



SPECIAL ISSUE: Biomaterial Foundations of Therapeutic Delivery

Hydrogel-based phototherapy for fighting cancer and bacterial infection

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ABSTRACT Hydrogels constitute a group of polymeric materials which can hold a large amount of water in their three-dimensional networks due to their hydrophilic structures. In the past few years, they have been researched for various biomedical applications, such as drug/cell carriers, tissue engineering, and biosensors. Particularly, the hydrogels used as drug delivery systems have shown distinct advantages in phototherapy. This review presents recent advancements of hydrogel's use in phototherapeutic applications by focusing on three kinds of phototherapeutic methods including photodynamic therapy (PDT), photothermal therapy (PTT), and phototherapy-containing combination therapy (PCCT). The applications of these therapies in anticancer and antibacterial fields have also been summarized. We hope that this review will inspire researchers to further develop promising materials for phototherapy applications.

Keywords: hydrogel, photodynamic therapy, photothermal therapy, anticancer, antibacterial

INTRODUCTION

Cancer and bacterial infection are the two main life-threatening human diseases which afflict ten millions of people annually [1–3]. The conventional remedies for cancer are surgery, chemotherapy, and radiotherapy. For bacterial infection treatment, the antibiotics-based chemotherapy is the most commonly used method. However, traditional chemotherapy is often associated with systemic toxicity, and the development of drug-resistant cancerous and bacterial cells makes this approach less effective. Meanwhile, the high rate of recurrence and/or metastasis is problematic for surgical resection of tumor. Regarding radiation therapy, severe side effects (including acute side effects, late side effects, and cumulative side effects) have

been observed during the treatment, which limits the increase of radiation dose. Thus, new strategies for fighting cancer and bacterial infection are urgently needed.

Recently, phototherapy as a medical treatment modality, in which light is used to treat diseases such as cancer and peripheral infections, has gained much attention to ease the symptoms or cure the diseases. Photodynamic therapy (PDT) and photothermal therapy (PTT) are the two main types of phototherapeutic methods used for the treatment of diseases so far [4]. PDT involves the administration of a photosensitizer (PS) followed by local illumination of the lesion using light of a specific wavelength to activate the PS. A series of photochemical reactions triggered by the PS can lead to the death of cancerous or bacterial cells. In PTT, a photothermal agent is usually employed to produce heat for selectively killing/disrupting abnormal cells or tissues. Besides, the use of near-infrared (NIR) light in PDT and PTT ensures greater penetration depths, leading to better therapeutic efficiency.

On the other hand, hydrogels are polymeric networks with three-dimensional configuration capable of imbibing high amounts of water or biological fluids [5–10]. They can be classified based on the sample sizes (macro gels or micro gels/nanogels), the source origins (natural or synthetic hydrogels), the type of cross-linking (chemical or physical hydrogels), polymeric composition (homopolymeric, copolymeric, or multipolymeric hydrogels), and degradability (degradable or non-degradable hydrogels) [11–14]. Recently, hydrogels have gained considerable attention as one of the most promising drug delivery systems due to their unique characteristics (e.g., hydrophilicity and extremely high water content) [5,15]. Thus, many

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hydrogel-based systems have been developed in the past few years with unique characters [16–20]. For example, the macrogels can stay at the target sites for quite a long time due to their inherent low fluidity. While for the microgels/nanogels, they are capable to integrate some superb properties of hydrogels and nanoparticles. In this review, we will highlight the advancements of hydrogels used in phototherapy.

HYDROGELS FOR PHOTODYNAMIC THERAPY

The basic principle underlying PDT includes a series of photochemical reactions triggered by a photo-activated PS drug. During the irradiation with light of a suitable wavelength, a PS absorbs a photon and is excited from the ground state to a short-lived excited singlet state (S_1). The excited PS may either decay back to the ground state by emitting a fluorescence photon or form a relatively long-lived triplet state (T_1) via intersystem crossing. The excited triplet PS can directly interact with a substrate, such as the cell membrane or a molecule, and produce an oxygenated product such as a hydroxyl radical or a hydrogen peroxide (type I reaction). Alternatively, the energy of the excited PS can be directly transferred to molecular oxygen to form toxic singlet oxygen (1O_2) (type II reaction). The byproducts formed as a result of the type I and type II reactions are responsible for the cell-killing and therapeutic effect for PDT. Even though both type I and type II reactions can occur simultaneously, most of the studies involve the type II reactions, which means that 1O_2 usually plays a dominant role in PDT. 1O_2 can immediately react with vital biomolecules (such as proteins, lipids, and DNA), thereby damaging tumor cells. However, the destruction of biomolecules is limited to the size of the diffusion sphere of 1O_2 , which is less than 0.1 μm due to the short lifetime of 1O_2 (half-life: 0.03–0.18 ms) [21,22]. Hence the localization of PS is crucial for the targeted as well as efficient PDT. Hydrogels are considered to be the ideal platforms for PS delivery, and the recent progresses of hydrogels used for PDT are summarized in Table 1 [23–39].

Microgels/nanogels for photodynamic cancer therapy

Microgels/nanogels represent a kind of emerging materials in PDT, which can overcome many limitations of classic PSs. They can be designed from natural or synthetic materials and can be used to carry various agents in a targeted manner. The use of microgels/nanogels in PDT may have at least some of the following advantages: (i) the small sizes of

these gels enable PS molecules to effectively reach the target sites (tissues or cells). They generally inherit the enhanced permeability and retention (EPR) effect of nanoparticles, facilitating both the diffusion of PS carriers into and their retention within the tumor tissue; (ii) the gels may prevent the premature release of PS molecules and the potential inactivation of the drugs by plasma components, thereby preventing their nonspecific accumulation in normal tissues and reducing overall photosensitivity; (iii) the surface of microgels/nanogels can be further modified with functional groups or targeting agents for altering the biological or physical properties, improving the biodistribution pharmacokinetics, cell uptake, and targeting ability. They can be designed as multifunctional platforms that carry multiple components such as diagnostic and imaging agents.

Generally, the entry of drug payloads into the circulatory system is limited by rapid removal by macrophages, especially large particles (>200 nm) [40]. Taking consideration of this, the polyacrylamide (PAA)-based nanogel is an example of many interesting materials used for drug delivery *in vivo*. The neutral surface property of the hydrophilic PAA-based nanoplateforms reduces their uptake by macrophages, making them a candidate for a therapeutic entity [41,42]. Furthermore, low protein adsorption and high water content further decrease the opsonization by plasma proteins, making the drug delivery system “stealthy” to the macrophages. Besides, the size of PAA-based nanogels can be easily tuned by synthetic approaches. PAA can easily react with other monomers to introduce functional groups. Based on these advantages, Gao *et al.* [23] used a nonaqueous microemulsion method to encapsulate the hydrophobic PS *meta*-tetra(hydroxyphenyl)chlorin (*m*THPC), which is approved by the European Union for head and neck, prostate, and pancreatic cancer therapy, into the PAA nanogels. Some potential advantages are available for these ultrafine *m*THPC-encapsulated nanoparticles. Their ultrasmall size not only helps the nanoparticles evade the reticulo-endothelial system (RES) but also enables the more efficient diffusion of 1O_2 out of the nanoparticles to kill tumor cells. Meanwhile, the ultrafine nanogels can be potentially removed from the body by renal clearance, decreasing the accumulation risk of drug.

