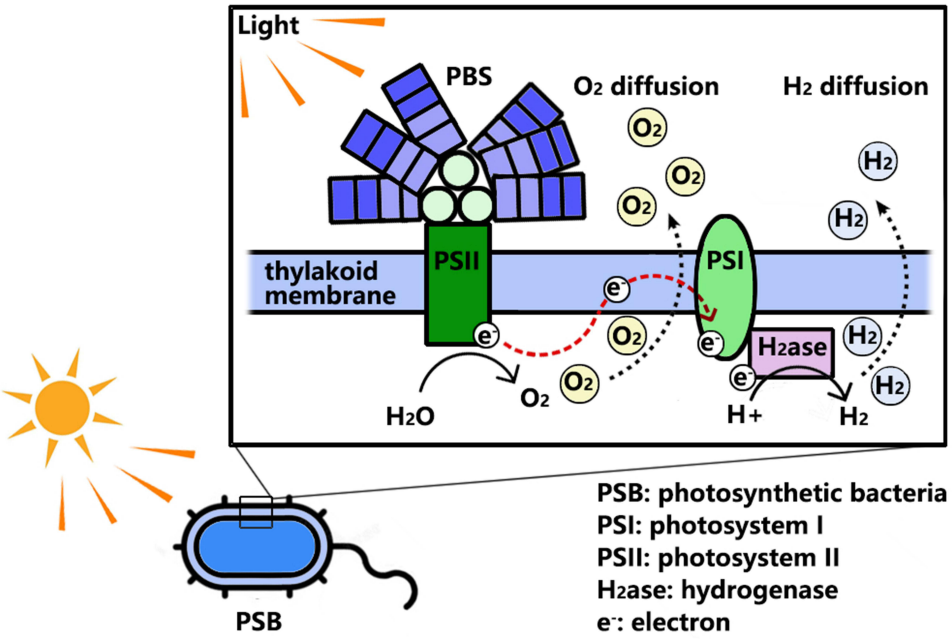

Figure 1 Schematic representation of photosynthetic oxygen production and hydrogen production in PSB.

photocatalytic water oxidation during photosynthesis. In non-nitrogen-fixing cyanobacteria, electrons are transferred to bidirectional [Ni, Fe]-hydrogenase to combine with hydrogen protons to produce H_2. In contrast, some electrons are transferred to nitrogenases for nitrogen fixation in nitrogen-fixing cyanobacteria. Nitrogenase-obtaining electrons consume the ATP, generated by photophosphorylation, to reduce hydrogen protons to H_2.[57,58] Anoxygenic PSB produce H_2 through photofermentation, mainly involving nitrogenase. Nitrogenase utilizes H+ and electrons derived from organic substrates to produce H_2 under hypoxic conditions. LHC capture and transfer light energy to the RC, generating high-energy electrons. Electron transfer establishes a proton gradient, resulting in ATP synthesis through cyclic phosphorylation. Subsequently, nitrogenase consumes ATP and electrons to reduce protons to H_2.[56,59,60] Another hydrogenase, [Ni Fe]-hydrogenase, can absorb the H_2 produced during nitrogen fixation, which may influence the overall hydrogen yields of nitrogenase to a certain extent.[61] In short, nitrogenase- and hydrogenase-containing PSB can produce photosynthetic hydrogen when exposed to light. Notably, oxygen can inhibit the activities of both hydrogenases and nitrogenases. Oxygenic photosynthesis in cyanobacteria may limit their H_2 production, but this limitation does not apply to anoxygenic PSB.

ROS Generation

During photosynthesis, the conversion of light energy can also lead to the formation of ROS. When the light absorbed by chlorophylls or BChls exceeds the amount required for photosynthesis, the generation of ROS significantly increases. Both PSI and PSII are involved in the generation of ROS.[62] PSI is the primary site for ROS production because the electron flow from PSII to PSI can be terminated and accumulated on the stromal side of PSI, leading to O_2 reduction to a superoxide radical ($O_2\bullet^-$). In contrast, PSII produces ROS under the following conditions: a) when the transfer of light energy from the PSII antenna complex to the RC is limited, chlorophylls or BChls can act as photosynthesizers, absorbing the energy and transitioning from the ground state to the triplet state. The triplet chlorophyll transfers the absorbed energy to surrounding molecular oxygen, forming singlet oxygen generation ($^1O_2$). b) when the electron transport chain between the photosystems is inhibited, electrons can leak from the electron acceptor side of PSII to molecular oxygen, forming $O_2\bullet^-$. Additionally, incomplete oxidation of water on the electron donor side of PSII can cause the production of hydrogen peroxide (H_2O_2). $O_2\bullet^-$ and H_2O_2 can be further reduced to the harmful hydroxyl radical (HO•) through a series of reactions. However, carotenoids present in PSB can quench excited BChls and $^1O_2$, preventing the photodamage to cells, which can affect the ROS generation.[63–65]

Photothermal Conversion

Excessive absorbed light energy during photosynthesis can damage the photosystems in PSB. However, PSB have a photoprotective mechanism to dissipate energy as heat through nonphotochemical quenching (NPQ).[66] For example, cyanobacterial orange carotenoid protein (OCP) dissipates excess absorbed energy from PSB as heat.[67] Carotenoids also play a role by quenching excited BChls and converting the excess energy into heat.[64] Zhao et al were the first to demonstrate that PSB could rapidly reach temperatures of 60 °C under NIR light irradiation. Even when inactivated at 65 °C, these bacteria maintained the same photothermal conversion efficiency.[68] More recently, scholars have found the photothermal conversion properties of cyanobacterium Synechococcus elongatus (S. elongatus), purple photosynthetic bacterium Rhodobacter johrii (R. johrii), Rhodopseudomonas palustris (R. palustris), and Blastochloris viridis (B. viridis). The photothermal conversion efficiency of these PSB is even higher than that of gold-based particles and metal selenide.[69–73] These findings confirmed the photoprotective mechanism endows PSB with photothermal conversion properties.

