



Stimuli-Responsive Nanoplatfom-Assisted Photodynamic Therapy Against Bacterial Infections

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Bacterial infections are common diseases causing tremendous deaths in clinical settings. It has been a big challenge to human beings because of the antibiotics abuse and the newly emerging microbes. Photodynamic therapy (PDT) is a reactive oxygen species-based therapeutic technique through light-activated photosensitizer (PS). Recent studies have highlighted the potential of PDT as an alternative method of antibacterial treatment for its broad applicability and high efficiency. However, there are some shortcomings due to the low selectivity and specificity of PS. Growing evidence has shown that drug delivery nanoplatfoms have unique advantages in enhancing therapeutic efficacy of drugs. Particularly, stimuli-responsive nanoplatfoms, as a promising delivery system, provide great opportunities for the effective delivery of PS. In the present mini-review, we briefly introduced the unique microenvironment in bacterial infection tissues and the application of PDT on bacterial infections. Then we review the stimuli-responsive nanoplatfoms (including pH-, enzymes-, redox-, magnetic-, and electric-) used in PDT against bacterial infections. Lastly, some perspectives have also been proposed to further promote the future developments of antibacterial PDT.

Keywords: bacterial infections, photodynamic therapy, stimuli-responsive, nanoplatfoms, drug delivery systems

INTRODUCTION

According to epidemiological reports, infections are a dominant contributor to the global disease burden. The mortality rates of bacterial infections are very high especially in developing countries, where medical resources such as vaccines and anti-infection therapeutics are less accessible (1). The use of antibiotics is a great milestone in fighting against bacterial infections. There are more than 38 antibiotics in clinical setting and 45 antibiotics have been undergoing clinical trials up to 2019. These antibiotics are developed to kill or inhibit the bacteria contagion through different mechanisms, including damage to the cell walls of bacteria, increase of the cell membrane permeability,

and inhibition of the nucleic acid or protein synthesis (2). Due to antibiotics abuse, more and more bacteria have evolved the antibiotic resistance, which leads to the ineffectiveness of antibacterial therapy (3). Increasing antibiotic resistance among pathogenic bacteria is one of the most challenging issues in the present medical field; It is estimated that around 0.7 million people die every year, and it is predicted that maybe 10 million people every year will die from drug-resistant bacterial infections by 2050 (4). Thus, it is highly imperative to understand the underlying mechanisms of drug resistant infections and overcome them. In general, resistance to antibiotics occurs mainly through drug inactivation, composition and permeability modification, drug efflux, and acquired genetic resistance (5). There are increasing evidences revealing that many infections are caused by polybacteria, either in terms of origins or in manifestation. This may lead to limiting the therapeutic efficacy of a single antibiotic (6). To overcome the shortcomings of antibiotics, photodynamic therapy (PDT) has been developed as a promising alternative to treat bacterial infections with broad-spectrum and multitarget features (7, 8).

Photodynamic therapy efficacies rely on efficient delivery of photosensitizers (PSs). Stimuli-responsive nanoplatfoms are a smart and promising delivery system that respond to endogenous stimuli (changes in pH, enzyme concentration, and redox gradients) or exogenous stimuli (magnetic field, ultrasound intensity, light, temperature, and electric pulses). These on-demand properties render the control of drug release in spatial-temporal and dosage-dependent manner (9). In this mini-review, we briefly introduced the unique microenvironment in bacterial infection tissues and the application of PDT on bacterial infections. Then we focus on the progress of stimuli-responsive nanoplatfom-assisted antibacterial PDT. The potential opportunities and challenges will be also outlook to boost the developments of antibacterial PDT.