Besides, other PSs such as methylene blue (MB) and 2-devinyl-2-(1-hexyloxyethyl) pyropheophorbide (HPPH) conjugated to PAA nanogels through covalent bonds have also been reported by Kopelman’s group [24–26]. For example, amine-functionalized biodegradable PAA nanogels were synthesized for cancer theranostics, including active

Table 1 Types of hydrogels and PSs used in photodynamic therapy

Hydrogel	PS	Size/Appearance	Significance	Ref
PAA	<i>m</i> THPC	2–3 nm	PS-loaded PAA nanogels for cancer therapy	[23]
PAA	MB	50–60 nm	PS covalently loaded PAA nanogel for tumor-targeted PDT	[24]
		30–99 nm		[25]
PAA	HPPH	44 nm	PAA-based nanogels for cancer theranostics, including active tumor targeting, fluorescence imaging, and PDT	[26]
Chitosan and alginate	TPPS	~560 nm	Antibody-conjugated chitosan/alginate nanogel significantly enhanced the therapeutic effectiveness of entrapped TMP	[27]
Molybdenum cluster and β -cyclodextrin polymer	Molybdenum cluster	~200 nm	Inorganic materials as both PSs and hydrogel component	[28]
PVA	TPP or TPpP or TPPS	Macrogel with a pore size in the range of 80–950 nm	Water-soluble and -insoluble PSs loaded hydrogel	[29]
Poly- β -cyclodextrin and modified dextran, ZnPc, nitric oxide photodonor	ZnPc, nitric oxide photodonor	Supramolecular macro hydrogel	Hydrogel having dual-color fluorescence and dual-modal photodynamic action	[30]
PVM/MA and glycerol	5-ALA	Hydrogel based microneedles	Hydrogel-based microneedle arrays for PSs/precursor delivery	[31]
Poloxamer 407	5-ALA	Thermosetting gel	Thermosetting gel for PS precursor delivery	[32]
PEGDA, PEG, PTA	ZnPc	Photopolymerisable hydrogel	<i>In situ</i> gelation through photopolymerization for localized PDT	[33]
TiO ₂ and PEGDA	TiO ₂	Photopolymerisable hydrogel	Inorganic/organic hybrid hydrogel system	[34]
PVA and sodium tetraborate	MB	Macrogels	PS-loading hydrogel for drug-resistant bacterial killing	[35]
HEMA and MAA	TMpPyP	Macrogels	Localizing the photocytotoxic effect of PSs at a biomaterial surface for PACT	[36]
PMVE and MA	MB	Macrogels	Electrically-responsive anti-adherent hydrogels for PACT	[37]
HPMC and chitosan	TBO	Macrogels	PS-loaded hydrogels for the treatment of biofilm	[38]
PAA	MB derivatives	Macrogels	PS-loaded hydrogel was found to be active for four-cycle PACT	[39]

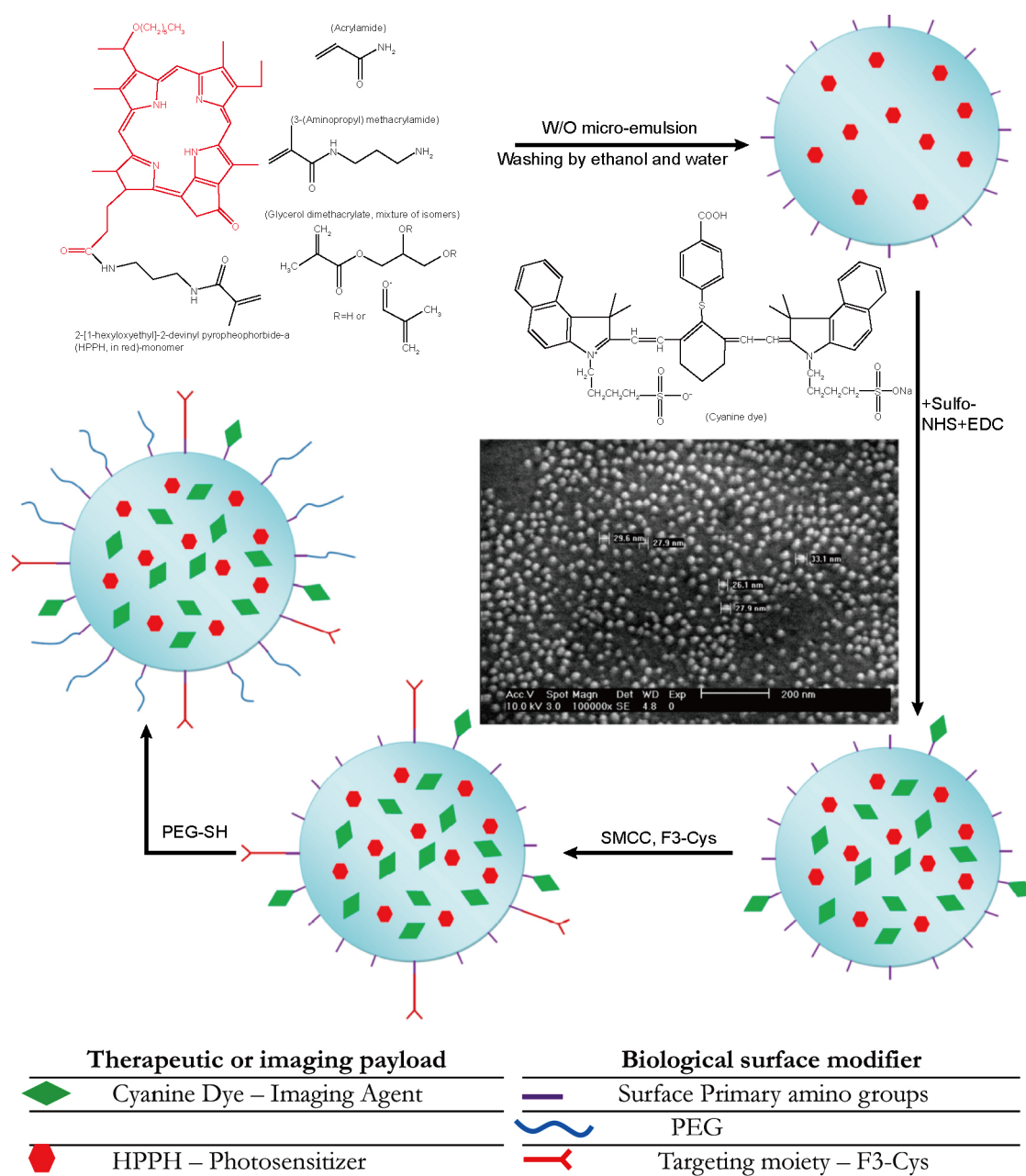


Figure 1 Synthetic route of the multifunctional polymeric nanomedicine. Reprinted with permission from Ref. [26]. Copyright 2012, American Chemical Society.

tumor targeting, fluorescence imaging, and PDT (Fig. 1) [26]. The structural design involves the introduction of primary amine groups and biodegradable cross-linkers during the polymerization, the incorporation of photodynamic and fluorescence imaging agents into the matrix, and the conjugation of polyethylene glycol (PEG) and tumor-targeting ligands onto the surface of the nanogels. The as-synthesized nanogels are spherical with an average

diameter of 44 nm and can collapse within several days after treatment with sodium hydroxide or porcine liver esterase. *In vitro* targeting studies indicate that the nanogels can be internalized efficiently by tumor cells and emit strong intracellular fluorescence. After irradiation with a light, significant and selective damage to the impregnated tumor cells inside the illuminated areas can be observed.

Negatively charged PSs, such as *meso*-tetra (*N*-methyl-4-

pyridyl) porphine tetra tosylate (TPPS) can also be used in PDT to induce cell death through the generation of reactive oxygen species (ROS) in targeted tumor cells. However, owing to their high hydrophilicity, their ability to accumulate intracellularly is limited. Abdelghany *et al.* [27] developed a strategy to improve the cellular uptake of TPPS by encapsulating the compound in a chitosan/alginate-based nanogel. The nanoparticles have an average diameter of 560 nm and can be endocytosed by human colorectal carcinoma HCT116 cells much more effectively than free TPPS. Antibodies targeting death receptor 5 (DR5), a cell surface apoptosis-inducing receptor up-regulated in various types of cancer and found in HCT116 cells, are then conjugated onto the particles, which further enhances the cellular uptake efficiency of the PS. Taken together, these results show that antibody-conjugated chitosan/alginate hydrogel nanoparticles significantly enhance the therapeutic effectiveness of entrapped TPPS.

PSs are usually organic materials, while some inorganic materials such as TiO₂ and molybdenum clusters can also produce ROS under light irradiation. Kirakci *et al.* [28] synthesized a luminescent octahedral molybdenum cluster complex, Na₂[Mo₆I₈(1-OOC-1,7-*closo*-C₂B₁₀H₁₁)₆], with a high photoluminescence quantum yield of up to 93% and a high quantum yield of ¹O₂ formation of approximately 70%. The self-assembly between the cluster and β-cyclodextrin polymer leads to the formation of monodisperse hydrogel particles with a diameter of around 200 nm, which may have potential applications in PDT.

In summary, both hydrophobic and hydrophilic PSs can be carried in a microgel/nanogel system through physical (encapsulation) or chemical (conjugation) methods. These PSs loaded in a microgel or nanogel have an enhanced cellular uptake efficiency as compared with free PSs, which may significantly increase their therapeutic performance. Furthermore, thanks to the facile modification of the polymers, the surfaces of the microgels/nanogels can be modified with functional groups such as targeting moieties or tumor microenvironment activatable agents, which may increase the efficacy of these phototherapeutic systems.