Application of PSB in Anti-Tumor PDT

In recent years, the application of bacteria in anti-tumor therapy has gained significant attention as a key area of research. Their unique properties and functions offer new perspectives on seeking potential biomaterials in this field. In addition to their inherent properties of PSB, including hypoxia chemotaxis, phototaxis, and light-triggered biological properties, PSB can be modified with special polymers, drugs, and NPs on their surfaces through various physical and chemical methods,

which has attracted considerable interest. Some PSB have been employed in research on anti-tumor PDT as hypoxia-targeted carriers for supplying O_2 and integrating multimodal treatments.[74,75]

Cyanobacteria as O_2 Suppliers and Photosensitizer Carriers

Most existing research findings are obtained from studies on cyanobacteria (see Table 1). Given their properties of hypoxia chemotaxis and photosynthesis, scholars initially considered using cyanobacteria as O_2 suppliers and carriers of photosensitizer to improve the effectiveness of anti-tumor PDT. Shi et al developed a hybrid combining cyanobacteria with the photosensitizer chlorine6 (Ce6) and they named it ceCyan. To form ceCyan, the modified Ce6 with dual-amide-terminated polyethylene glycol (NH_2-PEG-NH_2) polymers was incubated with cyanobacteria (Synechococcus elongatus PCC 7942, S.7942) (see Figure 2A). The ceCyan can deliver Ce6 to tumor cells while supplying O_2 under 660 nm laser light irradiation, which enhances the inhibiting effects of Ce6-induced PDT on tumor cell activity. The mice that received an intravenous injection of ceCyan had only tolerable inflammation, indicating that ceCyan has good biocompatibility. In addition to ceCyan, they also combined protoporphyrin (Ppix) with cyanobacteria to form Ppix-hybridized cyanobacterial cells (Ppix-Cyan), demonstrating that cyanobacteria can be employed to carry other negatively charged chlorin-based photosensitizers, thereby expanding the range of possible combinations between cyanobacteria and photosensitizer.[76]

Choosing an ideal photosensitizer for PDT requires considering the wavelength of its excitation light source. Most conventional photosensitizers can often be activated by short-wavelength visible light (400–700 nm) with a low penetration depth within tissues.[85] Some scholars chose rare-earth ion-doped upconversion nanoparticles (UCNPs) to address this limitation. Some scholars chose rare-earth ion-doped upconversion nanoparticles (UCNPs) to address this limitation. Shi et al developed a hybrid combining cyanobacteria (S.7942), photosensitizer Rose Bengal (RB), and UCNPs, and it is named UR-Cyan. The negatively charged cyanobacterial cells were incubated with the positively charged RB-loaded URNPs at room temperature (RT) for 1 hour. RB-loaded URNPs were combined with S.7942 to form UR-Cyan cells by electrostatic interactions. The UCNPs consist of a NaYF4: Yb3+, Tm3+, Er3+ @ NaYF4: Yb3+ core-shell structure that absorbs NIR light (980 nm) and converts it into visible light, including green (510–570 nm) and red light (630–680 nm, 680–710 nm). These visible lights are suitable for active S.7942 and RB. As a result, the UR-Cyan cells can provide combined effects of photosynthetic oxygenation and photosensitization effects, eradicating tumor cells in tumor-bearing nude mice when exposed to NIR laser irradiation[79](see Figure 2B).

Besides the wavelength of the excitation light source, a reasonable lighting control strategy is another important consideration. Zhang et al developed an injectable red blood cell membrane membrane-doped hydrogel system containing NaYF4: Yb/Er UCNPs, RB, and S.7942, namely UCNPs/S7942/RB-RHY (see Figure 3A). They used a 980 nm laser to irradiate UCNPs/S7942/RB-RHY to produce visible light for RB-induced PDT in the tumor-bearing mice. Before this step, the mice were treated with 640 nm laser irradiation three times to alleviate hypoxia in tumor tissue through the photosynthetic oxygenation provided by UCNPs/S7942/RB-RHY. The results indicated that this lighting control strategy led to a more efficient PDT treatment. Interestingly, the generated ROS also contributed to the simultaneous destruction of cyanobacteria within the tumor tissue after PDT.[80] Similarly, Sun et al developed a sodium alginate gel containing photosensitizer ICG loading mesoporous silica nanoparticles (MSN-ICG) and cyanobacteria (Synechococcus elongatus UTEX 2973, S. 2973), namely ALG-MI-S2973. After an intratumoral injection of ALG-MI-S2973, the tumor-bearing mice were treated with 640 nm laser irradiation for 3 days and then treated with 808 nm laser on the 4th day. They suggested that this lighting control strategy enhances O_2 generation in cyanobacteria under 640 nm laser irradiation, and tumor cells and cyanobacteria can be eliminated by PDT-induced ROS under 808 nm laser irradiation, ensuring therapeutic effect and biosafety[83](see Figure 3B). Chang et al reported a novel lighting control strategy based on persistent luminescence material. They developed a CaAl2O4:Eu, Nd blue persistent luminescence material (CAO PLM) that acted as a light source for activating cyanobacteria/photosensitizer hybrids in vivo. Briefly, they covalently linked the photosensitizer verteporfin (Vp) with the -NH2 groups of the outer membrane of S.7942 to form cyanobacteria-verteporfin (Cb-Vp). Subsequently, Cb-Vp was mixed with PEGylated CAP PLM (CaAl2O4:Eu, Nd@PEG) to assemble an exogenous irradiation-free PSB-based platform (CAP + Cb-Vp). They found that CAP + Cb-Vp generated blue persistent luminescence to stimulate photosynthetic oxygenation and photosensitization effects of Cb-Vp, leading to synergistic tumor killing in vivo after pre-excitation by UV light in vitro. Notably, after administering CAP + Cb-Vp,