UNIQUE MICROENVIRONMENT IN BACTERIAL INFECTION TISSUES

The unique microenvironment in bacterial infection tissues provides a prerequisite for designing stimuli-responsive nanoplatfoms (10). The anaerobic fermentation, acidogenic/acid-tolerant bacteria metabolism, and local accumulation of organic acids such as lactic and acetic acids create an acidic microenvironment (pH 4.5–6.5) in infectious sites (11–14). Additionally, bacteria can secrete several protein virulence factors including lipases, esterases, proteases, hyaluronidases, alpha toxins, and chemotactic factors to protect themselves (15–17). These enzymes are highly expressed in Gram-positive bacteria, and they are likely to help bacteria to obtain energy, promote spread, escape from immune detection, etc. (18–20). Metalloproteinase 9 (MMP9) expressed in local infection acts as a synergistic virulence factor (21, 22). At the same time, surrounding tissues increase the detoxication components synthesis and induce the activation of defense response. For instance, an increase of glutathione (GSH) in the epithelial lining fluid was found in the *Pseudomonas aeruginosa*

(*P. aeruginosa*) infection (23). Among the interaction between bacteria and hosts, a complicated inflammatory response is activated to combat infections (24–26). Interestingly, the excessive production of reactive oxygen species (ROS) by activated immune cells plays an essential role in the host immune defenses against pathogens, indicating a participation of oxidative stress in the pathology of bacterial infections (27).

Application of PDT on Bacterial Infections

Photodynamic therapy is a clinically approved technique and mainly applied in treating cancerous and non-cancer diseases on the basis of ROS that generates from light-activated PS. Recently, PDT has also been employed to eliminate pathogens for treating the bacterial infections because it is less affected by the known antibiotic-resistance pathway (28). The successful applications of PDT are dependent on three essential factors, including light sources, PSs, and oxygen. When a PS is irradiated by light with a specific wavelength, it can be excited from the ground state to a triplet state. Then the excited PS can transfer electrons to molecular oxygen to generate superoxide anion and hydroxyl radicals, and hydrogen peroxide subsequently (Type I reaction). In another pathway, the excited PS transmits energy to ground triplet state oxygen to generate excited singlet oxygen and finally stimulates the bursting production of ROS (Type II reaction) (29). ROS in PDT induce a lethal oxidative damage to biological macromolecules like membrane lipids and nucleic acids (30). Beyond the direct killing of pathogenic bacteria through structural disruption, studies found that PDT treatment can induce inactivation of physiologic function-relative protein in bacteria (31, 32). Furthermore, bacterial virulence factors can also be inactivated under PDT treatment (33). Limited by a short lifespan and diffusion distance of ROS, the cellular targets of ROS are mainly dependent on the cellular localization of the PS (34, 35). Innate immunity in host may also affect the therapy effect since the attraction and accumulation of neutrophils into the infection regions were required for PDT-mediated bacteria killing and infection clearance (36). The multitargets of ROS oxidation to biomacromolecules make bacteria hard to develop a resistance to PDT, but studies indicate that the efficiency of PDT could be affected by bacteria strains, genetic background, and its surrounding microenvironment (37–39). Mechanism underlying such a phenomenon is quite complex. Nevertheless, the correlations between the responses of different strains to PDT and the antioxidative systems, cell membrane contents, biofilm production ability, quorum sensing signaling systems have been previously reviewed (40–43).

The wide spectrum and credible effects have already promoted the clinical trials of PDT in antibacterial treatment (**Supplementary Table 1**). But there are still some shortcomings attracting an attention, such as the water-insolubility of PS, insufficient uptakes of PS by pathogenic bacteria, the oxygen shortage in infection lesions, and the phototoxicity-induced side-effects (44). New PS and drug delivery systems are under development, in which stimuli-responsive nanoplatfoms show an important role in promoting ROS production and enhancing antibacterial PDT efficacy (8).

Stimuli-Responsive Nanoplatfom-Assisted PDT on Bacterial Infections

The PS delivery is developed to improve efficacy of the conventional antibacterial PDT approaches. Owing to the advantages in both pharmacokinetics and pharmacodynamics, stimuli-responsive nanoplatfoms have been applied to overcome the issues of poor delivery performance (45). In the following section, we will review stimuli-responsive Nanoplatfom-Assisted PDT in fighting against bacterial infections. These specific stimuli include pH, enzymes, redox gradients, magnetic and electric field, and will be presented systematically below.

