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Smart responsive materials for antibacterial therapy: Progress, opportunities, and challenges

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ABSTRACT

Bacterial infections threaten global human health, driving the rapid development of antibacterial materials over the past two decades. However, the clinical application is limited due to the rapid presence of antibiotic-resistant bacteria and the brutal penetration of biofilm. 'Smart' responsive antibacterial materials (SRAMs) that respond to endogenous/exogenous stimuli to release antibacterial factors are appealing therapeutic agents for developing next-generation antibacterial materials. Those materials can evade existing mechanisms associated with acquired drug resistance and could also provide an alternative strategy to treat biofilms due to their spatiotemporal controllability and negligible side effects. SRAMs have emerged as a promising tool to combat bacterial infections that are difficult to treat. To better understand the interaction between SRAMs and biological tissues, this review highlights the mechanisms underlying SRAM-mediated eradication of both planktonic bacteria and biofilms and recent advances in designing SRAMs that respond to internal/external stimuli. Meanwhile, we also summarize the latest progress in the development of SRAMs. Properties of internal- or external-stimuli-responsive smart antibacterial materials are outlined, and we also discuss the potential features required for antibacterial

Abbreviations: DCPNAs, Dextran-coated copper peroxide nanoaggregates; SSPMs, PEG-b-PCL single-shellpolymeric micelles; Ti_3C_2-SD(Ti^{3+}), Slip dislocations with abundant Ti^{3+} species; AMVs, PBP2a antibody-presenting membrane nanovesicles; NanoCip, Ciprofloxacin nanoparticles; RP, Red phosphorus; LA, L-arginine; T790, Meso-tetra(4-carboxyphenyl)porphine; Ti–RP-SNO, NO-precursor-loaded MSN on Ti–red phosphorus; BODN-NP, Mdspe-PEG2000 co-assembled with 4,4-difluoro-4-boron-3a,4-diaza-indandiene; PPE, Polyethylene glycol-polycaprolactone-poly-β-aminoester triblock copolymer micelles; PPEL, PPE encapsulated with lactate oxidase; MSCO, MoS_2 nanosheets loaded with CuO_2 nanoparticles; MPH NPs, MIL-100@PMB@HA nanoparticles; BTA, 1,2,4,5-benzenetetramine; *P. aeruginosa*, Pseudomonas aeruginosa; Mn0.1PCC, Mn-doped porphyrin metal–organic framework loaded with calcium peroxide; 2DMOF-TiO_2, TiO_2-modified porphyrin-based two-dimensional metal–organic framework; 2DMOF-MoS_2, Vertical/planar mos_2 nanosheets are grown on a porphyrin-based 2DMOF; M_Fe_3O_4/Au, Macrophage membrane coated Fe_3O_4/Au nanoparticles; IBV-TENG, Vibrant triboelectric nanogenerator.

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applications of various infectious diseases. Furthermore, it also discussed the current challenges and future prospects, particularly emphasizing clinical translation for these smart antimicrobial platforms.

1. Introduction

1.1. Bacterial infection

As humans, it's our nature to want to improve our health and minimize our suffering. Biomaterials act as an interface between a living system and a therapeutic system, facilitating the restoration of the biological function of tissue and mitigating symptoms in injured or diseased states [1]. The term 'bacterial infection' is commonly used to portray various illnesses or conditions related to pathogenic bacteria growth, which may cause sickness in various tissues, including skin, gut, bone, lungs, heart, brain, blood, or anywhere else in the body. Bacterial infectious diseases pose a significant threat to global public health [2,3], causing various infectious diseases such as bacterial osteomyelitis [4], bacterial pneumonia [5], bacterial infections on the surface of implants [6], etc [7]. Annually, it is estimated that approximately 7.7 million fatalities are linked to bacterial infections. Among these, 4.95 million deaths are associated with drug-resistant pathogens, while 1.27 million are attributed explicitly to bacterial pathogens that exhibit resistance to currently available antibiotics [8]. It is projected that 10 million individuals will succumb to illnesses brought on by bacteria and other microbial infections by 2050 [9,10]. The Global Burden of Diseases, Injuries, and Risk Factors Study 2019 identifies *Escherichia coli* (*E. coli*, Gram-negative bacteria) and *Staphylococcus aureus* (*S. aureus*, Gram-positive bacteria) as the most common pathogenic bacteria [11].

Antibiotics remain the cornerstone of clinical management for bacterial infections [12]. The seminal discovery of penicillin by Alexander Fleming in the 20th century marked a revolutionary advancement in antimicrobial therapy [13]-[14]. Unfortunately, overuse and misuse of antibiotics result in the rapid emergence of antibiotic-resistant bacteria [15]. The solution to this dilemma is to develop new antibiotics, typically requiring over 10 years to build. However, bacteria often only take 10 days to develop resistance under laboratory conditions [16]. The first challenge is the imbalance between new antibiotics' development time and resistant bacteria's evolution period.

Another major challenge is clearing bacteria within a biofilm in treating bacterial infectious diseases [17]. Biofilm is common throughout various organisms in the Archaea and Bacteria lineages, with fossil evidence dating back approximately 3.25 billion years [18]. Clinically, biofilms account for nearly 80 % of chronic and nosocomial infections, harboring either monospecies or multispecies microbial communities [19]. The pathogen in bacterial biofilm is shielded from antibiotics, antibodies, and immune cells due to the structure of the biofilm, which is composed of a densely packed community of bacterial cells, a non-biological surface, and extracellular polymeric substances [20]. In biofilms, tolerance is mainly obtained by the adaptive behavior of bacteria in the presence of bactericidal antimicrobial agents, and they would reduce the growth rate or a subpopulation of non-metabolic persistent cells to survive [21]. The resistance is developed and propagated by spontaneous mutations or horizontal gene transfer [22]. The pathogenic bacterial tolerance and resistance mechanisms in biofilms and the biofilm structure make eliminating biofilm another challenge [23].

1.2. Current strategies for antibacterial therapy

Antibiotics are the cornerstone of contemporary healthcare [24]. Those have saved countless lives from bacterial infections for nearly a century. Basic surgical procedures and immunosuppressing chemotherapies will pose a life-threatening infection risk without antibiotics [25]. However, the ongoing development of resistance mechanisms and their spread among bacteria has led to a global shortage of effective treatment options [26]. Antibiotic-resistant bacteria lead to an approximated 4.95 million deaths every year [27,28]. Meanwhile, high doses of antibiotics will bring a lot of adverse side effects, including disruption of intestinal and vaginal microflora [29], neurotoxic effects [30], hepatorenal toxicity [31], and so on. Conventional approaches for developing new antibiotics primarily rely on structural modifications of existing drug scaffolds. However, these attempts can no longer keep up with the rapid spread of resistance due to years of refining the same chemical compositions [25].