Table 1 Literature Examples of Cyanobacteria in Anti-Cancer PDT

Strains	Combined component (s)	Nanoplatforms	Light source wavelength	Tumor type	Route of administration	Main function of cyanobacteria	Mode of cancer therapies	Reference
Synechococcus elongatus PCC 7942	Chlorine6	ceCyan	660 nm	Murine mammary tumor	Intratumoral injection	Oxygen supply	Photodynamic therapy	[76]
Synechococcus elongatus PCC 7942	Black phosphorus nanosheets	Cyan@BPNSs	660 nm	Murine mammary tumor	Intratumoral injection	Oxygen supply	Photodynamic therapy	[77]
Synechococcus elongatus PCC 7942	Indocyanine green, Human serum albumin	S/HSA/ICG	660 nm	Murine mammary tumor	Intravenous injection	Oxygen supply	Photodynamic therapy	[78]
Synechococcus elongatus PCC 7942	Rose Bengal, Upconversion nanoparticles	UR-Cyan cells	980 nm	Murine mammary tumor	Intravenous injection	Oxygen supply	Photodynamic therapy	[79]
Synechococcus elongatus PCC 7942	Rose Bengal, Upconversion nanoparticles	UCNPs/S7942/ RB-RHY	640 nm, 980 nm	Murine mammary tumor	Intratumoral injection	Oxygen supply	Photodynamic therapy	[80]
Synechococcus elongatus PCC 7942	Verteporfin, Persistent luminescence materials	CAP+Cb-Vp	UV light, White light	Murine mammary tumor	Intratumoral injection	Oxygen supply	Photodynamic therapy	[81]
Synechococcus elongatus PCC 7942	Chlorine6, Au nanoparticles	Bac@Au-Ce6	660 nm, 808 nm	Murine mammary tumor	Intravenous injection	Oxygen supply	Photodynamic therapy, Photothermal therapy	[82]
Synechococcus elongatus PCC 7942	_	_	660 nm	Murine mammary tumor	Intratumoral injection	Generate heat	Photothermal therapy	[73]
Synechococcus elongatus UTEX 2973	Indocyanine green, Mesoporous silica nanoparticles	ALG-MI-S2973	640 nm, 808 nm	Murine mammary tumor	Intratumoral injection	Oxygen supply	Photodynamic therapy	[83]
Spirulina platensis	Doxorubicin	SpiD	650 nm	Human osteosarcoma	Intratumoral injection	Oxygen supply, Generate ROS	Photodynamic therapy, Chemotherapy	[84]

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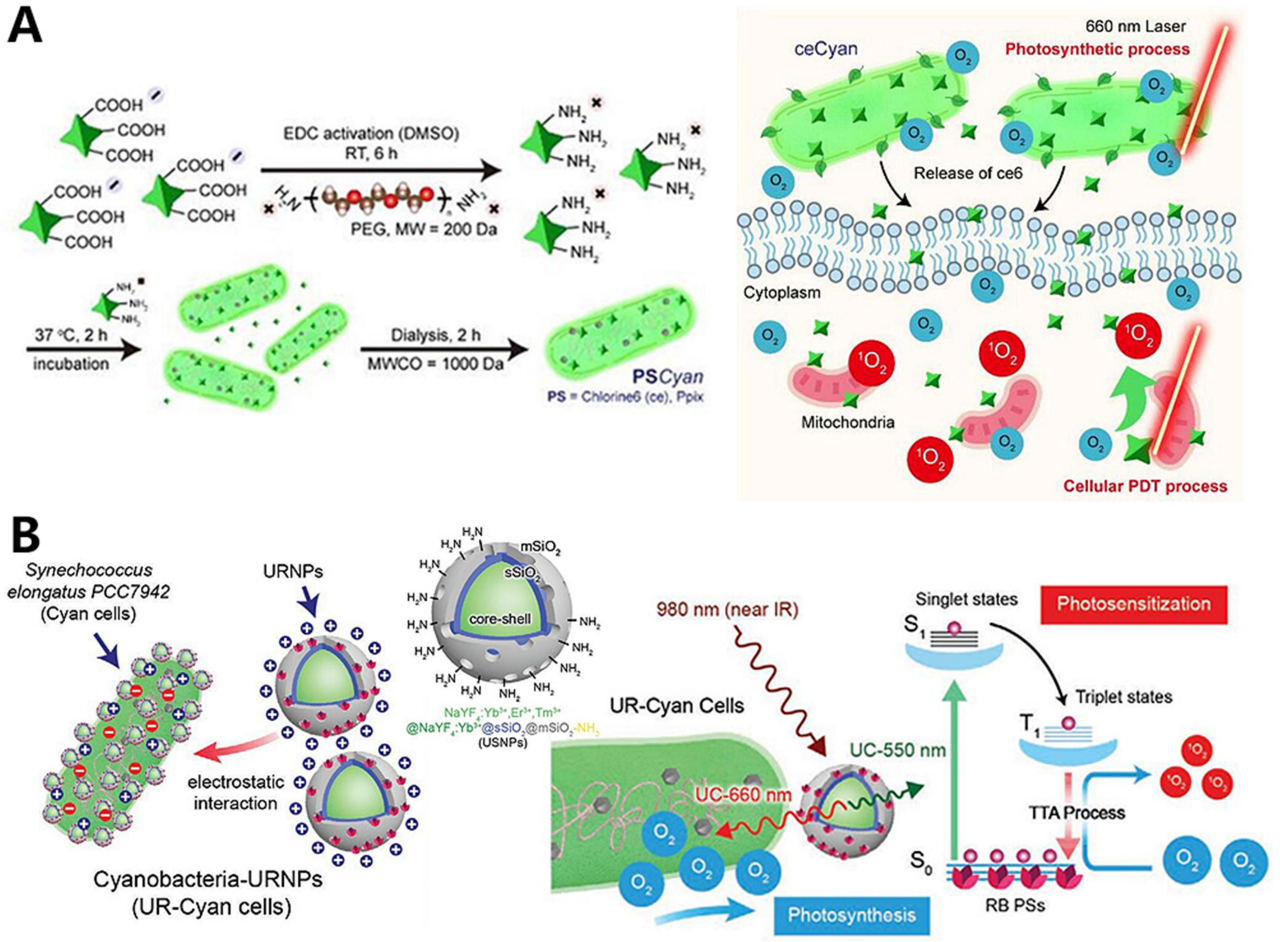