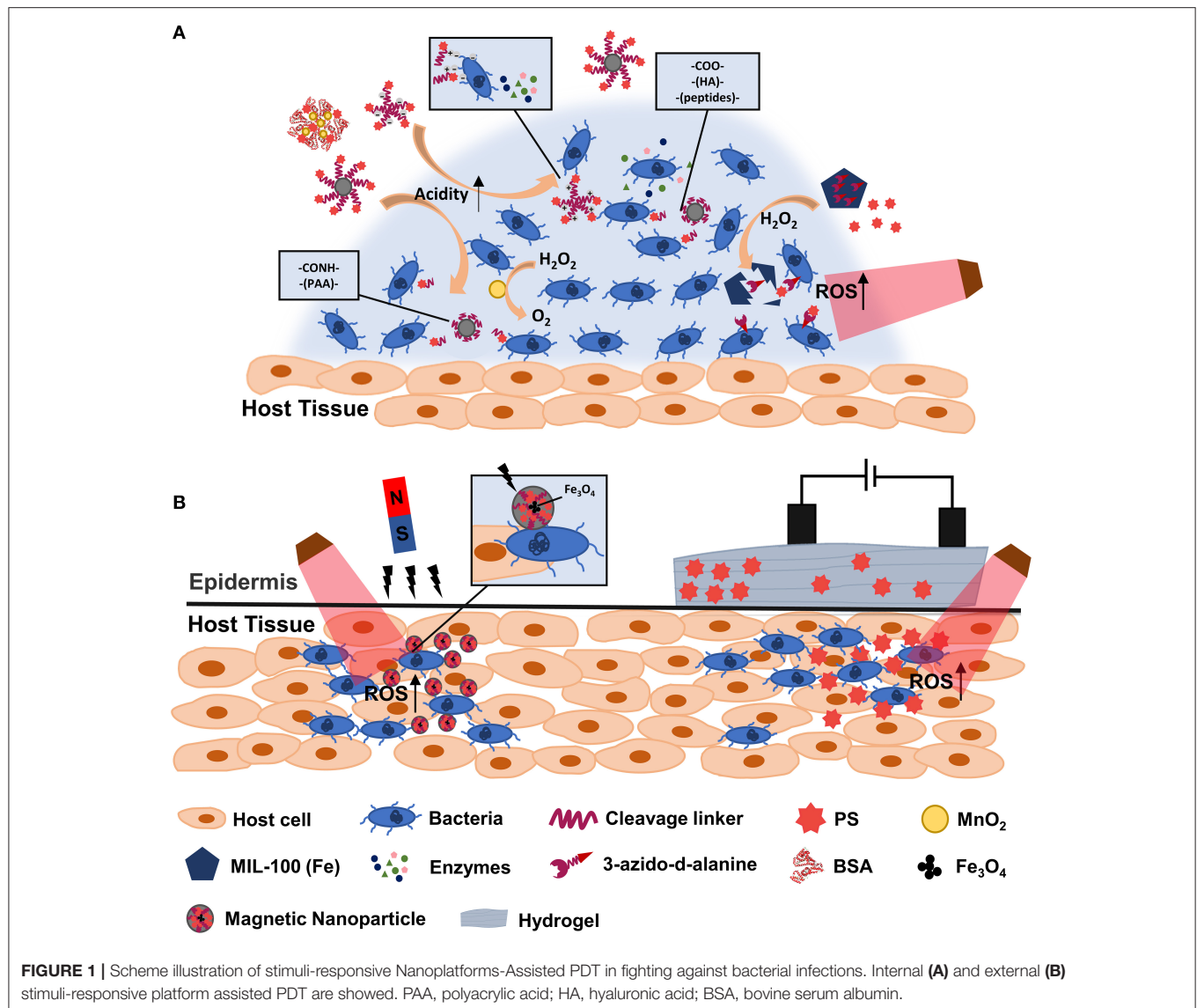
pH-Responsive Nanoplatfom-Assisted PDT in Bacterial Infections