The treatment of biofilm-associated infections presents another significant challenge. Many conventional antibiotics demonstrate limited efficacy due to either poor penetration through the extracellular polymeric matrix or excessive retention within the biofilm structure [32,33]. Furthermore, the increased levels of innate antimicrobial tolerance [34] and resistance of bacteria within these communities further compromise treatment outcomes. The lack of immunogenicity and insufficient immune response rate makes innate immune cells, such as neutrophils and macrophages, less satisfactory against biofilm [35–37]. More troubling, mature bacterial biofilms can disrupt antigen presentation pathways, thereby impairing immunosurveillance mechanisms and preventing effective microbial clearance [38,39]. Therefore, conventional antimicrobial chemotherapies cannot fully eradicate bacteria in a biofilm, leading to the emergence of resistant strains and the recurrence of persistent clinical infections.

Researchers increasingly turn to alternative strategies to address these challenges, which may achieve better therapeutic results more easily [40,41]. Biomaterial-based strategies are highly tunable compared with antibiotics, making invalid antibiotics valid or eradicating pathogen bacteria without producing antibiotic resistance or overcoming biofilm barriers [17]. While several biomaterial-based antibacterial therapies have entered clinical trials with moderate success since 2006, none have been approved by the FDA (Table 1). Recently, novel and emerging methods use engineered biomaterials that can be triggered by specific endogenous cues (such

as pH, redox potential, enzymatic activity, and so on) and exogenous cues (such as light, ultrasound (US), microwave (MW), and so on) against planktonic bacteria or biofilm [42–44], resulting in precise spatiotemporal control of the antibacterial effect. The strategies can't produce drug resistance or make ineffective drugs useful.

1.3. Smart responsive materials

1.3.1. What are the smart responsive materials?

Smart materials are materials whose certain properties can be altered controllably or reversibly when they encounter external/endogenous stimuli such as temperature, pH, etc. Smart materials are the product of the generation and development of cell biology, chemistry, and materials science [45]. Smart materials are also named responsive materials due to their responsiveness. They were often translated as 'active' materials previously, although 'reactive' materials might be more accurate. Responsive materials change one or more of their properties when subjected to one or more stimuli [46]. A pioneering study used responsive materials that could respond to endogenous/exogenous signals for spatially and/or temporally release signals for biomedical applications in the 1970 s [47–49]. Dynamic responsive systems are undoubtedly widely found in nature and are often involved in the integral processes in living systems [50]. For example, cells could respond to temporal variations in their surrounding environment [51].

1.3.2. The historical developments of smart responsive materials

According to the historical development of smart responsive materials, they can be divided into four stages. Due to the limited understanding of the immune system, the first-generation materials mainly focus on bioinert materials. In 1949, British ophthalmologist Ridley discovered for the first time during World War II that polymethyl methacrylate (PMMA) does not cause inflammation in the eyeball and can be used as an intraocular lens material to prevent cataracts [52]. Biomaterials are slowly coming into people's field of vision. In the 1960 s and 1970 s, the first generation of biomaterials was developed [53], mainly aiming to obtain appropriate physical properties that matched alternative tissues while producing fewer side effects in the host [54]. At this stage, a common feature of biomaterials is that they are biologically 'inert', meaning they do not cause an inflammatory response when implanted in the body. As times progressed, 'inert' biomaterials could no longer meet people's demand. Bioactive ingredients were introduced into biomaterials, resulting in the second generation of biomaterials [53]. The bioactive components in these materials can react and be controlled with endogenous stimuli in the physiological environment, forming bioactive substances that influence cellular behavior and promote the integration of biomaterials and tissues [55]. However, poor adaptability to the changing biological environment leads to low effectiveness and survival time for second-generation biomaterials *in vivo*. Normal tissues of an organism can respond to changed physiological load or biochemical stimuli, a concept partly borrowed from third-generation biomaterials, which are characterized by the ability to modulate specific cellular responses at the molecular level [53]. Immobilizing specific proteins, peptides, and other biomolecules on materials mimics the extracellular matrix environment, providing cells with a multifunctional cell adhesion surface [53,56]. This generation of biomaterials can provide signals to cells, which has improved the survival rate and survival time of biomaterials *in vivo* to some extent. However, their ability to provide signals in space and time is still minimal. This urgent problem has led to the developing the fourth generation of biomaterials, i.e., the successful development of smart responsive materials (SRMs). For example, Blumenthal's group [47] used an engineering method to construct liposome particles encapsulated with neomycin, and utilized local mild hyperthermia to cause a phase transition of liposomes, thereby regulating the release rate of neomycin. In the presence of serum, the rate of neomycin release at 44 °C was 100 times higher than at 37 °C. Such SRMs have a relatively good therapeutic effect on bacterial infections. Brownlee's group [49] synthesized a bioactive glycosylated insulin derivative that binds to the major binding site of concanavalin so that the release of the hormone is proportional to the amount of glucose. Using glucose content to control the release of exogenous insulin has a good therapeutic effect on diabetes.

Table 1
Clinical translation of biomaterial-based antibacterial therapy.

Starting year	Trade name	Biomaterial type	Active agent	Target infection	Clinical stage	Clinical trials.gov identifiers	Ref.
2018	Arikace	liposomal	Amikacin	Gram-negative	III	NCT01315691	[276]
2019	NA	Bioceramic Sealer	AgNP and Chitosan	Gram-positive	IIII	NCT04481945	[277]
2018	Pulmaquin	liposomal	Ciprofloxacin	Gram-negative	III	NCT02104245	[278]
2021	Fuji IX	Glass Ionomer	TiO_2 and Chitosan	Gram-positive	III	NCT04365270	[279]
2008	Silvasorb	Ag NPs	Silver	Topical infection	III	NCT00659204	[280]
2006	NA	PEI NPs	PEI NPs	Gram-positive	II	NCT00299598	[281]
2011	AgTive	Ag NPs	Silver	Central venous catheter-related infection	IV	NCT00337714	[282]
2018	NA	Dental Adhesive pure	ZnNP and CuNP	Gram-positive	NA	NCT03635138	[283]
2018	NA	Polymeric NPs	Doxycycline	Chronic periodontitis	II	NCT02726646	[284]
2022	NA	PLGA	Ciprofloxacin	Endodontic infections	I	NCT05442736	[285]
2013	NA	Polymeric NPs	Ammonium polyethyleneimine	Oral infection	II	NCT01167985	[286]

AgNP, silver nanoparticle; NA, not applicable. PEI: alkylated polyethylenimine.