Figure 2 (**A**) Schematic illustration of the synthesis and and mechanism of ceCyan. Reproduced from Huo M, Wang L, Zhang L, Wei C, Chen Y et al. Photosynthetic Tumor Oxygenation by Photosensitizer-Containing Cyanobacteria for Enhanced Photodynamic Therapy. *Angew Chem Int Ed Engl*. 2020; 59: 1906–1913. © 2020 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.[76] (**B**) Schematic illustration of the synthesis and and mechanism of UR-Cyan cells. Reproduced from Huo M, Liu P, Zhang L, Wei C, Wang L et al. Upconversion Nanoparticles Hybridized Cyanobacterial Cells for Near-Infrared Mediated Photosynthesis and Enhanced Photodynamic Therapy. *Advanced Functional Materials*. 2021; 31: 2,010,196. © 2021 Wiley-VCH GmbH.[79]

intermittent supplementation with S.7942 and re-irradiation with white light from an LED lamp in subcutaneous tumor tissues can increase blue persistent emission and enhance O_2 levels, thereby improving PDT therapeutic outcomes.[81]

Cyanobacteria Integrate Multimodal Treatments

Some scholars have also explored the synergistic anti-tumor effects of cyanobacteria/photosensitizer hybrid-induced PDT combined with other therapeutic methods, such as PTT. Yin et al incorporated the photothermal agent Au NPs into the combination of S. 7942 and Ce6 to form a cyanobacteria/photosensitizer/photothermal agent hybrid, and they named Bac@Au-Ce6. They observed that S. 7942 facilitated the accumulation of Au-Ce6 in tumor tissues due to its tumor-targeting ability. Under 660 nm laser irradiation, Bac@Au-Ce6 continuously generated O_2 and ROS. Subsequently, Bac@Au-Ce6 generated heat under 808 nm laser irradiation. They found necrosis and apoptosis in the treated tumor tissue, indicating that Bac@Au-Ce6 can simultaneously trigger photosynthetic oxygenation, PDT, and PTT in tumor tissues using different laser irradiation[82](see Figure 4A). Qi et al developed a cyanobacteria hybridized with inorganic two-dimensional black phosphorus nanosheets (BPNSs) using amide chemistry-enabled bioconjugation methodology, namely Cyan@BPNSs. Under irradiation with a 660 nm laser, the BPNSs generated singlet oxygen via photosensitization, while the cyanobacteria produced O_2 in the tumor tissue[77](see Figure 4B). Notably, BPNSs can convert NIR light