Macrogels for photodynamic cancer therapy

With the excellent characteristics of water-solubility, non-toxicity, non-carcinogenicity, and biodegradability, poly(vinyl alcohol) (PVA) is commonly used in biomedical applications. The PVA macrogel has superb mechanical, water absorption, and swelling properties. Patachia *et al.* [29] reported the preparation of nanoporous hydrogels by a freezing-thawing method. Three types of

porphyrins, including water-soluble (TPPS) and water-insoluble (5,10,15,20-tetra-pyridyl porphyrin or TPYP and 5,10,15,20-tetra-phenyl porphyrin or TPP) ones, are encapsulated into PVA hydrogels. Sorption of the water-soluble porphyrin is achieved by directly immersing the pre-weighed PVA hydrogel tablet into the porphyrin solution. For water-insoluble porphyrins, the porphyrin-encapsulated hydrogels are prepared in two consecutive steps: (i) a pre-weighed PVA hydrogel tablet is immersed into a porphyrin solution in dimethyl sulphoxide (DMSO) and (ii) DMSO is eliminated from the hydrogel by extraction with distilled water. It is demonstrated that the PVA hydrogels can work as an efficient encapsulation vehicle for porphyrins. Hydrogels prepared by using high-molecular-weight PVA have a better sorption profile for porphyrins, and are better suited for the preparation of controlled release vehicles.

Fraix *et al.* [30] developed a supramolecular hydrogel in the absence of any toxic solvents or reagents by self-assembling the following four different components: a poly-β-cyclodextrin polymer, a hydrophobically modified dextran, a commercial zinc phthalocyanine (ZnPc), and a tailored nitric oxide photodonor (Fig. 2). The formation of this supramolecular assembly is based on a “lock-and-key” mechanism in which the alkyl side chains of the modified dextran form inclusion complexes with the cyclodextrin cavities of the poly-β-cyclodextrin polymer. The multivalent character of the interactions between all different components ensures the stability of the hydrogel and the negligible leakage of the photoactive components from the gel network under physiological conditions, even in the absence of protective coating agents. The results obtained from steady-state and time-resolved spectroscopic techniques along with photoamperometric measurements indicate that the two chromo-fluorogenic components have little interference with each other while being enclosed in the supramolecular matrix and thus can be operated in parallel under the light stimuli. Under the excitation of a visible light, the hydrogels can produce red and green fluorescence emissions and generate cytotoxic ¹O₂ and nitric oxide.

5-Aminolevulinic acid (5-ALA), which is a precursor of protoporphyrin IX (PpIX) in the cellular biosynthetic pathway of heme, can be used in PDT [31,32]. Donnelly *et al.* [31] presented hydrogel-forming microneedle (MN) arrays for enhanced delivery of 5-ALA. MN arrays are minimally invasive and painless, without causing bleeding. They can penetrate through the skin's stratum corneum barrier to enhance intradermal and transdermal drug delivery. MNs

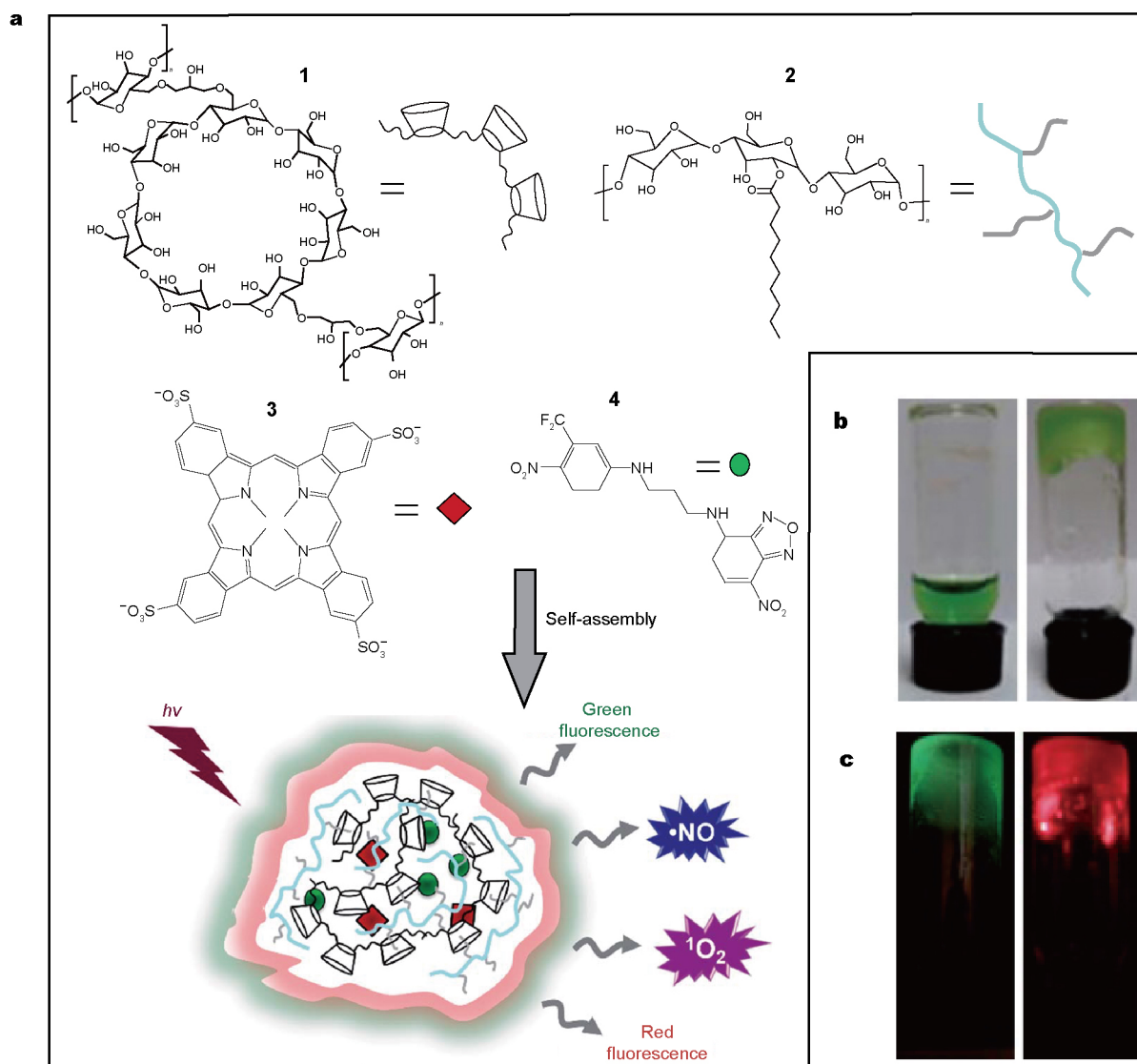


Figure 2 (a) Schematic representation of the multi-photo-responsive supramolecular hydrogel and molecular structures of the corresponding compounds; (b) typical photographs of the mixture before and after gelation; (c) photographs of the hydrogel under irradiation of 470 and 650 nm, respectively. Reprinted with permission from Ref. [30]. Copyright 2014, the Royal Society of Chemistry.

prepared from poly(methylvinylether/maleic acid) (PVM/MA) and cross-linked with glycerol by esterification to form hydrogels upon skin insertion, are combined with patches containing 5-ALA for drug delivery, which significantly enhances transdermal delivery of 5-ALA.

Photopolymerization can be easily controlled under mild conditions and completed in a single and rapid process. For these reasons, photopolymerization is widely used to construct hydrogels for biological applications such as drug delivery and tissue engineering. It has been previously reported that the biocompatible poly(ethylene glycol) double acrylates (PEGDA) can be photo-cross-linked to form

a hydrogel under certain conditions. Taking these reasons into consideration, Wang *et al.* [33] reported the preparation of a novel hybrid hydrogel (HHG) containing PEGDA, poly(ethylene glycol) 400 (PEG400), ZnPc, and phosphotungstic acid (PTA) *via in situ* photopolymerization. ZnPc is used as both the photoinitiator for initiating the formation of HHG and the PS for producing 1O_2 to kill tumor cells. PTA is the co-initiator in the photopolymerization process and can accelerate the generation of 1O_2 . The HHG exhibits good biocompatibility, good swelling and drug retention abilities, and can be easily and rapidly formed on tumor cells *in situ* by irradiating the precursor with NIR

light. The HHG shell not only prevents the diffusion of the PS, but also maintains a high ZnPc concentration inside or on the tumor cells for more effective PDT. In another study, Zhang *et al.* [34] also designed a novel inorganic/organic hybrid hydrogel system containing titanium dioxide (TiO₂)/PEGDA by *in situ* photopolymerization on tumor cells for PDT. TiO₂ nanorods act as a PS causing the formation of hydrogel under NIR irradiation. The hybrid hydrogel retains the TiO₂ around the tumor cell to form a hydrogel shell, resulting in the formation of massive ¹O₂ under NIR irradiation and the apoptosis of tumor cell. Also, the hydrogels can reduce the side effects by preventing TiO₂ from migrating to normal tissues.