1.3.3. Why can smart responsive materials be used to replace antibiotics?

The discovery of antibiotics is one of the most significant scientific accomplishments of the 20th century [57]. When bacteria encounter antibiotics, they become tolerant and then resistant [58]. Dormant and non-dividing cell subpopulations of bacteria can survive in high concentrations of penicillin, leading to bacterial persistence [59,60]. Slowing or arresting bacterial proliferation can promote the ability of bacteria to tolerate antibiotics [61,62]. Bacteria develop resistance through genetic mutations or horizontal gene transfer [63]. Antibiotic treatment failure is typically due to bacterial resistance [64].

How do SRMs address the issue of antibiotic resistance? In general, SRMs can utilize various mechanisms to overcome the problem of antibiotic resistance. Initially, the antibiotic resistance of a pathogen is mainly related to a specific target structure, known as the 'key-lock principle' [65]. In this instance, the pathogen can develop resistance to antibiotics through specific mutations or efflux pumps [66]. However, SRMs have different targets than antibiotics due to their non-selective nature, making it challenging for bacteria to develop resistance to SRMs. Additionally, drug internalization is not a prerequisite for SRMs, unlike most antibiotics, which further helps overcome bacterial resistance [67]. Furthermore, SRMs can interact with the key components of biofilms, potentially eradicating drug resistance induced by biofilms [68]. Also, SRMs are locally applied to the infected area in small doses, resulting in minimal harm to host cells and making it difficult for bacterial resistance to develop. These factors have led to SRMs becoming a promising method to eliminate life-threatening pathogens.

Therapeutics can be divided into antibiotic therapy and non-antibiotic therapy in antibacterial treatments. The former mainly focuses on designing and incorporating stimuli-responsive carriers to amplify the effect of antibiotics and make invalid drugs work. The latter is directly related to SRMs producing antibacterial substrates, including reactive oxygen species (ROS), heat, etc. Over time, the formation principle is switched from static to dynamic, bioinert to biocomplex, and surface to depth through controlled structure and dynamic functionality. During the SRAT process, smart materials are triggered by endogenous and exogenous stimuli, including redox substrates, pH, enzymes, light, temperature, US, MW, and so on, to release antibacterial factors, including ROS, heat, metal ions, antibiotics, antibacterial peptides, biological extracts, and so on (Fig. 1). The smart materials can be classified into three kinds based on

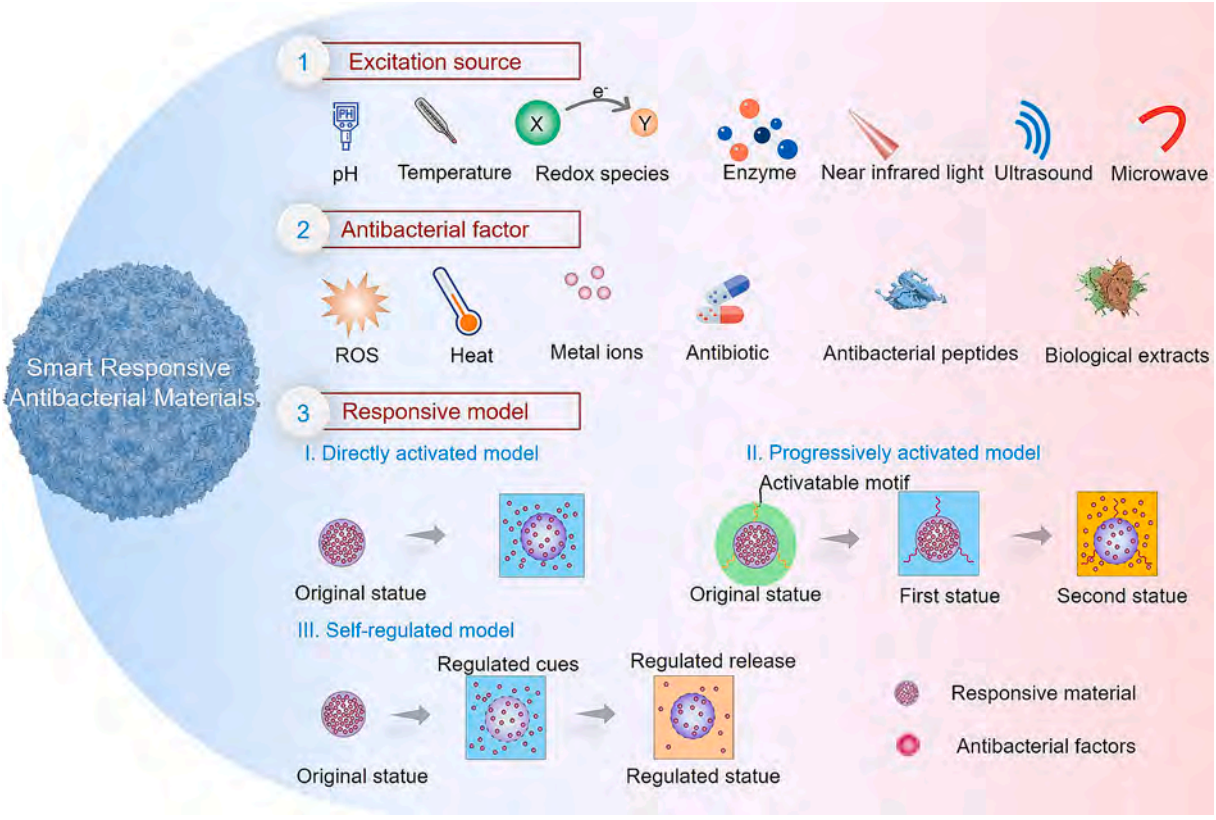

Fig. 1. SRAMs incorporated with endogenous/exogenous stimuli for antibacterial therapies. pH, temperature, redox species, chemo, near-infrared (NIR) light, US, and MW are representative endogenous/exogenous stimulating factors for enhancing the treatment of antibiotics and producing non-antibiotic antibacterial factors. The antibacterial factors are mainly ROS, heat, metal ions, antibiotics, antibacterial peptides, and biological extracts. The antibacterial models triggered by SRAMs are mainly divided into three kinds. **I.** The directly activated model includes responsive materials that could release cues upon endogenous/exogenous stimuli. **II.** The progressively activated model often referred to the systems where the released cues relied on two or more stimulus signals. **III.** The self-regulated model best reflects the intrinsic properties of biological tissue. This system is currently in its initial stages. Engineered living materials are representative cues for producing suitable antibacterial substances, modulating tissue functions, and controlling the following antibacterial effect.

the relationship between activation time and cues released (Fig. 1). The first was a directly activated model. The first kind is that they can respond directly to the stimuli to release cues. The second was a sequential model based on successful step-by-step responses towards each stimulus [69]. In the progressively activated systems, the materials can change into an activated model upon exposure to the first type of stimulus and then react with the second stimulus to release cues. The third was a self-regulated model based on a feedback-responsive modality. As for self-regulated platforms, the cues are released when the materials are encountered with the original stimulus, and the released cues change the microenvironment in biological tissues. The regulated microenvironment would give feedback to the smart materials to regulate the process of releasing cues. Until now, many investigations have been involved in designing a series of SRAMs that could be triggered by endogenous stimuli (e.g., redox species, pH, temperature, and so on) and exogenous stimuli (e.g., light, ultrasound (US), microwave (MW), and so on). And those could further release antibacterial factors (e.g., ROS, heat, metal ions, antibiotics, antibacterial peptides, biological extracts, and so on) to treat bacterial infectious diseases with limited systemic side effects. The treatment based on SRAMs is named smart responsive antibacterial therapy (SRAT).