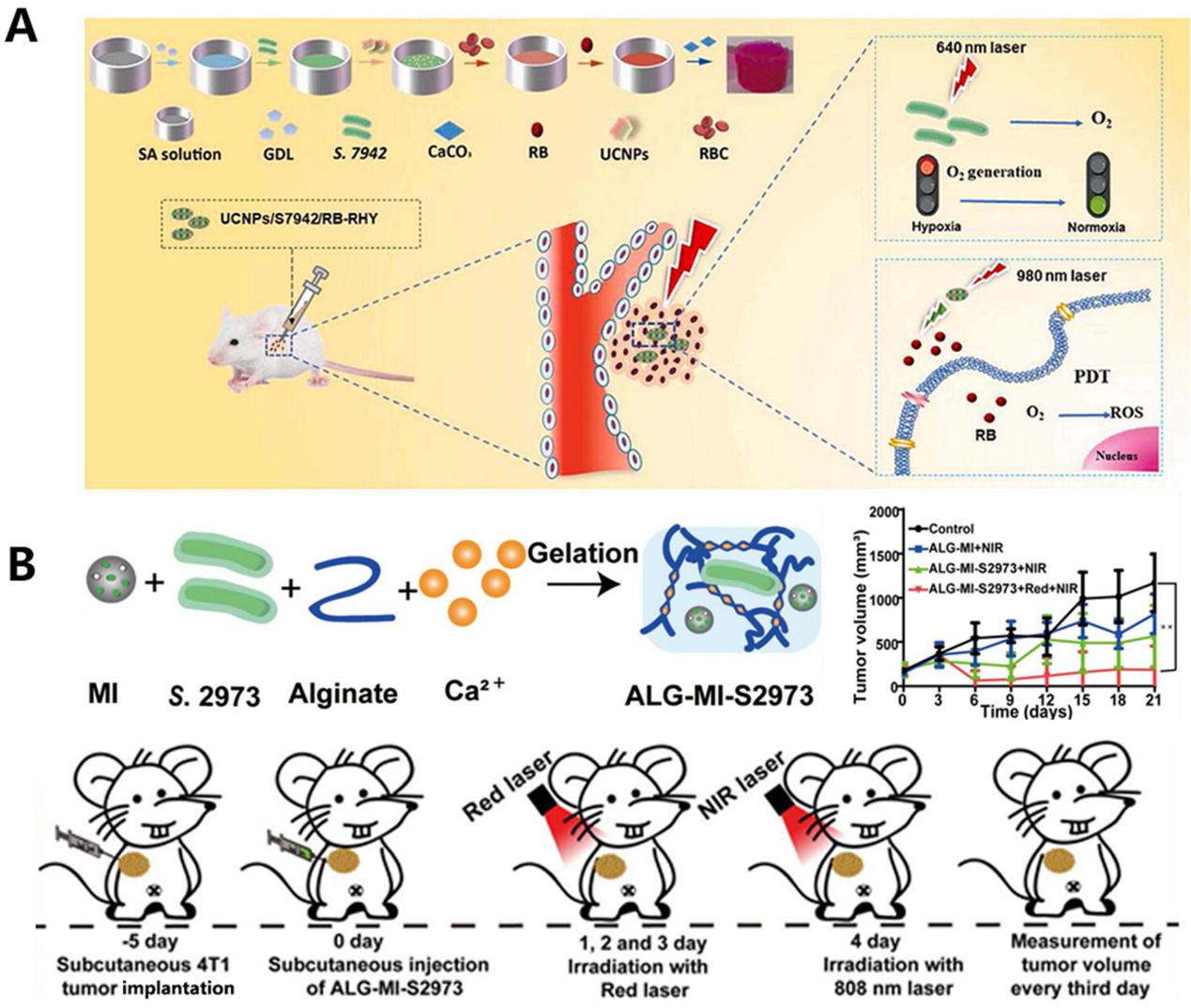

Figure 3 (**A**) Schematic illustration of the synthesis and mechanism of UCNPs/S7942/RB-RHY. Reprinted from *Colloids Surf B Biointerfaces*. Volume 201, Zhang X, Zhang Y, Zhang C, Yang C, Tian R et al. An injectable hydrogel co-loading with cyanobacteria and upconversion nanoparticles for enhanced photodynamic tumor therapy. 111640, Copyright 2021, with permission from Elsevier.[80] (**B**) Schematic illustration of the synthesis and animal experiments of ALG-MI-S2973, and tumor growth curves of tumor-bearing mice with different treatments (**$P < 0.01$ compared with untreated group). Reproduced from Sun T, Zhang Y, Zhang C et al. Cyanobacteria-Based Bio-Oxygen Pump Promoting Hypoxia-Resistant Photodynamic Therapy. *Front Bioeng Biotechnol*. 2020; 8: 237. Creative Commons.[83]

into heat, leading to PTT.[86] Therefore, the hybridization of cyanobacteria and BPNSs can further provide a synergistic strategy for anti-tumor PDT and PTT.

Cyanobacteria as Therapeutic Agents

Previous studies employed some cyanobacteria extracts as photosensitizers, such as tolyporphin (TP),[88] phycocyanin (PC),[89] and hydrophilic chlorine derivatives.[90] Scholars have further investigated the photosensitizing performance of cyanobacteria to explore novel, safe, and effective natural photosensitizers for anti-tumor PDT. To date, S. platensis has been employed as an unconventional photosensitizer in PDT to kill tongue, oral, and hypopharyngeal cancer cells, while they have no cytotoxic effect on normal cells.[87,91] Recently, An et al used an S. platensis-based drug delivery system (SpiD) to transport and release doxorubicin (DOX) into osteosarcoma cells for chemotherapy. S. platensis can provide photosensitization effects under 650 nm laser irradiation, resulting in a synergistic anti-tumor strategy of PDT and chemotherapy[84](see Figure 4C). A study found that S. 7942 exhibited photodynamic effects at the tumor site under 660 nm laser irradiation,[78] indicating that they may be natural photosensitizers like S. platensis. Another study found that