It can be seen that the macrogel-based drug delivery systems have several distinct advantages in PDT. First, similar to microgels/nanogels, macrogels have an amphiphilic matrix, making them suitable for encapsulating various molecules or nanoparticles (such as hydrophilic or hydrophobic PSs, imaging agents, etc.) in the same system. Second, macrogel-based PDT can reduce the side effects and unexpected release of PSs. Generally, PSs have no selectivity to the cancer cells, which means that they can also kill normal cells in the therapeutic process. Taking advantage of the low fluidity of the macrogels, the PSs can stay at the tumor site for a long time without unwanted diffusion, which can therefore reduce the side effects of PDT. Finally, it is expected that the combination of hydrogels and other drug administration methods (e.g., the method with a microneedle) can enhance the *in vivo* penetration depth of the PSs.

Macrogels for photodynamic antibacterial applications

Bacterial wound infections are currently treated with topical antibiotics, such as mupirocin, fusidic acid, and neomycin, or systemic antibiotics, such as the β -lactams, macrolides, and metronidazole, or a combination of both. However, bacterial resistance to all of these agents has been widely reported and numerous antibiotic-resistant bacteria have emerged, including methicillin-resistant *Staphylococcus aureus* (MRSA) which is the primary pathogen isolated from antibiotic-resistant wound infections [43]. The increasing resistance of wound infections to both systemic and topical antibiotics has made effective treatment more difficult and accordingly, the development of new treatment regimens is in urgent need.

Photodynamic antimicrobial chemotherapy (PACT) has emerged as an attractive strategy for killing bacteria. PACT is based on the PSs, which can be activated by light with an appropriate wavelength to generate highly toxic, but short-

lived ROS such as ¹O₂, superoxide radical, hydroxyl radical, and hydrogen peroxide. Unlike antibiotics, which usually have a single-target mechanism leading to biocidal action, ROS acts *via* a multi-targeted mechanism, thereby reducing the probability of the development of new resistance mechanisms and helping in retaining the activity of conventional antibiotics by limiting their inappropriate use.

meso-Tetrakis (1-methylpyridinium-4-yl) porphyrin (TMPyP) and MB as positively charged PSs are commonly used in PACT due to their strong attraction with bacterial cells through electrostatic interaction [35–37]. Donnelly *et al.* [35] used PVA-borate hydrogel as a novel drug delivery platform for *in vivo* use in PACT of wound infections. The MB molecules loaded in the hydrogel can release to the receiver compartment, causing phototoxicity to both planktonic and biofilm-grown MRSA.

Bacterial attachment onto intraocular lenses (IOLs) during cataract extraction and IOL implantation is a prominent aetiological factor in the pathogenesis of infectious endophthalmitis. Parsons *et al.* [36] demonstrated a method for localizing the photocytotoxic effect of a PS at a biomaterial surface to prevent bacterial colonization by attaching a porphyrin PS. Anionic hydrogel copolymers can permanently bind to a cationic porphyrin derivative (TMPyP) through electrostatic interaction to form a thin surface layer. The mechanical and thermal properties of the materials show that the porphyrin acts as a surface cross-linking agent, and renders the surfaces more hydrophilic. Importantly, *Staphylococcus epidermidis* adherence is reduced by up to 99.02% under light irradiation and 91.76% in the dark.

Biofilm is the main growth form of microorganisms in nature. It is a non-homogeneous system consisting of microorganisms and extracellular polymer substrate (EPS). This EPS matrix provides structural stability and protection to the biofilm against adverse environmental conditions. Generally, biofilm has a higher resistance to antimicrobial drugs, 500–1000 times higher compared to the planktonic cells. Consequently, biofilm presents a difficult challenge due to their persistent nature, inability to be cultured with standard techniques, and resistance to conventional antimicrobial therapy. Chen *et al.* [38] developed a chitosan hydrogel containing chitosan, hydroxypropyl methylcellulose (HPMC), and toluidine blue O (TBO) to improve the bactericidal efficacy for topical applications. The PACT efficacy of hydrogel was examined *in vitro* against the biofilms of *Staphylococcus aureus* (*S. aureus*) and *Pseudomonas aeruginosa* (*P. aeruginosa*). Confocal scanning laser microscopy (CSLM) was used

to investigate the penetration level of TBO into viable *S. aureus* biofilms. Incorporation of HPMC can improve the physicochemical properties (e.g., hardness, viscosity, and bioadhesion) of the chitosan hydrogel; however, a higher HPMC concentration also results in reduced antimicrobial effect. CSLM analysis further demonstrates that a higher HPMC concentration constrains the diffusion of TBO into the biofilm. After light irradiation, compared to the mixture of TBO and chitosan, the hydrogel treated sample shows increased PACT efficiency, indicating that the incorporation of HPMC indeed improves the antimicrobial effect.

Besides, Spagnul *et al.* [39] reported the synthesis, characterization, and antibacterial activity of a PAA hydrogel conjugated with a new MB derivative used as a novel water-sterilizing device. The hydrogel has a non-ordered microporous structure and is able to generate ROS, enabling the inactivation of *S. aureus* and *E. coli* after 25 min of irradiation with white light. Moreover, the hydrogel system is found to be active for four cycles, suggesting the possibility of reuse.

The above researches show that the hydrogel-based PACT has excellent antibacterial performance for both Gram-negative and Gram-positive bacteria, indicating that it is a broad-spectrum antimicrobial method. Besides, this strategy may be also effective to kill the multidrug-resistant bacteria or the bacteria in the biofilm, which cannot be killed by traditional antibiotics. Furthermore, the PACT can be repeated for many times at one site due to the low fluidity of the hydrogels.

HYDROGELS FOR PHOTOTHERMAL THERAPY

In PTT, a photothermal agent can selectively heat and kill abnormal cells or tissues under light irradiation. Depending on the magnitude of the induced temperature increase, the thermal treatments and the related effects on tumors can be classified into three types: irreversible injury treatment (above 48°C), hyperthermia treatment (41–48°C), and diathermia treatment (below 41°C) [44]. Irreversible injury treatment is highly efficient but lacks selectivity, in which the cell death is achieved as a consequence of drastic and non-reversible necrosis processes. For hyperthermia treatment, it is usually applied in combination with other cancer treatments, such as radiation therapy or chemotherapy, to increase the treatment efficiency. In the 41–48°C temperature range, the rate of biochemical reactions is significantly increased, which leads to the appearance of oxidative stress and causes oxidative damage to proteins,

lipids, and nucleic acids. For the diathermia treatment, the temperature does not induce relevant modifications at the cellular level, which is mainly applied in physiotherapy, sometimes in combination with electric currents.

One example of hydrogel-based PTT was provided by Curry *et al.* [45], who conjugated a photothermal agent Coomassie Brilliant Blue G with PAA nanogels, and realized effective PTT-induced thermolysis in human cervical cancer cell line (HeLa) cells. Besides nanogels, macrogels are also used in PTT to fight against the aggressive and drug resistant nature of tumors through repeated cancer treatments. Hsiao *et al.* [46] prepared a chitosan derivative that contains self-doped polyaniline (PANI) side chains, which can self-assemble into micelles and then transform into hydrogels driven by a local pH change. Photothermal efficacy of the micellar hydrogel was evaluated using a tumor-bearing mouse model through intratumoral injection. The micelles formed in the chitosan hydrogel function as nanoscaled heating sources upon exposure to NIR light, thereby enabling the selective killing of cancer cells in a light-treated area (Fig. 3). Given the ability of the micellar hydrogel to provide spatial stability within a solid tumor, which prevents its leakage from the injection site after repeated treatments with NIR irradiation, the therapeutic efficacy of this hydrogel outperforms that of hollow gold nanospheres (which are used for comparison). To reduce the toxicity of the long-term retention of macrogels in the body, an injectable and on-demand degradable alginate-calcium hydrogel was designed [47]. The hydrogel bearing dendrimer-encapsulated platinum nanoparticles (DEPTs) in its matrix presents excellent biocompatibility and is degradable upon injecting chelates. *In vivo* studies revealed that the hydrogel/DEPTs-mediated repeated PTT can suppress tumor growth efficiently, and the hydrogel is degraded on-demand to allow renal secretion of DEPTs out of the body.