In previous decades, some reviews related to SRAT have been published [70–76]. However, these papers seldom provide a systematic overview of the antibacterial/antibiofilm mechanism, classification, designing principles, responsive mechanisms, and practical applications. Therefore, a timely and comprehensive review is needed. This review will mainly state the latest research progress of smart responsive antibacterial materials in the past 5 years. The responsive mechanism of materials is divided into three parts, including endogenous, exogenous and complex responsive materials. The designing principles, advantages, antibacterial mechanism, and practical applications in treating bacterial infectious diseases are also discussed in this review (Fig. 2). Infectious diseases include bone infections, lung infections, osteomyelitis, periodontitis, implant-associated infections, and so on. Additionally, it also provides a forward-looking perspective on the current challenges and future directions for designing the next generation of SRAT and *in vivo* translational potential. We hope to offer valuable and comprehensive information for researchers engaged in smart stimuli materials-based disinfection and materials science.

2. Antibacterial mechanisms of smart responsive materials

SRAMs, such as films, nanoparticles, or microparticles, are alternative strategies against bacterial infections [77–79]. Understanding their antibacterial mechanisms on planktonic bacteria and biofilms helps prepare more useful SRAMs and apply them to various applications of SRAT. This section will discuss the antibacterial mechanisms of SRAMs.

Among all antibacterial mechanisms, bactericidal and bacteriostatic effects are the fundamental mechanisms. “Bacteriostatic” refers to agents that inhibit bacterial growth, effectively maintaining bacteria in a stationary phase, while “bactericidal” denotes agents that actively kill bacteria [80]. In practice, no pure antimicrobial agents exclusively fall into one category or the other. As for antibiotics, the bactericidal agents may eliminate more than 99.9 % of bacteria within 18 ~ 24 h post-testing. Conversely, there is a 90 % ~99 % reduction for bacteriostatic agents. The clinical definitions tend to be even more subjective. Most antibacterials have the potential to exhibit both bactericidal and bacteriostatic properties [81].

SRAMs have properties other than antibiotics and traditional antibacterial materials (AMs). The negatively charged AMs usually exhibit better antibacterial ability against Gram-positive bacteria, while positively charged AMs show a more efficient antibacterial effect on Gram-negative bacteria due to their structural differences [82]. Fig. 3**a** indicates the bacterial membrane structures of Gram-

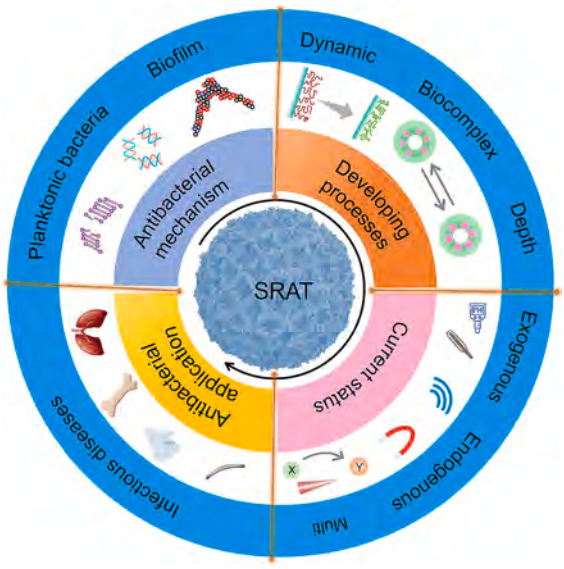

Fig. 2. Schematic illustration of the outline for SRAT. The SRAT were divided into four parts: the antibacterial mechanism, the development history of controllable properties, the design principles of SRMs, and the application of SRAMs for treating infectious diseases.

positive and Gram-negative bacteria [82]. However, SRAMs have no limitations, and they can be activated by various stimulus factors (SFs) to release antibacterial factors (AF), resulting in a great antibacterial effect on different bacteria (Fig. 3**a**).

When used as carriers of antibiotics, SRAMs can further enhance the treatment effect of antibiotics and protect them from degrading enzymes. The SRAMs can modulate the release profiles of antibiotics, which is suitable for maintaining effective local drug concentrations at the infection site. The antibacterial mechanisms of these materials involve antibiotics and the additional elements of SRAMs. The introduction of SRAMs improves the therapeutic efficiency of antibiotics and further reduces adverse side effects by decreasing the required systemic dose and off-target effects. In addition, several evolved mechanisms of antibiotic resistance in bacteria include deactivating enzymes, reduced antibiotic uptake, efflux pumps, inactive metabolic state, extracellular polymeric substances limiting antibiotic penetration, etc [83]. The antibiotic-based SRAMs can disrupt the cell wall or membrane and damage intracellular components to overcome bacterial resistance mechanisms. SRAMs take advantage of these mechanisms to make useless