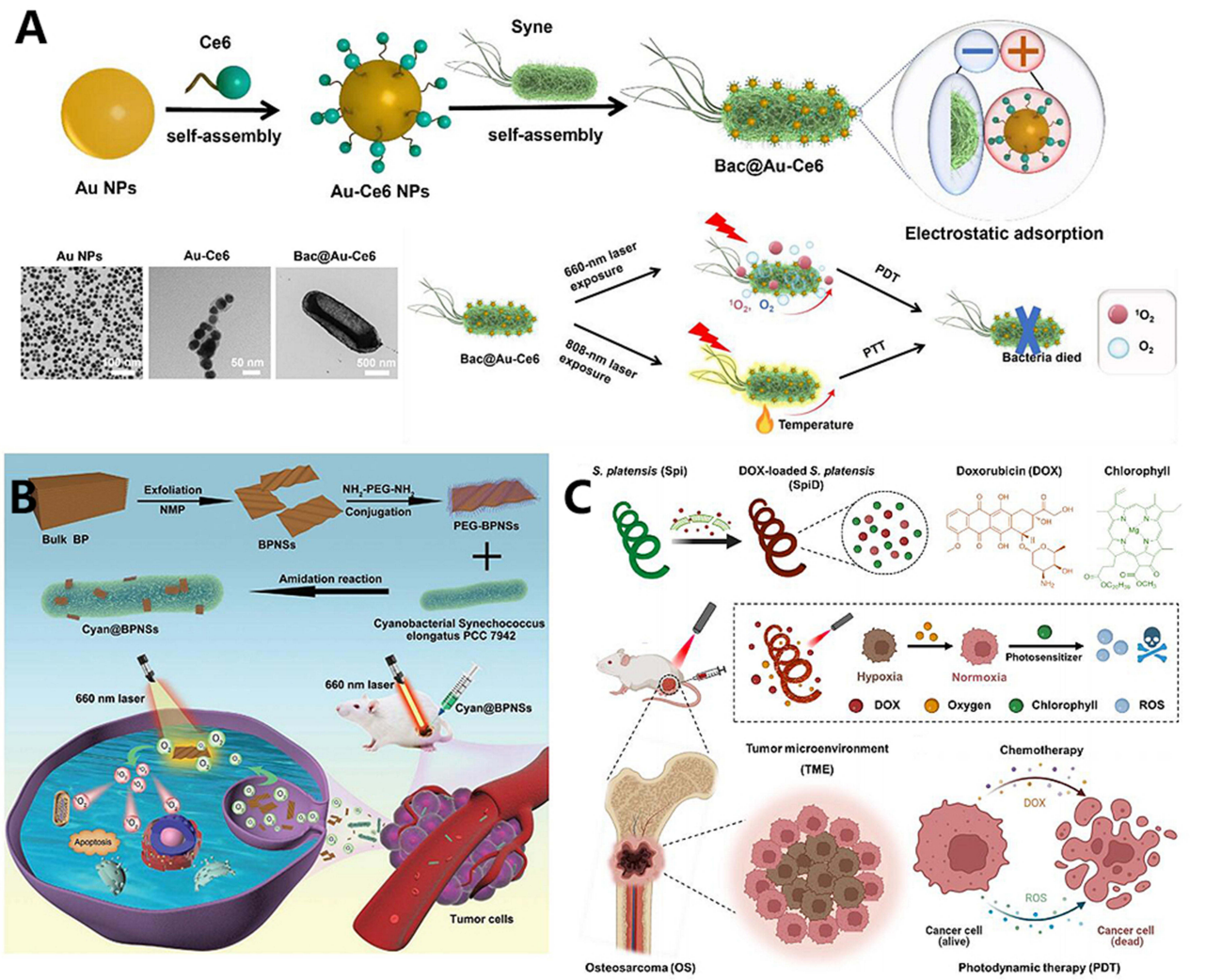

Figure 4 (**A**) Schematic illustration of the synthesis and mechanism of Bac@Au-Ce6, and transmission electron microscope (TEM) images of Au NPs, Au-Ce6, and Bac@Au-Ce6. Reproduced Yin C, Wang Z, Dai C et al. Light-triggered photosynthetic engineered bacteria for enhanced-photodynamic therapy by relieving tumor hypoxic microenvironment. *Theranostics*. 2023; 13:1632–1648. Creative Commons.[82] (**B**) Schematic illustration of the synthesis and mechanism of Cyan@BPNSs. Reproduced from Qi F, Ji P, Chen Z, Wang L, Yao H et al. Photosynthetic Cyanobacteria-Hybridized Black Phosphorus Nanosheets for Enhanced Tumor Photodynamic Therapy. *Small*. 2021; 17: e2102113. © 2021 Wiley-VCH GmbH.[77] (**C**) Schematic illustration of the synthesis and mechanism of SpiD. Reproduced with permission from An X, Zhong D, Wu W, Wang R, Yang L et al. Doxorubicin-Loaded Microalgal Delivery System for Combined Chemotherapy and Enhanced Photodynamic Therapy of Osteosarcoma. ACS Appl Mater Interfaces. 2024; 16: 6868–6878. Copyright © 2024 American Chemical Society.[84]

S. 7942 can be used as a photothermal source to generate heat, eliminating tumors under excessive 660 nm light irradiation. Moreover, S. 7942 can release a series of pathogen-associated molecular patterns and act as adjuvants for immune stimulation, leading to an anti-tumor immune memory effect to prevent tumor recurrence.[73] In short, whether cyanobacteria act as photosensitizers, photothermal agents, adjuvants, or combined with other drugs, that represents a flexible strategy for enhancing the efficacy of anti-tumor of PDT.

PPSB and Anti-Tumor of PDT

It is also crucial to pay attention to the research findings on light-triggered anaerobic PSB in tumor treatment, such as focusing on PPSB (see Table 2). Unlike cyanobacteria, anaerobic PSB do not produce O2 during photosynthesis. However, scholars have recently harnessed some of their properties to eliminate tumor cells under light irradiation. Zheng and Li's research team first documented that R. johrii moves from the injection site to the hypoxic tumor regions of tumor-bearing mice due to its property of hypoxic chemotaxis. Subsequent NIR light irradiation further facilitated the localization of R. johrii in tumor tissue due to its NIR phototaxis. Simultaneously, R. johrii converted NIR light into heat

Table 2 Literature Examples of Light-Triggered PPSB in Tumor Treatment

Strains	Combined component (s)	Nanoplatforms	Light source wavelength	Tumor type	Route of administration	Main function of PPSB	Mode of cancer therapies	Reference
Rhodobacter johrii	_	_	808 nm	Murine melanoma, Human mammary tumor	Intravenous injection	Generate heat	Photothermal therapy	[71]
Rhodobacter johrii	_	_	Xenon lamp	Human mammary tumor, Murine melanoma,	Peritumoral injection	Generate hydrogen	Hydrogen therapy, Immunotherapy	[96]
Rhodopseudomonas palustris	_	_	808 nm	Murine colon carcinoma	Intravenous injection	Generate heat Generate ROS	Photothermal therapy, Photodynamic therapy	[94]
Rhodopseudomonas palustris	Maleimide	PSB-MAL	808 nm	Murine melanoma, Murine mammary tumor	Intratumoral injection	Generate heat	Photothermal therapy, Immunotherapy	[92]
Rhodobacter sphaeroides	Imiquimod, Liposomes	R.S-R837@TSL	808 nm	Murine mammary tumor	Intravenous injection	Generate heat	Photothermal therapy, Immunotherapy	[93]