Chemical reactions, protonation, or degradation of administrated compounds can occur under acidic circumstances. Therefore, the pH-responsive strategy has been applied in antibacterial PDT. Polyacrylic acid (PAA) is often used in the delivery of PS for its pH responsive property. Hao et al. synthesized zeolitic imidazolate framework-8 (ZIF-8) for the local delivery of ammonium methylbenzene blue. Then PAA is incorporated for pH responsiveness and higher drug loading capacity. This nanoplatfom had long blood circulation in physiological environment and pH responsive drug release in bacterial infection site. The *in vitro* and *in vivo* experiments showed better therapeutic efficacy than PS treatment alone (46). Similar to the above mentioned platform, Perni et al. constructed a silica-toluidine blue O (TBO) nanoconjugate by the formation of amide bonds between silica nanoparticles and TBO. The controlled delivery of TBO released from the conjugates because of the amide bond cleavage in bacterial infection tissues. In this research, TBO shows an enhanced photosensitive activity in eliminating methicillin-resistant *Staphylococcus aureus* (MRSA), *Staphylococcus epidermidis* (*S. epidermidis*), and *Escherichia coli* (*E. coli*) (47). Protonation in low pH environment often results in a charge change, which is conducive to the accumulation of PS in bacteria surface with negative charge. Thus, Wang et al. used chlorin e6 (Ce6)-linked supramolecule to develop a self-assembled micelle to treat bacterial infections. The negatively-charged micelles could change to positive charge in bacterial infection sites, subsequently adhering to bacteria membranes. This micelle significantly enhanced the inhibition effect of Ce6-based PDT on a variety of bacteria including MRSA, and showed a great anti-infection activity in the subcutaneous infection model (48). The strategy was also implemented in Ce6 loaded SiO₂-polymer nanoparticles (named SiO₂-P_{Ce6-IL}). Ce6 COO- and 1-vinyl imidazole with dodecyl were assembled by anion exchange reaction, and SiO₂ nanoparticles were introduced to control the density of Ce6-IL polymers. With the protonation of Ce6 in bacterial infection sites, the charge of SiO₂-P_{Ce6-IL} was inverted from negative to positive. And the acquired positive charge of polymer led to an interaction of SiO₂-P_{IL+} with negative charge extracellular polymeric substances, which induced a rapid release of Ce6 from nanoparticles and dramatically improved the PDT efficacy against MRSA

biofilm infection (49). Aggregation-induced emission (AIE) PSs exhibit potential application prospect in the PDT because of their aggregation-enhanced ROS production (50). Bibo et al. fabricated an AIE PS loaded in the zwitterionic polyurethane nanomicelles. The AIE PS aggregated around bacteria when zwitterionic moiety acquired positive charge by acid protonation, thus the nanomicelle achieved a superior antibacterial activity (51). In addition to the delivery of PS, low pH also offers possibilities for overcoming the limitations of low oxygen level. Since manganese dioxide (MnO₂) can produce oxygen by its catalytic activity at low pH and high H₂O₂ in the infected sites, Deng et al. synthesized a multicomponent nanoparticle by coencapsulating ultrasmall-sized Hf (IV)-porphyrin Metal-Organic Framework (MOF) and MnO₂ in human serum albumin. In this nanoplatfom, the production rate of ROS was much higher than porphyrin-based MOF treatment alone by *in situ* O₂ generation. With the alleviated hypoxia, it realizes great therapeutic outcomes in *S aureus*-infected models (52). Meanwhile, the magnetic resonance signal of Mn²⁺ provides the detection of bacteria, which is favorable to build up the theranostic platform (53, 54).