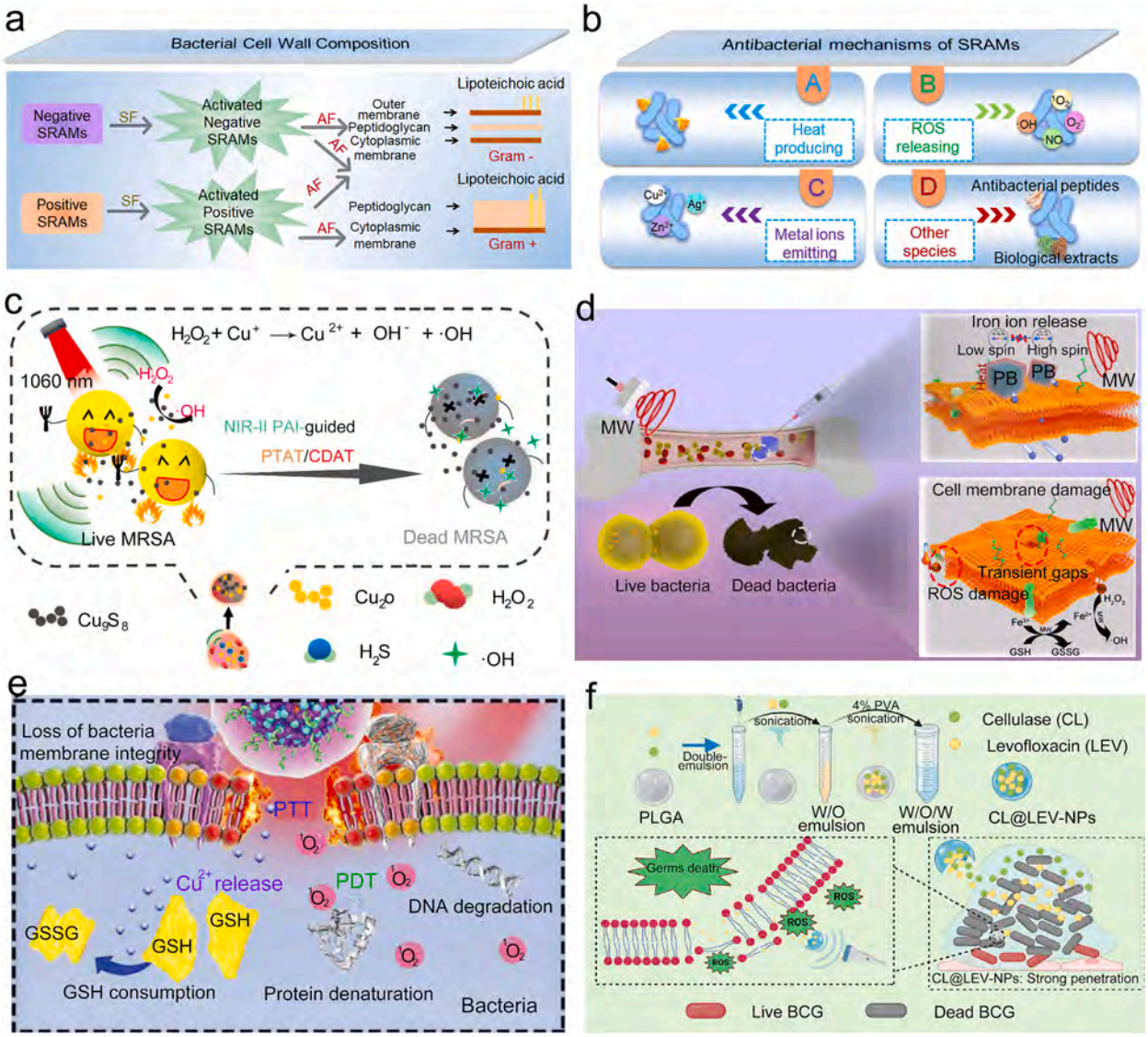

Fig. 3. Schematic illustration of the interaction between SRAMs and bacteria. (a) Schematic representation of positive and negative SRAMs against Gram-positive and Gram-negative bacteria. SF and AF are the abbreviations of stimulus and antibacterial factors, respectively. (b) The illustration of antimicrobial mechanisms of SRAMs. SRAMs would produce various substrates, including heat, metal ions, ROS, and other species, to clear bacteria. (c) The illustration of Cu_2O NPs against bacterial infections by reacting with H_2S and H_2O_2 in the bacterial infection microenvironment.[89] Adapted with permission. Copyright 2021, Elsevier B.V. (d) The illustration of PB against bacterial infections under the MW irradiation.[90] Adapted with permission. Copyright 2021, Elsevier B.V. (e) The illustration of hollow-structured $Cu_{2-x}S$ nanoparticles against bacteria under the NIR light irradiation.[95] Adapted with permission. Copyright 2021, Wiley-VCH. (f) Schematic diagram of biofilm disperses combined with antibiotic composite nanoparticles for sonodynamic antimicrobial chemotherapy of BCG biofilm infections. [96] Adapted with permission. Copyright Form Li et al. 2023, Fig. 1.

antibiotics work again.

The non-antibiotic SRAMs are activated by various external stimuli to produce bactericidal substances such as ROS, heat, metal ions, and so on (Fig. 3**b**). ROS can act on the bacterial cell membrane and organelles due to its highly active oxidants, eventually resulting in bacterial death [84]. The heat will disrupt bacterial membrane permeability [85] and further change the bacterial metabolism, resulting in bacterial death. The metal ions will alter the bacterial metabolism and enhance the ROS production in bacteria, leading to bacterial death. Other substances like antibacterial peptides, biological extracts, and so on, also influence bacterial viability.

In general, SRAMs primarily interact with bacterial membranes, subsequently affecting intracellular substances and ultimately causing bacterial death. Additionally, SRAMs can effectively eradicate bacterial biofilms. The following section will discuss the antibacterial mechanisms against planktonic bacteria and biofilms in detail.