https://doi.org/10.2147/IJN.S500314

in tumor tissue, showing photothermal conversion properties. These findings suggested that R. johrii can act as a photothermal agent providing hypoxia-targeted PTT and act as carriers of other anti-tumor agents (eg, photosensitizers, chemotherapeutics, and prodrugs) providing a combination of multiple strategies.[71] Subsequently, they utilized R. palustris to develop an engineered PSB-based tumor vaccine to enhance anti-tumor immunity after PTT. They modified the surface of R. palustris with maleimide to form PSB-MAL through membrane insertion of DSPE-PEG-MAL. Under NIR light irradiation, PSB-MAL-induced PTT leads to tumor cell death and the subsequent release of antigens. PSB-MAL captures the released antigens through a Michael addition reaction. After 1-day and 2-day intervals, NIR light was applied at the tumor periphery to drive PSB-MAL to the tumor margin. At last, PSB-MAL transports tumor antigens to normally functioning antigen-presenting cells (APCs) and promotes dendritic cell (DCs) activation, leading to systemic immune responses and immune memory effects in a mouse tumor model.[92] Niu et al combined Rhodobacter sphaeroides (R. sphaeroides) with immunoadjuvant imiquimod (R837)-loaded thermosensitive liposomes (R837@TSL) to form nanoimmunoadjuvant-armed bacteria (R.S-R837@TSL). They found that R.S-R837@TSL effectively targeted hypoxic tumor tissue and converted NIR light into heat for PTT under 808 nm light irradiation. High-temperature-melted R837@TSL released R837 in situ, activating DC-mediated immune responses. Thus, R. S-R837@TSL enables the simultaneous application of PTT and immunoadjuvant-enhanced immunotherapy.[93] In addition to its photothermal properties, Yang et al found that R. palustris can generate ROS, leading to effective cytotoxicity in tumor tissues under NIR light irradiation.[94] Previous studies have shown that extracts of R. palustris and R. sphaeroides containing bacteriochlorophyll-a can induce photocytotoxicity in promyelocytic leukemia cells under 400 nm-800 nm light irradiation,[95] indicating that certain PPSB can act as photosensitizers. However, other scholars have reported that R. johrii produces more H_2 after exposure to xenon lamps than after exposure to 808 lasers and red LED light. Elevated levels of H_2 can disrupt mitochondrial function, leading to oxidative stress and increased ROS levels.[96] In short, light-triggered PPSB can provide benefits for tumor treatment. However, the light-triggered biological properties of PPSB may be affected by the choice of light sources and bacterial strains. Therefore, further experimental research is needed to enrich our understanding of this area.

Challenges of PSB in Anti-Tumor PDT

The above research showed that light-triggered PSB can integrate O_2 supplementation and multimodal treatments without complex design and modifications. These findings will encourage scholars to seek new insights and achievements in anti-tumor PDT. However, we also realize that the studies of PSB as biomaterials for anti-tumor PDT are still in their early stages. There are still many challenges in the preparation and application of PSB.

Safety

PSB are commonly found in various natural environments, including soils, paddy fields, swamps, lakes, rivers, and oceans. Scholars believe that PSB hold significant potential for research and applications in fields, such as food, nutrition, cosmetics, and medicine. However, similar to other bacteria-based tumor therapies, safety is the primary concern and challenge in the preparation and application of PSB. Yang et al demonstrated that dead R. palustris lost their unique light-triggered biological properties and formed visible aggregations after autoclaving. The solution containing dead bacteria is not suitable for intravenous injection into mice due to the risk of lethal pulmonary embolus,[93] suggesting that live PSB remain the preferred option. Notably, PSB contain pathogen-associated molecular patterns (PAMPs) similar to those found in other pathogenic bacteria, such as lipopolysaccharide, peptidoglycan, and flagellin, which can activate the systemic immune response. Previous animal studies have demonstrated that PSB are not pathogenic to major organs, except for causing tolerable inflammation. Cohen et al discovered that only a small amount of PSB remained in the interstitium of Wistar rats 24 hours after the direct intramyocardial injection of S. elongatus. There was no evidence of abscess formation or residual S. elongatus present four weeks after injection. In addition, the rats receiving intravenous injections of S. elongatus had no signs of infection, and blood cultures remained persistently negative for bacterial growth throughout a one-week study period.[97] However, the growth and development of live PSB in tumor tissues make their pharmacokinetics differ from those of traditional drugs. Tumor-bearing rodent models cannot fully replicate clinical scenarios in humans,[98] meaning that the dosage, administration method, and treatment course of PSB established in

existing animal experiments may not be appropriate for human applications. There is also a lack of relevant experimental observations on the clearance process of PSB in human organs, and the potential harm of residual PSB and their biofilms remains unknown. Moreover, certain cyanobacteria have been reported to produce highly toxic secondary metabolites known as cyanotoxins. Prolonged exposure to these cyanotoxins, even at relatively low doses, may lead to liver and kidney damage, cytotoxicity, neurotoxicity, skin toxicity, gastrointestinal disturbances, and other problems.[99] However, some scholars have suggested that the immunogenicity of PSB could offer potential benefits for tumor immunotherapy. Large numbers of PSB disappear after PDT/PTT treatment and eradication of tumor lesions, thereby avoiding the need for antibiotics. Many scholars have realized that bacteria are double-edged swords in tumor therapy.[100,101] Therefore, ensuring the safety of PSB in the human body while enhancing their effectiveness is crucial. Scholars need to conduct strict clinical trial supervision and long-term follow-up observations in the future.