COMBINATION THERAPY

Combination therapy for the treatment of cancer is becoming more popular because it generates synergistic anticancer effects, reduces individual drug-related toxicity, and suppresses multi-drug resistance through different mechanisms of action. Hydrogel-based systems can also be used in combination therapy (Table 2) [48–59].

Combination of PDT and PTT

Light is both needed in PDT and PTT, so PSs and photothermal agents can work simultaneously under the same laser irradiation if light of a suitable wavelength is chosen.

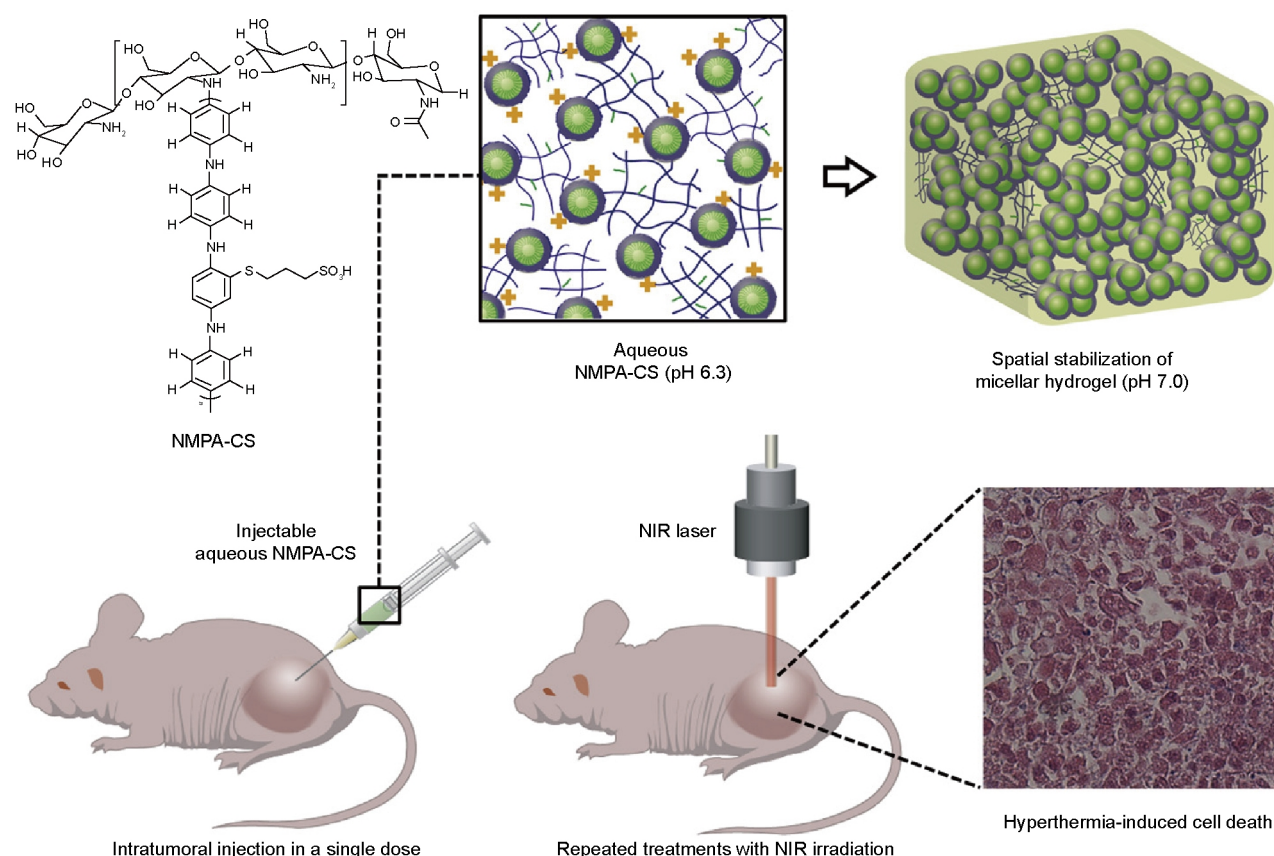


Figure 3 The chemical structure of chitosan derivative that contains self-doped PANI side chains and the mechanism of its photothermal cancer treatment. Reprinted with permission from Ref. [46]. Copyright 2015, Elsevier.

The combination of PDT and PTT may have the following two advantages: (i) the combination therapy can be more effective than a single treatment; (2) more importantly, it is considered that the photothermal effect can be utilized to promote the delivery/release of PSs, further enhancing the PDT efficiency.

Wang *et al.* [48] designed a novel composite hydrogel containing spinach extract (SE), gold nanorods (Au NRs), and PEGDA through a one-step *in situ* photopolymerization under 660 nm laser irradiation for localized antitumor treatment. Here SE serves as a photoinitiator for initiating the formation of the PEGDA hydrogel and as an excellent PS for generating cytotoxic $^1\text{O}_2$ to kill tumor cells. Au NRs are used as a photothermal agent to generate heat from optical energy. Most importantly, the introduction of Au NRs assists the formation of hydrogel and accelerates the rate of $^1\text{O}_2$ generation. The composite hydrogel can prevent the PS from migrating to normal tissues and maintain a high PS concentration in lesions, thereby enhancing the curative effect. Therefore, the combination of the photothermal effect of Au NRs, the photodynamic effect of SE, and the local-

ized gelation by photopolymerization exhibits great advantages and a synergistic effect for the destruction of cancer cells. Besides, they also prepared a hydrogel containing reduced graphene oxide (rGO), amaranth extract (AE), and gold nanoparticles (Au NPs) using AE as both reductant and cross-linking agent [49]. The chlorophyll derivatives in AE are employed as the photodynamic agent, while Au NPs and rGO both exhibit excellent photothermal effects. Similarly, the acceleration of the $^1\text{O}_2$ generation is also observed.

Xing *et al.* [50] reported the formation of an injectable and self-healing collagen-protein-based hydrogel *via* a gold-biomineralization-triggered self-assembly. The locally synthesized Au NPs can tune the mechanical properties of the collagen-based hydrogel and endow the hydrogel with shear-thinning and self-healing properties. The hydrogel itself can be used for PTT due to the locally formed Au NPs under light irradiation. Furthermore, the hydrogel sequesters water-soluble PSs (TMPyP), providing a means for combined PDT/PTT treatment. More importantly, the intratumorally injected hydrogel confines drugs

Table 2 Various phototherapy-involving synergistic treatments for cancer

Hydrogel	Drug	Type of therapy	Ref.
Au NRs, spinach extract, PEGDA	Spinach extract	PDT	[48]
	Au NRs	PTT	
rGO, Au NPs, and amaranth extract	Amaranth extract	PDT	[49]
	rGO, Au NPs	PTT	
AuCl ₄ ⁻ and collagen protein	TMPyP	PDT	[50]
	Au NPs	PTT	
Alginate	Hypocrellin B	PDT	[51]
	DOX	Chemotherapy	
Amphiphilic porphyrin and SPPCL-b-PEG	Porphyrin derivatives	PDT	[52]
	DOX	Chemotherapy	
DNA	Au NRs	PTT	[53]
	DOX	Chemotherapy	
Gelatin, SWNT, PNIPAM-NH ₂	SWNT	PTT	[54]
	DOX	Chemotherapy	
Chitosan and β-glycerophosphate salt	GO/IONP	PTT	[55]
	DOX	Chemotherapy	
Polypeptide	Ce6	PDT	[56]
	I ¹²⁵	Brachytherapy	
rGO, Au nanocages, and spinach extract	Spinach extract	PDT	[57]
	rGO, Au nanocages	PTT	
TiO ₂ @MWCNTs and PEGDA	5-FU	Chemotherapy	[58]
	TiO ₂	PDT	
Dextran aldehyde	MWCNTs	PTT	[59]
	DOX	Chemotherapy	
	Au NRs	PDT	
	KRAS (siRNA)	Gene therapy	
	Avastin	Chemotherapy	

in the diseased lesion and provides locally sustained release of the drugs (Fig. 4). Such a delivery vehicle based on protein hydrogel with shear-thinning and self-healing properties can efficiently lower drug dosage to a minimal level, resist clearance of the immune system, and reduce damage of normal tissues to a maximum extent, thereby realizing the purpose of “one injection, multiple treatment”.