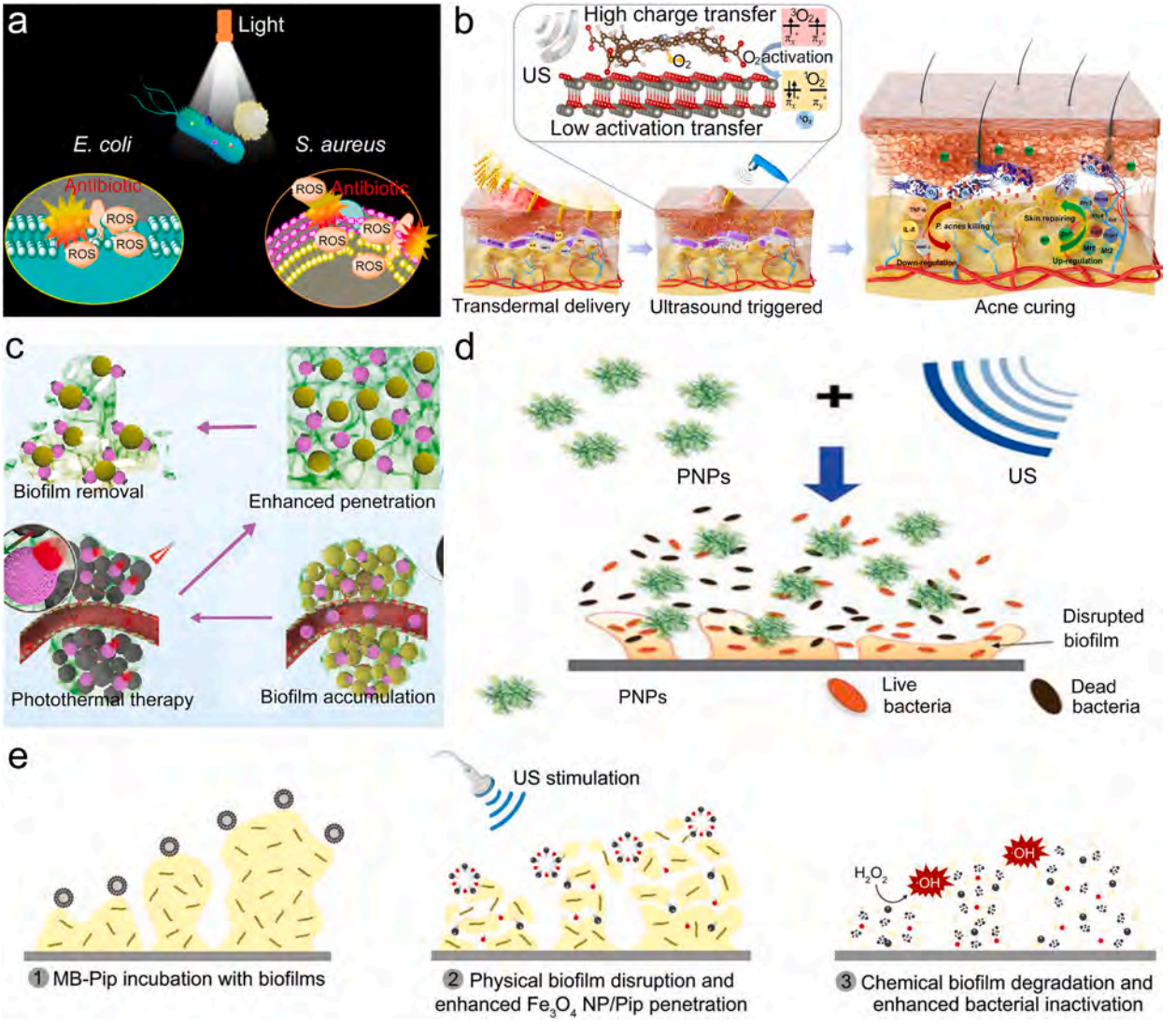

Fig. 4. Schematic illustration of the influence of SRAMs on bacterial metabolism or biofilm. (a) Schematic illustration of light-excited antibiotic polymyxin b producing ROS to kill E. coli.[100] Adapted with permission. Copyright 2020, American Chemical Society. (b) Schematic diagram of sonocatalytic mechanism and the treatment of acne through efficient sonodynamic ion therapy-based MN patch.[101] Adapted with permission. Copyright 2023, The American Association for the Advancement of Science (AAAS). (c) Janus Dex-BSe nanoparticles are prepared by a nonsolvent-aided counterion complexation strategy.[108] Adapted with permission. Copyright 2023, Springer Nature. (d) Schematic representation of the effect of combination treatment on bacterial biofilms and scheme depicting rapid biofilm disruption and enhanced antibacterial activity due to US treatment.[109] Adapted with permission. Copyright 2022, Wiley-VCH. (e) Scheme for the elimination process of P. aeruginosa biofilms by US-responsive catalytic Pip-loaded MBs (MB-Pip) under US stimulation.[116] Adapted with permission. Copyright 2023, AAAS.

2.1. Planktonic bacteria

The antimicrobial mechanisms of SRAMs on planktonic bacteria primarily involve disrupting the cell wall and membrane, damaging intracellular components, and interfering with bacterial metabolism.

2.1.1. Cell wall and membrane disruption

The physical barriers of bacterial cell membranes/walls are vital to maintain bacterial viability, which limit the penetration and accumulation of antibacterial agents [86]. The ability of hydrophobic antibacterial medicines to pass through membranes is especially compromised by this highly polar environment caused by negatively charged bacterial surfaces [83]. Furthermore, the bacterial cell wall or outer membrane may malfunction due to mechanical or physical harm, allowing cytoplasmic components to leak and eventually produce bacteriostatic and bactericidal effects [87].

When SRAMs are used as drug carriers, they will initially damage the bacterial wall and membrane. Those increase the antibiotic's effectiveness and give it better antibacterial qualities than SRAMs and antibiotics alone. For example, the thermo-responsive-inspired drug-delivery nano-transporter (TRIDENT) would permanently damage bacterial membranes driven by increasing temperature, making it easier for the imipenem to penetrate. This disrupts the biosynthesis of cell walls and ultimately causes the bacteria to die quickly [85]. Pores caused by MW irradiation also damage bacterial membrane integrity, promoting Garcinia nanoparticles into bacteria [88]. Those methods overcome the bacterial resistance caused by the bacterial membrane/wall.

SRAMs can also directly act as antibacterial agents, disrupting the bacterial wall and membrane. For example, the Cu_2O NPs could catalyze H_2O_2 at the site of inflammation to generate •OH through a Fenton-like reaction. Meanwhile, Cu_2O NPs reacted with the endogenous H_2S to form Cu_9S_8 NPs, further presenting the photothermal effect when exposed to 1060 nm laser radiation (Fig. 3**c**). These effects damaged bacterial membranes, leading to bacterial death [89]. MW also could be a stimulus to activate Prussian blue (PB) to produce heat and weaken the Fe II-(CN) and Fe III-(NC) bonds in physiological saline solution (Fig. 3**d**) [90]. The release of Fe^{2+} and Fe^{3+} ions from PB is accelerated, and the thermal effect changes the membrane's permeability under MW irradiation. Together with the consumption of glutathione (GSH), the synergistic effects of MW, MW-induced thermal effects, and the Fe^{2+}/Fe^{3+}-induced Fenton-like reaction lead to bacterial death.

2.1.2. Damage to intracellular components

Intracellular components are essential for bacterial survival and function. And SRAMs disrupt those components. It further leads to the alteration of gene expression, the change of protein synthesis, and the damage of DNA [91,92]. Metal-containing materials can release metal ions that interact directly with the − NH, −SH, and − COOH groups from DNA and proteins [93], causing bacterial mortality. For example, ZnO NPs can damage bacterial components, including lipids, DNA, and proteins [94]. The hollow $Cu_{2-x}S$ nano-homojunction (nano-HJ) produced heat, Cu^{2+}, and singlet oxygen ($^1O_2$) upon NIR laser irradiation through the d–d band transition of Cu (II) ions and localized surface plasmon resonance, which synergistically led to DNA degradation, protein denaturation, and GSH consumption in bacteria (Fig. 3**e**) [95]. Furthermore, sonodynamic antimicrobial chemotherapy offers a high target specificity and superior penetration, which can surmount resistance from the local microenvironment [96]. A composite nanoparticle loaded with cellulase (CL) and levofloxacin (LEV) (CL@LEV-NPs) would produce ROS under the US irradiation to break the intracellular components and enhance the treatment effect of levofloxacin (Fig. 3**f**) [96].