Bacterial Size and Distribution

Tumor-targeting bacteria can passively enter tumor tissue through leakage from the tumor vascular system and penetrate the tumor interior through intercellular translocation.[102] However, the approximately 2 μm length of PSB may hinder their ability to infiltrate solid tumors owing to their sizable dimensions.[60] The heterogeneity of tumors and the immune conditions of the tumor microenvironment (TME) can also affect the distribution of PSB, resulting in uneven bacterial colonization in the tumor tissue. These factors are detrimental to PSB-based therapy in tumor treatment.[103] In recent years, nanosized outer membrane vesicles (OMVs) derived from bacteria have been used as natural drug nanocarriers for tumor treatment and have gained increasing attention. Similar to other gram-negative bacteria, PSB also produces OMVs. A recent study confirmed that PSB-OMVs can target and accumulate in tumor tissues, inhibit tumor growth, and improve immunosuppressive effects in tumor areas without obvious toxicity and side effects.[60] Notably, these nanosized vesicles contain a small amount of chlorophyll or BChls, indicating that they may possess some light-triggered biological properties of the parent PSB, such as ROS production. Hence, PSB-OMVs could replace their parent bacteria and play a more favorable role in anti-tumor PDT. However, similar to the challenges of OMVs in PDT discussed in the previous review,[17] scholars may face challenges, such as low yield and heterogeneity.

Preparation of Engineered PSB

Researchers can combine PSB with drugs, nanomaterials, and functional groups using various physical or chemical methods such as covalent conjugation, electrostatic interactions, and streptavidin-biotin binding. The modifiability of PSB allows researchers to achieve tumor-targeted drug delivery and multimodal anti-tumor therapies. However, engineering methods affect the drug loading and release rate of PSB. Lu et al summarized and compared the advantages and disadvantages of different engineering methods in their published review.[91] Thus far, scholars have often chosen engineering methods based on their research purposes and experimental conditions, which may lead to different experimental results. Some engineering methods may affect the size, charge potential, membrane rigidity, integrity, and activity of PSB, resulting in undesirable alterations in properties, cell motility, immunogenicity, blood clearance, and body metabolic status. It is necessary to avoid external contamination during separation, purification, and engineering processes due to live PSB cannot be sterilized by filtration or heating. Furthermore, there is no unified standard for the storage parameters of engineered PSB, such as temperature, time, and solvents, which can affect their stability.

Conclusion and Outlook

PDT has considerable therapeutic effects and clinical application prospects in superficial tumors and precancerous lesions. However, the efficacy of PDT in deep tumors is affected by factors such as low light penetration depth, non-targeting photosensitizers, and hypoxia in tumor tissues.[104] Tumor hypoxia remains an unavoidable challenge in the clinical application of photodynamic therapy (PDT). In the present review, we introduced the NP-based carrier system for supplementing oxygen and integrating non-oxygen-consuming treatments to enhance the anti-tumor efficacy of PDT. In contrast to NPs, PSB have unique advantages as biomaterials that deserve attention. First, hypoxia chemotaxis gifts PSB

a natural tumor-targeting ability, while phototaxis facilitates PSB to achieve light-guided movement to the tumor, which does not require extra modification with tumor-targeting ligands. Second, PSB can carry photosensitizers using a simple coincubation process, while light-triggered PSB can supply O_2 by photosynthesis to enhance the photodynamic effects of photosensitizers. Third, light-triggered PSB can be eliminated during PDT, avoiding bacterial residue after treatment. Lastly and most importantly, light-triggered PSB exhibited good performance in photothermal conversion, ROS-induced photocytotoxicity, and H_2 production, indicating that PSB can serve as potential photothermal agents, photosensitizers, or H_2 suppliers, not just carriers and O_2 suppliers of photosensitizers. These advantages make light-triggered PSB supply O_2 and integrate various treatment modalities such as PTT, PDT, and gas therapy to reverse the hypoxic limitation of PDT in tumor tissues. Some scholars have identified other light-triggered biological properties of PSB, such as photoacoustic (PA) imaging and second near-infrared (NIR-II, 1000–1700 nm) thermal imaging, which may enable them to act as active PA contrast agents and NIR-II probes for visualizing anti-tumor PDT.[95] Notably, engineered PSB possess superior tumor targeting and drug loading capacity, which opens up opportunities for collaboration with additional anti-tumor treatments, such as immunotherapy,[92] gene therapy,[105] sonodynamic therapy (SDT),[106] and chemotherapy.[90] Combining with superparamagnetic magnetite endows the engineered PSB external magnetic actuation and magnetic resonance imaging properties.[107] The development of an all-in-one diagnostic and therapeutic platform based on engineered PSB could significantly enhance the efficacy of PDT in treating solid tumors and advance the developments in this field. However, the application of PSB in anti-tumor PDT is still in its infancy and faces several challenges. In addition to the already mentioned challenges, we also need to understand the physiological behavior of PSB in the body, including their viability/proliferation manner, OMV biogenesis, and the interaction with quorum sensing (QS) systems quorum sensing (QS) systems. In particular, understanding how QS systems regulate PSB aggregation in tumor tissues and monitoring their numbers have positive implications for the clinical application of PSB. In summary, PSB represents a promising new area of research in anti-tumor PDT and has the potential for various applications. Therefore, we are confident that deepening our understanding of PSB and encouraging the progress of advanced engineering technology will contribute to the clinical transformation of PSB as a light-activatable biomaterial in anti-tumor PDT.

Data Sharing Statement

Data are contained within the article.

Ethics Approval and Consent to Participate

Not applicable.

Consent for Publication

The author gave his consent for publication.

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Disclosure

The author declares no conflicts of interest in this work.

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