Combination of PDT and chemotherapy

As we stated above, PDT agents and chemotherapeutics can be easily loaded in a hydrogel-based drug delivery system. The inherent properties of hydrogels make the local PDT and local sustained-releasing chemotherapy possible, which can reduce the side effects of PDT and chemotherapy. Recently, several multifunctional multi-compartment systems, which can effectively encapsulate multiple drugs within the same matrix, have been designed by using different techniques, such as layer-by-layer assembly, emulsi-

fication, and so on [60,61]. However, it is a big challenge to construct elaborate drug delivery systems that combine chemotherapy and PDT at the action site [62,63]. Du *et al.* [51] used a reactive template method to fabricate doxorubicin (DOX)-loaded hydrogel microcapsules. After being coated by a folate-linked lipid mixture on the surface, the capsules possess higher cell uptake efficiency *via* the molecular recognition between folate and the folate receptor overexpressed by the cancer cells. Moreover, the lipid can encapsulate the hydrophobic PS hypocrellin B, which achieves the combination of chemotherapy and PDT. The therapeutic effect of these microcapsules is much more effective than chemotherapy or PDT alone.

Jin *et al.* [52] used an amphiphilic porphyrin-cored, star-shaped poly(ε-caprolactone)-*b*-poly(ethylene glycol) (SPPCL-*b*-PEG) copolymer for constructing supramolecular hydrogels. With the aid of α-cyclodextrin (α-CD), thixotropic and reversible supramolecular hydrogel can be

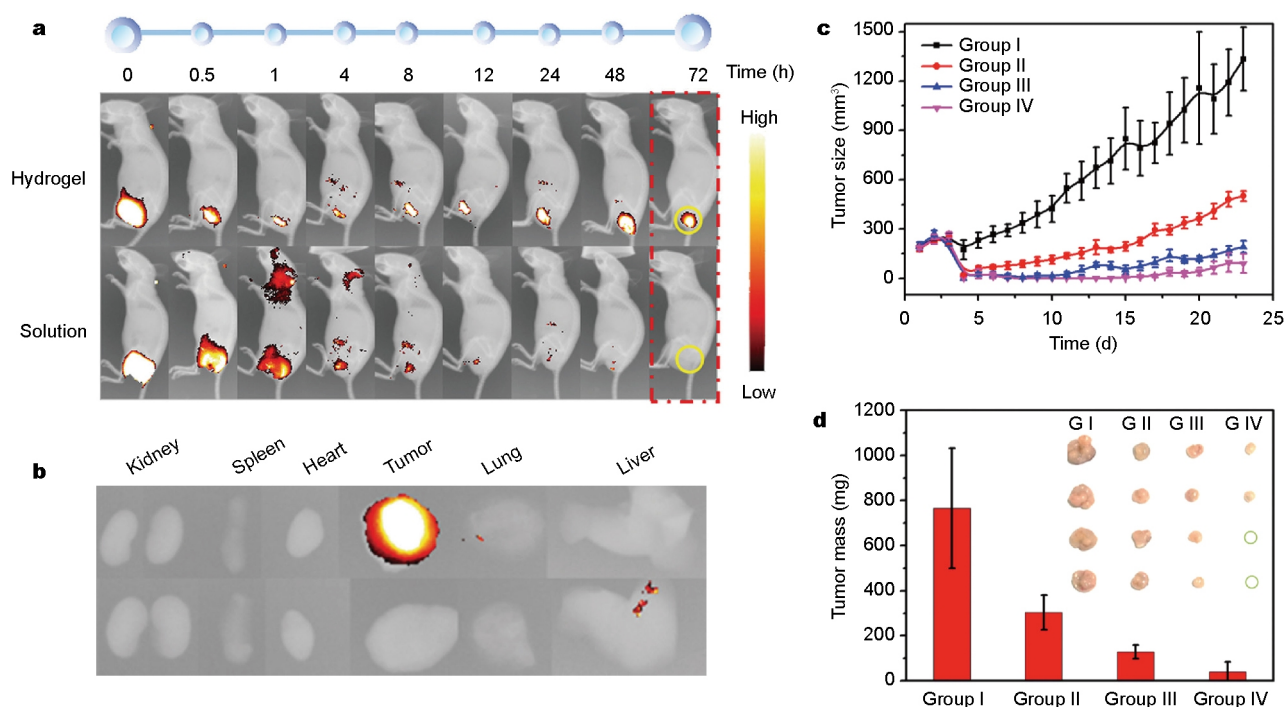


Figure 4 (a, b) Locally sustained drug release through a collagen-based hydrogel after intratumoral injection; (c, d) *in vivo* antitumor activity evaluation using the collagen-based hydrogel. Reprinted with permission from Ref. [50]. Copyright 2016, Wiley Weinheim.

formed by copolymers based on the host-guest inclusion complexation (IC). Because of the biodegradable and biocompatible properties, this IC-based supramolecular hydrogel is used as a carrier for DOX delivery. The DOX release process presents a triphasic drug-release profile, which lasts for more than 3 weeks. Also, upon irradiation with light (650 nm), cytotoxic $^1\text{O}_2$ can be generated by the porphyrin core and easily released from the hydrogel matrix.

Combination of PTT and chemotherapy

As mentioned above, the hyperthermia treatment is usually applied in combination with other cancer treatments, such as chemotherapy. The combination of PTT and chemotherapy has two great merits in a hydrogel system. On one hand, the combination therapy can enhance the tumor inhibition efficiency as compared to the single therapeutic approach [55]. On the other hand, in the thermo-sensitive hydrogels, the release of the drug can be facilitated under irradiation [64,65].

Song *et al.* [53] reported a novel Au NR-based thermo-chemo combinational therapy platform with a DNA hydrogel (Dgel). Because the DNA backbone is highly negatively charged, Au NRs which are positively charged can be stably incorporated into the Dgel pores by electrostatic

attractions. Dgels can be used as a biocompatible scaffold with unique melting characteristics, suitable for triggered drug release and/or programmed disassembly after therapy. The Dgel platform with NIR-responsive Au NRs and DNA-binding anticancer drugs allows stable NR and drug loadings and “on-demand” activation of the therapeutic action by external light triggering.

Zhou *et al.* [54] reported a single-walled carbon nanotube (SWNT)-based thermo-sensitive hydrogel (SWNT-hydrogel), which provides an injectable drug delivery system as well as a medium for photothermal transduction. SWNT-hydrogel alone appears to be nontoxic to gastric cancer cells but leads to cell death with NIR radiation through a hyperthermia proapoptosis mechanism. By incorporating hyperthermia therapy and controlled *in situ* DOX release, DOX-loaded SWNT-hydrogel combined with NIR irradiation achieves a higher tumor suppression rate on mice xenograft gastric tumor models without detectable organ toxicity compared to free DOX.

GhavamiNejad *et al.* [66] reported an intelligent composite hydrogel with both pH-dependent drug release in a cancer environment and heat generation based on NIR laser exposure, for the combined application of PTT and multidrug chemotherapy (Fig. 5). For the first time, dopamine (DP) nanoparticle is used as a highly effective