Enzymes-Responsive Nanoplatfom-Assisted PDT in Bacterial Infections

The specific high expression and selective catalytic activity endow enzymes with an excellent trigger for controlled delivery of drugs. Based on the cleavage of ester linkage by lipase, more than one team have reported lipase-responsive nanoplatfoms for antibacterial PDT (55–57). For example, nanoliposomes were used to deliver PS pheophorbide A. Erythromycin-loaded liposomes were coated with pullulan-pheophorbide A conjugates. Once the nanoplatfom reached the infection site, pheophorbide A and erythromycin release were triggered by the lipase-dependent cleavage of ester linkage in lipid as well as the one between pullulan and pheophorbide A. This formulation fulfilled the synergistic therapy in skin infection by PS and erythromycin codelivery (55). In another study, pheophorbide A was conjugated with DSPE-PEG to form the nanoliposome, and the photoactivity of pheophorbide A quenched in spherical shape was gradually recovered by the cleavage of ester linkage by *P. acnes* lipases in infection foci, and the formation of nanoliposome enhanced the skin penetration of pheophorbide A (56). Songhee et al. generated a hypocrellin A-loaded methoxy poly(ethylene glycol)-block-poly(ϵ -caprolactone) polymer micelle. This lipase-sensitive micelle not only overcomes the aggregation and low water solubility of hypocrellin A *in vivo*, but also enhances the efficiency of PDT in a MRSA-induced acute peritonitis model (57). For developing MMP-responsive nanoplatfom, MMP9 sensitive peptide (YGRKKRRRQRRR-GPLGVRG-EEEEEE) was conjugated with Ce6 to construct a polypeptide nanoparticle. Negatively charged surface by EEEEE peptide shell was removed by overexpressed MMP9 in the keratitis microenvironment. Subsequently, the exposed cationic peptides helped the nanoparticles to penetrate and accumulate in biofilms as well as bind to Gram-negative bacteria, thereby improving the antibacterial PDT efficacy (58). Hyaluronidase secreted by MRSA was also applied as an endogenous stimulus



in antibacterial PDT. Yuwen et al. prepared a MoS₂@HA-Ce6 nanosheet. MoS₂ nanosheets served as a fluorescence quencher, and hyaluronic acid conjugated with Ce6 (HA-Ce6) was assembled on the surface of MoS₂ nanosheets. These nanosheets could restore the photodynamic activity of Ce6 after the hyaluronic acid shell degraded by hyaluronidase, and *in vivo* study shows an excellent MRSA eradication effect (59).

Redox-Responsive Nanopatform-Assisted PDT in Bacterial Infections

The high levels of GSH and/or H₂O₂ in bacteria-infected lesions provides alternatives for the design of redox-responsive systems. Michael et al. conjugated porphyrin to hyperbranched polyglycerol nanoparticles with disulfide linker with GSH-responsive property. Experiments *in vitro* showed that disulfide

linker in conjugates could significantly improve the phototoxicity of porphyrin against *S. aureus*, despite the lack of additional targeting groups (60). Mao et al. reported a metabolic labeling strategy for precise delivery of AIE PS. They used MIL-100 (Fe), a MOF composed of iron (III) metal centers and trimesic acid ligand nanoparticles, as the carrier for 3-azido-D-alanine delivery firstly. MIL-100 (Fe) would be dissociated as a result of coordination breaking between trimesic acid and iron (III). In this way, the specific release of the encapsulated 3-azido-D-alanine can be achieved. When MIL-100 (Fe) accumulated and degraded within the infection environment with high levels of H₂O₂, 3-azido-D-alanine was released and selectively integrated into the cell walls of bacteria. Then the dibenzocyclooctyne-modified AIE PS nanoparticles can subsequently react with the 3-azido-d-alanine labeled bacteria. Through this modification, the implementation of

TABLE 1 | Summary of stimuli-responsive Nanoplatfoms-Assisted PDT in anti-bacterial.