2.1.3. Alter the bacterial metabolism

ROS are byproducts of cellular oxidative metabolic processes that influence cell differentiation, signaling, survival, and cell demise [97]. Excessive accumulation of ROS can cause fatal oxidative stress [98]. In particular, the superoxide radicals and •OH can react with protein thiols on bacterial membranes [99]. SRAMs will produce antibacterial substrates after reacting with different stimuli. The antibacterial substrates further enhance the production of ROS in bacteria to alter bacterial metabolism. ROS-based chemical oxidation is considered the most crucial working mechanism of photocatalytic antimicrobial materials, including •OH, $•O_2^-$, $^1O_2$, and H_2O_2, etc [84]. For example, antibiotic polymyxin b could generate ROS under light irradiation, which further induces the ROS generation in bacteria. Ultimately, the antibiotic-based PDT strategy could efficiently kill bacteria with a low dosage of antibiotics with light assistance (Fig. 4**a**) [100]. A sodium hyaluronate microneedle patch containing zinc porphyrin-based metal–organic framework and zinc oxide (ZnTCPP@ZnO) (MN patch) cleared methicillin-resistant *Staphylococcus aureus* (MRSA) by enhancing the ROS production in bacteria, leading to bacterial death (Fig. 4**b**) [101].

2.2. Biofilms

Biofilms contribute approximately 80 % to chronic infections and 65 % to microbial infections [102]. They are challenging to treat and eliminate due to their recalcitrant behavior [103]. Breaking down extracellular polysaccharides and disrupting the matrix of biofilms can make the bacteria within it become planktonic bacteria, which is the primary mechanism against biofilms. The microenvironment in biofilm infection sites has increased levels of H_2O_2, lower pH, and bacterial products (such as enzymes, glutathione, etc.) compared to normal tissue [104]. These factors could serve as stimuli to activate SRAMs to release antibacterial factors. Additionally, some external stimuli, including light, heat, MW, and magnetic fields, can also clear bacteria.

2.2.1. Breaking extracellular polymeric substances

The extracellular polymeric substance (EPS) in biofilms can shelter bacteria from host immune responses and also block the entry of

antibiotic substances [105–107]. Breaking down extracellular polymeric substances is an effective strategy against biofilm. For example, dextran-bismuth selenide (Dex-BSe) nanoparticles with an asymmetrical Janus structure could target extracellular polymeric substances to disperse or use NIR-activated photothermal eradication to eliminate drug-resistant biofilms, respectively. Specifically, the self-propelled active motion resulting from the unique Janus structure amplified the impact of photothermal death by concentrating nanoparticles at infection sites (Fig. 4**c**) [108]. The antimicrobial polymeric nanoparticles (PNPs) would disrupt the biofilm by US treatment, which also improved the antibacterial action of PNPs by enhancing their penetration into bacterial biofilms (Fig. 4**d**) [109].

2.2.2. Disrupting the structure of biofilms

Matrix-degrading enzymes (MDEs) can break down cohesive elements and help sessile biofilm organisms transition into free-floating bacteria [21]. Microbubbles (MBs) have been considered alternative drug delivery platforms due to their unique acoustic characteristics [110,111]. MBs can oscillate and create local microstreams through inertial cavitation under US irradiation, breaking down biofilm structures and making holes and channels that allow drug molecules to penetrate more easily [111]. For example, liposome-shelled microbubbles (MBs) could break up *Staphylococcus epidermidis* biofilms and improve vancomycin penetration under US irradiation [112]. Although MBs may physically shatter biofilms under US stimulation, the intact biomacromolecules in the EPS hinder the complete elimination of bacteria within biofilms through antibiotic treatment [113]. Additionally, H_2O_2 can be catalyzed by Fe_3O_4 NPs with peroxidase-like catalytic activity to produce free radicals and break down the biofilm matrix [114,115]. As shown in Fig. 4**e**, nanocatalyst-shelled microbubbles with US-responsive properties were designed to effectively treat chronic lung infections caused by *P. aeruginosa* biofilms through the simultaneous physical/chemical destruction of biofilms. The Fe_3O_4 NPs can produce free radicals and break down the biofilm matrix by catalyzing H_2O_2. Through physical shear stresses, the MB-Pip may break up biofilms during US irradiation, allowing Fe_3O_4 NPs and Pip to enter the deep layer of *P. aeruginosa* biofilms. Fe_3O_4 NPs can catalyze infected tissues' overexpressed H_2O_2 to create •OH, which chemically breaks down biofilms and eliminates the bacteria they contain. The exposed *P. aeruginosa* can also be effectively inactivated by the penetrating Pip [116].

2.3. Kinetics of the bactericidal or bacteriostatic activity of SRAMs under exogenous stimuli

The time-kill and concentration-kill studies elucidate the kinetics of bactericidal or bacteriostatic activity. The AF generated by SRAMs was related to treatment duration and material concentration, resulting in an enhanced antibacterial efficiency rate. Compared with endogenous responsive smart materials, the exogenous responsive smart materials presented an excellent antibacterial efficiency within a short time, specifically within half an hour. Understanding the kinetics of antimicrobial or bacteriostatic action is crucial for designing exogenous responsive smart materials. The number of bacteria will decrease sequentially with the prolonged stimulation time [43]. Longer treatment time will produce more AF and increase its bactericidal or bacteriostatic activity. For example, the antibacterial rates of Fe_3O_4/ CNT/Gent were 6.96 %, 47.82 %, 72.68 %, and 99.72 % against MRSA after exposure to MW irradiation for 5, 10, 15, and 20 min, respectively [43]. Furthermore, treatment cycling could further boost antibacterial performance [117]. For example, the antibacterial rates achieved by Ti–RP-SNO + US (one cycle) and Ti–RP-SNO + US (two cycles) were 93.40 % and 99.99 %, respectively [117]. When the concentration of SRAMs exceeds a certain threshold value, the killing rate is also related to the concentration of SRAMs [42]. For example, effective bacterial eradication was not observed when the concentration of $Bi_2S_3/Ti_3C_2T_x$-5 was 50 ppm or 100 ppm for both *S. aureus* and *E. coli*. However, the bacteria-killing efficiencies of $Bi_2S_3/Ti_3C_2T_x$-5 would reach up to 99.86 % and 99.92 % against *S. aureus* and *E. coli*, respectively, after performing NIR irradiation for 10 min, when the concentration was 200 ppm [42].