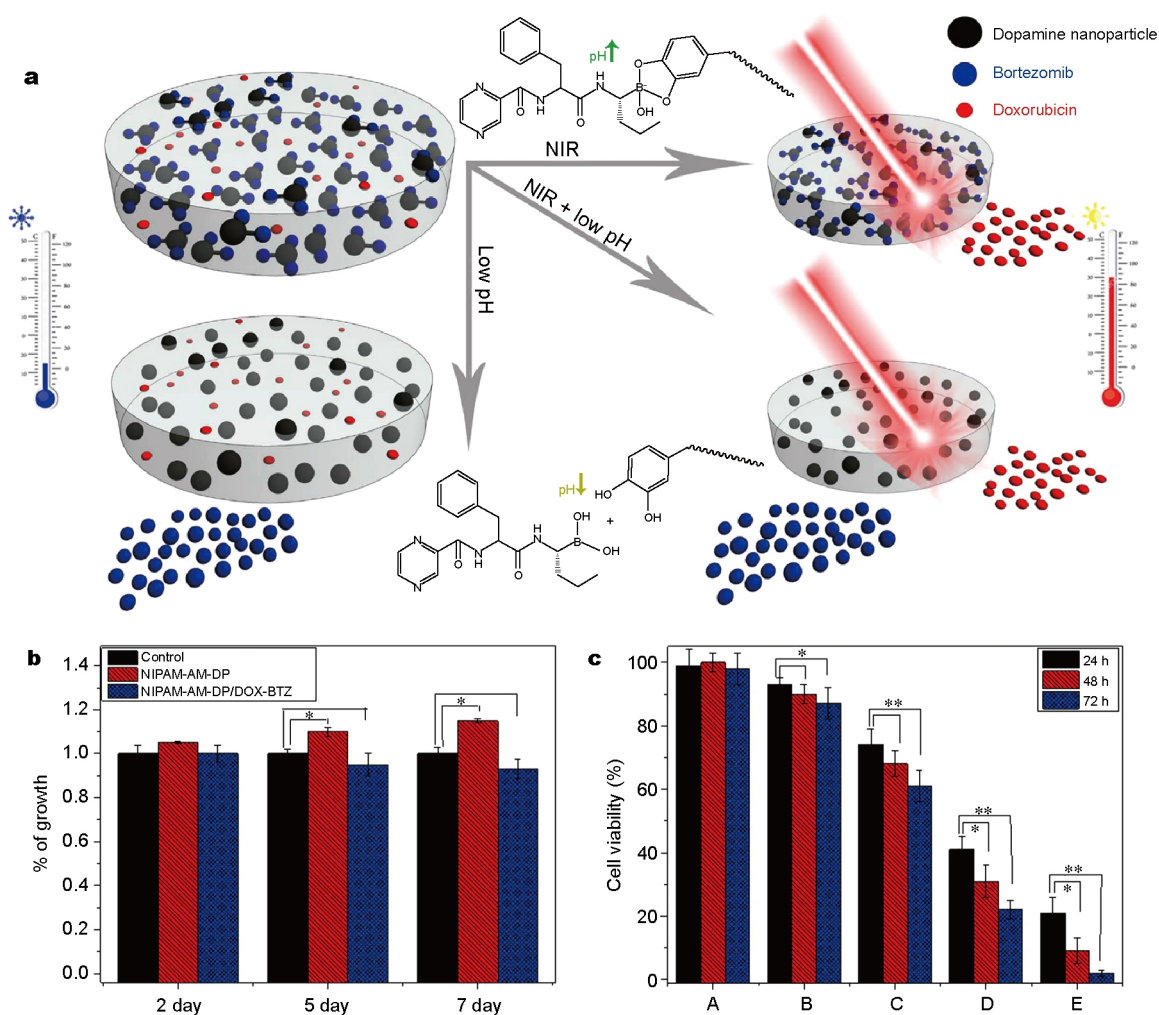


Figure 5 (a) Schematic illustration of the multi-stimuli responsive mussel-inspired hybrid hydrogel as a platform for synergistic anticancer treatment, combining both PTT and multidrug chemotherapy; (b) graph showing the MC3T3-E1 cell viability after exposure to NIPAM-AM-DP and NIPAM-AM-DP/DOX-BTZ for 2, 5, and 7 d; (c) cell viability of CT26 colon cancer cells treated with (A) NIPAM-AM/DP, (B) NIPAM-AM/DP+NIR, (C) NIPAM-AM/DP-BTZ+NIR, (D) NIPAM-AM/DP-DOX+NIR, and (E) NIPAM-AM/DP-BTZ-DOX+NIR. Reprinted with permission from Ref. [66]. Copyright 2016, Macmillan Publishers.

photothermal agent as well as a carrier for the anticancer drug, bortezomib (BTZ), inside a stimuli responsive pNIPAAm-co-pAAm (NIPAM-AM) hydrogel to form NIPAM-AM-DP. When light is applied to the composite hydrogel, DP nanoparticles absorb the light, which is dissipated locally as heat to impact cancer cells *via* hyperthermia. On the other hand, facile release of the anticancer drug BTZ from the surface of NIPAM-AM-DP/BTZ hydrogel is achieved due to the dissociation between the catechol groups of DP and the boronic acid functionality of BTZ in a typical acidic cancer environment. To increase the synergistic effect by dual drug delivery, DOX is also loaded in NIPAM-AM-DP/BTZ hydrogel and the effect of monotherapy as well as combined therapy was carefully

evaluated. It is expected that this nanocomposite with excellent heating property and controllable multi-drug release capability may be powerful for cancer therapy.

Other phototherapy-involving combination therapy

Besides the above-mentioned combination therapies, radionuclide therapy can also combine with phototherapy. In an attempt to spatiotemporally control both tumor retention and the coverage of anticancer agents, Mukerji *et al.* [56] developed a photoradiation-controlled intratumoral depot (PRCITD) driven by convection enhanced delivery (CED). This intratumoral depot consists of recombinant elastin-like polypeptide (ELP) containing periodic cysteine residues and is conjugated with a PS,

chlorin e6 (Ce6). The cysteine-containing ELP (cELP) can be cross-linked through disulfide bonds upon exposure to oxidative agents, specifically the $^1\text{O}_2$ produced during photodynamic stimulation. Upon intratumoral injection, CED drives the distribution of the soluble polypeptide freely throughout the tumor interstitium. Formation and retention of the depot are monitored using fluorescence molecular tomography imaging. When it is shown that polypeptides distributed throughout the entire tumor, a 660-nm light is applied externally at the tumor site. The light irradiation excites Ce6 and generates ROS in the presence of oxygen. The ROS induces the *in situ* disulfide cross-linking of the cysteine thiols, thus turning the ELP biopolymer into a stable therapeutic depot. These depots exhibit high stability in subcutaneous tumor xenografts in nude mice and significantly prolong intratumoral retention compared to controls without cross-linking. The combination of PDT and intratumoral radionuclide therapy co-delivered by PRCITD provides a better antitumor effect than either monotherapy alone.

Triple-combination therapy, such as PTT/PDT/chemotherapy and PTT/gene therapy/chemotherapy, can be integrated into a hydrogel system for drug delivery. To combine localized drug release with multimodal therapy for malignant tumor, a composite hydrogel as an integrative drug delivery system was prepared by Chang *et al.* [57]. The system contains SE, rGO, and gold nanocages (AuNCs). SE facilitates the formation of hydrogel, and also serves as a green material for improving the biocompatibility of hydrogel and a natural PS for killing tumor cells under laser irradiation (660 nm). AuNCs show pronounced photothermal efficiency and can enhance the generation of $^1\text{O}_2$. The composite hydrogel shell on cancer cells exhibits several competitive advantages including enhanced antitumor effect by retaining the high concentration of drugs around cancer cells, excellent PDT/PTT compatibility as well as high loading and controllable release of fluorouracil (5-FU) for synergistic multimodal treatment. In another work, Zhang *et al.* [58] developed a DOX-loaded PEGDA photoinduced hydrogel triggered by NIR laser irradiation. In this *in-situ* drug delivery system, the TiO_2 @multi-walled carbon nanotube (TiO_2 @MWCNT) nanocomposite was explored as the photoinitiator and a PS-photothermal agent for intermittent tumor therapy with multi-mechanisms by a single NIR laser. The DOX/ TiO_2 @MWCNTs/PEGDA hydrogel exhibits a more effective tumor inhibitory action with less toxicity and higher DOX accumulation in the tumor after local injection at the tumor site, indicating that it can be used as an injectable drug depot, allowing for sustained and

long-lasting drug release.

Conventional cancer therapies involve the systemic delivery of anticancer agents that neither discriminate between cancer and normal cells nor eliminate the risk of cancer recurrence. To address these issues, Conde *et al.* [59] demonstrated that the combined use of gene, drug, and phototherapy *via* a prophylactic hydrogel patch in a colon cancer mouse model leads to complete tumor remission when applied to non-resected tumors. This also prevents the tumor recurrence when applied following the tumor resection. The adhesive hydrogel patch enhances the stability and provides the local delivery of embedded nanoparticles. Gold nanospheres (AuNSs) are used as a first wave of treatment to deliver siRNAs against Kras which is a key oncogene driver. And then Au NRs are used to mediate the conversion of NIR irradiation into heat, causing the release of a chemotherapeutic as well as the heat-induced cell damage (Fig. 6). This local, triple-combination therapy can be adapted to other cancer cell types and to molecular targets associated with disease progression.

Because many diseases are very complicated, a single therapeutic approach may not be effective, and combination therapy is becoming increasingly important for achieving a better long-term prognosis with less side effects. When treating a disease, combination therapy generally refers to either the simultaneous administration of two or more pharmacologically active agents or the combined use of different types of therapies (e.g., surgery, chemotherapy, phototherapy, and radiotherapy). Unlike “single-agent” therapy, multi-agent therapy can modulate different signaling pathways in cells, maximize the therapeutic effect, and overcome the drug resistance of cancer cells.