Source of respond	Responsive method	Bacteria species	PS	Vehicle	Advantages	References
pH	Proton; Amide bond break; PAA; MnO ₂ catalysis	MRSA; <i>S. epidermidis</i> ; <i>E. coil</i> ; <i>S. aureus</i>	Ce6; TBO; DHTPY; ICG; Porphyrin; MB	Micelle; Nanoparticle; MOF; ZIF-8; Nanosheet;	Enhance bacterial affinity; Control delivery; Enhance biocompatibility; Prolong circulation; Targeting property; High ROS generation; Biofilm penetration; Hypoxia alleviation; Bioimaging functionality; Synergistic effect	(46–54)
Enzyme	Ester linkage; Hyaluronic acid; MMP-9- sensitive peptides	<i>P. acnes</i> ; MRSA; <i>P. aeruginosa</i> ;	Pheo A; HA; Ce6;	Liposome; Micelle; Nanosheet; Nanoparticle;	Prevent PS aggregation; Enhance water solubility; High selectivity and penetration property; Enhance retention time	(55–59)
Redox	MIL-100 (Fe); Disulfide bond	MRSA	TPETM; Porphyrin	Nanoparticle	Precise detection and therapy; Multivalent targeting	(60, 61)
Magnetic	Fe ₃ O ₄ ; Fe	<i>S. sanguinis</i> ; <i>P. gingivalis</i> ; <i>F. nucleatum</i> ; <i>Salmonella</i> DT104; MRSA; VRE; <i>E. faecalis</i> ; <i>S. aureus</i> ; <i>B. cereus</i> ; MSSA; <i>E. coli</i> ; <i>S. typhimurium</i>	Ce6/C6; MB; MgPc; t-PtCP	Nanoparticle	Good biocompatibility; Real-time monitoring; Magnetically-targeting; Multimodel treatment; Improve ROS generation	(64–68)
Electric	Hydrogel lysis	MRSA	TMP; MB	Hydrogel	Rapid release	(69)

MRSA, Methicillin-resistant *Staphylococcus aureus*; *S. epidermidis*, *Staphylococcus epidermidis*; *E. coil*, *Escherichia coli*; *S. aureus*, *Staphylococcus aureus*; *P. acnes*, *Propionibacterium acnes*; *P. aeruginosa*, *Pseudomonas aeruginosa*; *S. sanguinis*, *Streptococcus sanguinis*; *P. gingivalis*, *Porphyromonas gingivalis*; *F. nucleatum*, *Fusobacterium nucleatum*; VRE, (VAN)-resistant *Enterococcus*; *E. faecalis*, *Enterococcus faecalis*; *B. cereus*, *Bacillus cereus*; MSSA, Methicillin-sensitive *Staphylococcus aureus*; *S. typhimurium*, *Salmonella typhimurium*. Ce6, Chlorin e6; TBO, Toluidine blue O; DHTPY, Pyridinium, 1-(2,3-dihydroxypropyl)-4-[2-[4-(diphenylamino)phenyl]ethenyl]; ICG, Indocyanine green; MB, Methylbenzene blue; Pheo A, Pheophorbide A; HA, Hypocrellin A; TPETM, 2-(1-[5-(4-(1,2,2-tris(4-methoxyphenyl)vinyl)phenyl)th-iophen-2-yl]ethylidene)malononitrile; C6, Coumarin 6; MgPc, Mg (II) or Al (III) phthalocyanine; t-PtCP, [5,15-bisphenyl-10,20-bis(4-methoxy-carbonylphenyl)-porphyrin] platinum; TMP, meso-Tetra (N-methyl-4-pyridyl) porphine tetra tosylate.

PDT in the infected tissue can significantly reduce bacteria growth (61).

External Stimuli-Responsive Nanoplatfoms-Assisted PDT in Bacterial Infections

Different from the internal stimuli, external stimuli can control the drug release more precisely, and external stimuli can be controlled accurately either by the local or the intensity to meet the treatment requirements (62, 63). For example, magnetic field has been used in the targeted delivery of magnetic materials. Sun et al. developed a Ce6-and C6-loaded Fe₃O₄-silane core-shell nanoparticle to fight against periodontal biofilms growing in dentin disks. Under the magnetically driven force, this nanoparticle could increase the penetration of the PS into biofilms. The results demonstrated that the magnetic nanoparticle had a strong antibiofilm activity with excellent biocompatibility, real-time monitoring, and magnetically-targeting capacities (64). Several other magnetic nanoparticles have constructed on the basis of the iron or Fe₃O₄

magnetic properties to deliver PS. They enhanced bacterial killing significantly by achieving targeting and combination therapy (65–68). In addition to the magnetic field, the electric field has also served as a novel switch for controlled delivery in PDT on infection. Steven et al. designed an electric-responsive hydrogel carrying PS to treat wound infections. The hydrogel was composed of polyelectrolyte poly (methyl vinyl ether-co-maleic acid) (PMVE-co-MA), which can regulate the ionic conductivities of the hydrogel by PMVE/MA concentration ratio. The hydrogel acquired a rapid release of excess PS in a PMVE/MA ratio-dependent manner upon electric stimulation. Thus, this electric responsive hydrogel is a potential option in antibacterial PDT at an open wound (69).

Summary and Outlook

Stimuli-responsive nanoplatfoms have unique advantages in spatial and temporal manipulations of drug release and elongation of blood retention, which provide a promising strategy for drug delivery (70). Currently, regarding unique

microenvironment of bacterial infections, various responsive strategies have been widely developed on the basis of pH, enzymes, and redox gradients to improve the efficiency of antibacterial PDT. In addition, external factors such as magnetic and electric field were also applied as trigger sources (Figure 1). Compared with already recent developments, stimuli-responsive platforms can not only improve the solubility of PS, but also confer other advantages (Table 1). On one hand, stimuli-responsive platforms triggered by the unique microenvironment in bacterial-infected tissues confer the selective drug release. On the other hand, these nanoplatfoms can provide targeting ability for PS, for example, by stimuli-responsive charge converting and magnetically-driven force. Therefore, stimuli-responsive platforms avoided potential side-effects and enhanced the PDT eradication of bacterial infections. What is more, the codelivery of stimuli-responsive catalytic activity components like manganese dioxide (MnO₂) can lead to an *in situ* oxygen generation in bacterial infection sites for hypoxia alleviation (52). Lastly, stimuli-responsive nanoplatfoms with excellent loading performance exhibit broad prospects for synergetic therapies (55). These properties make stimuli-responsive nanoplatfoms a great option in assisting PDT for fighting against bacterial infections. Among them, the external stimuli-responsive platforms may be superior to those responsive to internal stimuli since they can be designed to artificially control the drug release more easily. Besides, a dual-responsive nanoplatfom with more smart features may have greater potential to further enhance the antibacterial PDT efficacy.

Recent evidences have shown that the stimuli-responsive nanoplatfom-assisted PDT is a promising way to combat bacterial infections *in vitro* and *in vivo*. However, a stimuli-responsive property often means more tedious preparation and complicated characterization. Additionally, there are heterogenicity among bacterial species and patient population in the application process, these diversities may make the stimuli-responsive elements ineffective and ultimately affect the drug-releasing and PDT efficacy. While this problem can be settled by personalized-medicine approaches, it needs a complex diagnostic approach (13). Currently, the

encouraging stimuli-responsive Nanoplatfoms-Assisted PDT in bacterial infections are all reported by *in vitro* and *in vivo* experimental studies, but no clinical trials are undergoing so far. The curative effect of these nanoplatfoms needs to be demonstrated by more extensive clinical data. Furthermore, there are challenges such as uncertainty of the *in vivo* fate of nanoplatfoms, limiting the development of stimuli-responsive nanoplatfoms. Therefore, further addressing the above shortcomings should be an important task for translating stimuli-responsive nanoplatfom-assisted PDT to clinical antibacterial infections.

AUTHOR CONTRIBUTIONS

YZ, CX, and WC contributed to the conception and structure of this review. YZ prepared the manuscript. WD did the literature search and wrote the introduction. CX and WC reviewed and revised the manuscript. MM, DL, HL, and YJ provided written comments. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fmed.2021.729300/full#supplementary-material>

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