CONCLUSIONS AND OUTLOOK

Because of the severe side effects of systemic clinical treatments, localized therapeutic methods are in urgent need. Encapsulation of drugs into a hydrogel system can achieve the aim. In this review, we summarized the recent advancements of hydrogel-based phototherapy. In PDT, hydrogels can encapsulate both hydrophobic and hydrophilic PSs, making them easy to access to the target site. In the case of PTT, the hyperthermia treatment is commonly used and is often in combination with other therapeutic methods. So hydrogels are used as carriers in which drugs and photothermal agents can be integrated in one system. Thanks to the convenience of hydrogels in drug delivery, other treatments such as chemotherapy, gene therapy, and brachytherapy can be also combined

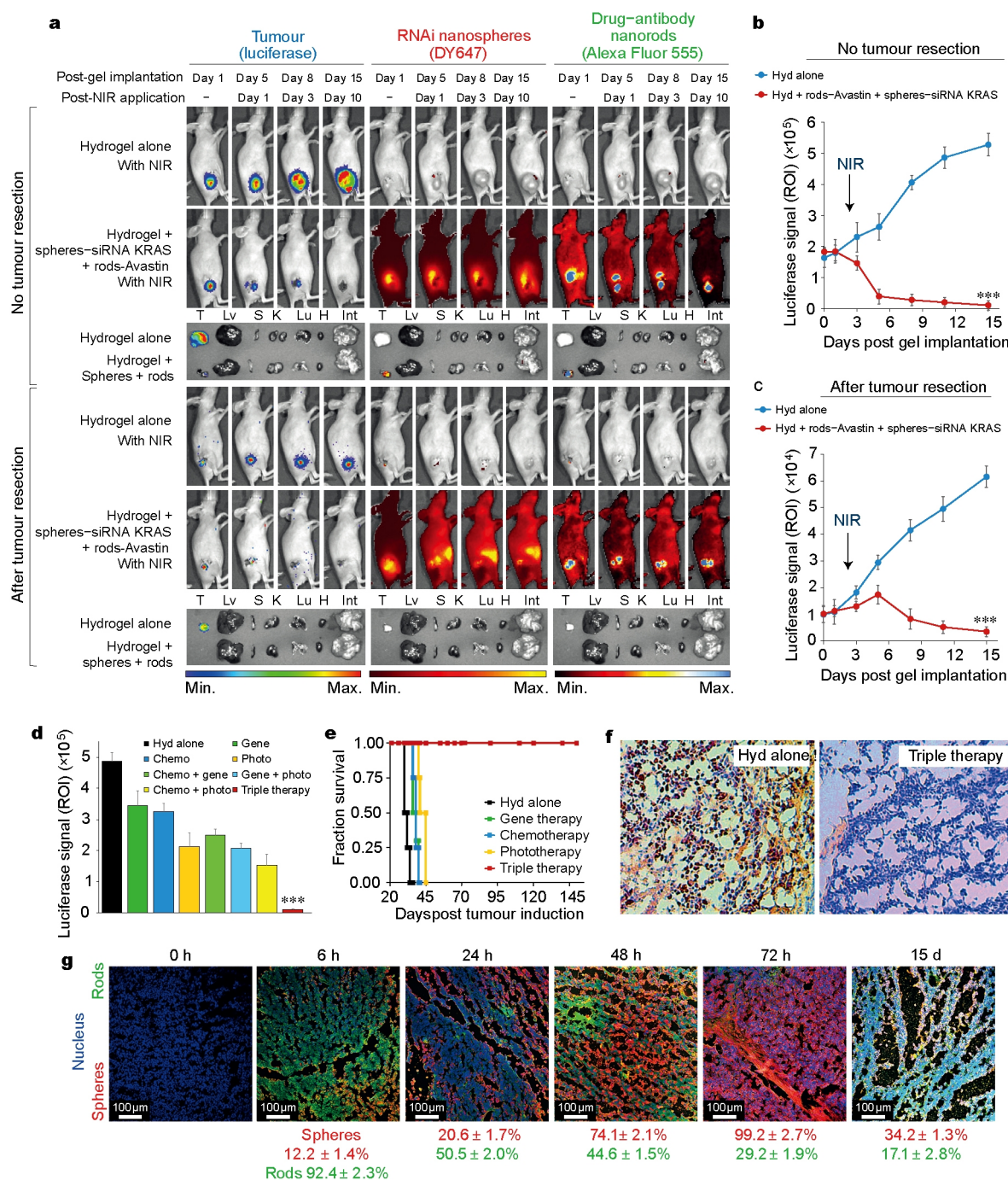


Figure 6 (a) Live imaging of mice with colorectal tumor xenografts implanted with hydrogels that are embedded with drug-Au NRs and siRNA-Au NSs with NIR treatment, either with no tumor resection or after tumor resection. *Ex vivo* images of tumors and whole body organs (T, tumor; Lv, liver; K, kidneys; S, spleen; H, heart; Lu, lung; Int, intestines) are also depicted; (b,c) tumor burden following treatment as measured by luciferase activity, without tumor resection and after tumor resection; (d) tumor burden of mice treated with gene therapy (siRNA-Au NSs), chemotherapy (drug-Au NRs), phototherapy (Au NRs) or double (chemo + gene, gene + photo, chemo + photo) and triple therapy (gene, chemo and phototherapy combination), as measured by luciferase activity; (e) Kaplan-Meier survival curves for mice treated with hydrogel scaffolds for gene therapy, chemotherapy, phototherapy or triple therapy (gene therapy, chemotherapy and phototherapy combination); (f) immunohistochemical evaluation of Ki67 for tumors treated with hydrogels alone or following triple therapy; (g) histopathology and biodistribution analyses of tumor tissue from mice treated with triple-therapy combination for several time points (from 6h to 15d) (blue, nucleus, DAPI; red, RNAi nanospheres, DY647; green, antibody-drug nanorods, Alexa Fluor 555). Reprinted with permission from Ref. [59]. Copyright 2016, Macmillan Publishers.

with phototherapy.

Both macrogels and microgels/nanogels are commonly used as drug delivery systems in phototherapy. Owing to the inherent low fluidity and the reaction between hydrogels and tissue, macrogels can stay at the focal region for quite a long time after being injected or patched at the specific site, which can reduce the drug dose and side effects of the drugs. While for the microgels/nanogels, they can integrate some distinct properties of nanoparticles (such as high surface-to-volume ratio, EPR effect, and magnetic/fluorescence properties) into the hydrogel systems, enabling the efficient drug accumulation within the tumor site/infected area and introducing more theranostic modalities for the anticancer/antibacterial treatments. Besides, both macrogels and microgels/nanogels can be modified with a variety of functional groups such as tumor/bacteria targeting moieties or tissue microenvironment activatable agents to increase the efficacy of these phototherapeutic systems, which could promote the advancements of hydrogel-based phototherapy.

Although many efforts have been devoted to exploring hydrogels for phototherapy in recent years, there are still several issues that need to be addressed in the future. First, when a PS or a photothermal agent is encapsulated in a hydrogel, the role the hydrogel medium plays in the $^1\text{O}_2$ generation of the PS under light irradiation and the photothermal conversion efficiency of the photothermal agent needs to be investigated. Second, more hydrogels with unique characteristics, such as injectable, light-triggerable, and biodegradable, need to be developed. Besides, for clinical uses, the evaluation on the biocompatibility and *in vivo* therapeutic efficacy of most hydrogel delivery systems are urgently needed. Finally, more efforts on hydrogel-based phototherapy or phototherapy-involving combination therapy should be devoted for antimicrobial applications. We believe that hydrogels will have increasing phototherapy-based biomedical applications in the future.

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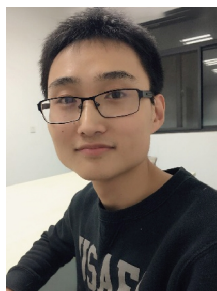
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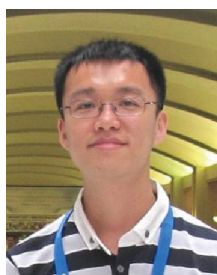
Conflict of interest The authors declare that they have no conflict of interest.



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基于水凝胶的光疗: 对抗癌症和细菌感染

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摘要 水凝胶构成了一类高分子材料, 它们的亲水结构使得其能够在三维网络中保有大量的水. 在过去几年中, 水凝胶在生物医学领域的应用获得了很大的关注, 如作为药物或细胞的载体、组织工程和生物传感器等. 特别地, 水凝胶作为药物输运系统在光疗中拥有显著优点. 本综述总结了水凝胶在光疗应用中的最新进展, 尤其重点讨论了三种光疗方法(包括光动力治疗、光热治疗和组合治疗)及其在抗癌和抗菌领域的应用. 我们希望本综述将有助于启发未来的相关研究以进一步拓展这种材料在光疗领域的新应用.