3. Developing processes of smart responsive materials

Since their first appearance, "smart response materials" have gradually evolved from a simple static response to a complex dynamic response with multiple factors, from biological inertia to biological complexity. Materials are more intelligent and better integrated with the physiological environment. More complex physical and biological properties can be adjusted and manipulated to better adapt to the complex and dynamic environment in the body. First, the multifunctional design of materials is achieved by combining the intrinsic properties of organisms and materials; second, physiological signals and remote stimulation are used to manipulate and control biomaterial properties, introducing dynamic behavior into biomaterials to obtain complex biological functions. Finally, responsive materials triggered by light, US, and MW are used to endow SRMs with the ability to treat deep infectious tissue diseases. And the antibacterial activity of SAMs was mainly involved with the bactericidal or bacteriostatic properties.

3.1. From static to dynamic

Examining the development history of SRMs, it can be seen that they have developed from being able to respond only to a single response to multiple responses. Biomaterial design advances enable the incorporation of dynamic features into biomaterial platforms [118]. And they can also provide signals to surrounding cells and tissues [119]. "Living cells" have received increasing attention because they can respond to complex metabolites and release signals autonomously. In addition, living cells have evolved a variety of metabolic pathways during everyday life activities and have strong biocatalytic capabilities. They can convert raw materials such as water, carbon dioxide, inorganic salts and nutrients into a series of biological materials (such as polysaccharides, proteins, lipids and biominerals). Some natural materials, such as bone, wood, or bacterial biofilms, can respond to changes in environmental factors (pH,

salinity, temperature, light intensity or direction, mechanical stress, etc.) through adjustments in composition, structure, and properties [120–122]. Autonomous growth, sensing, metabolite secretion, and regeneration are properties inherent to many natural biomaterials [119]. In a specific living environment, this type of material will make a series of reactions based on the characteristics of the environment, introducing dynamic properties to the material. However, when living cells/living bacteria are used alone, there are great requirements for the use environment and storage conditions. The most effective way is to use non-biological components to combine with living cells or living bacteria to improve the environmental tolerance of living cells/living bacteria and form 'living materials' [123]. For example, live bacterial preparations were formed by encapsulating live *Bacillus subtilis* into thermoresponsive hydrogels [124]. The material's mechanical characteristics can be adjusted by altering the ratio between polymer concentration to bacterial culture medium, inhibiting bacterial growth, etc. As shown in Fig. 5, live bacterial preparations penetrate the stratum corneum and accumulate in the epidermis without penetrating the inner dermis layer, quickly solidifying on the skin surface after use. The live *Bacillus subtilis* (*B. subtilis*) in the gel secretes antifungal substances during normal life metabolism, effectively inhibiting the growth of *Candida*. In addition, because *B. subtilis* is encapsulated in the gel, it does not come into direct contact with the tissue, and there is no problem of potential tissue bacterial infection. The bacteriostatic effect of this bacterial preparation is comparable to that of clinically used ketoconazole.

3.2. From simple to biocomplex

Another latest direction of SRMs is designing material systems responsive to and integrated into biological functions. Such material systems go beyond the simple needs of biological tissues for materials, focusing on the characterization of biological tissues. From the signal processing and exchange perspective, material systems were designed to interact more complexly with biological tissues. In other words, smart responsive material systems pay more attention to the interaction between materials and cells/bacteria, which is based on thoroughly understanding the characteristics of the material/biological interfaces. In nature, dynamic physicochemical interactions, kinetics, and thermodynamic exchanges between materials and biological elements such as proteins, cell membranes, vesicles, organelles, DNA, and biological fluids are examples of the interaction between materials and cells [125]. For example, Hu's group [126] designed nanohole-enriched molybdenum disulfide (NR-MoS_2), which could influence the electron transfer between materials and bacteria through nanopores based on the characteristics of the biomaterial interface, destroying the integrity of the extracellular matrix of biofilm. NR-MoS_2 and biofilm act as electron donors and acceptors, respectively. After them come into contact, the electrons in NR-MoS_2 are transferred to the bacterial biofilm. The expression of genes related to biofilm formation in bacteria was significantly down-regulated. The key components of biofilms were also damaged, including proteins, polysaccharides for intercellular adhesion, extracellular DNA, etc [126]. The cell membrane-coated nanoparticles could form nanobionic carrier particles [127]. The cell membrane type could imitate specific natural cells' functions to adapt to complex physiological environments and endow the nanoparticles with good biocompatibility and immune evasion [127]. Zhang's group[128] constructed HA-mRNA-NP composite nanocarrier using cell membrane of engineered cells expressed the influenza virus fusion protein hemagglutinin (HA) to wrap poly (lactic-co-glycolic acid) (PLGA) loaded with mRNA (HA-mRNA-NP composite nanocarrier). The cell membrane coating provides a biological interface to the nanocarriers, giving NPs immune evasion properties. After the composite nanocarrier is endocytosed by target cells, the low pH in the endosome causes the conformation of HA to change, triggering the membrane fusion process, and the loaded mRNA escapes into the cytoplasm. It is translated into protein products, treating subsequent diseases.

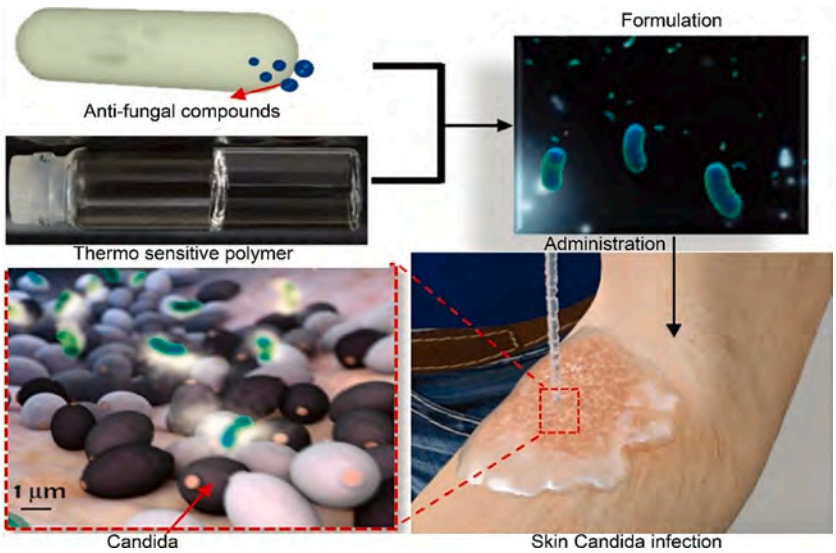

Fig. 5. The illustration of the formation of living bacterial agents and their treatment of skin infection.[124] Adapted with permission. Copyright 2018, Wiley-VCH.

3.3. From surface to deep

With further research and understanding of the optoelectronic properties of materials and the requirements for material structure from the perspective of physiological indicators, smart response materials have developed from short-wavelength (ultraviolet) response to long-wavelength (MW) response. Among them, light in the ultraviolet and visible spectrum has a penetration depth of only a few millimeters in biological tissue [129]. NIR has a tissue penetration depth of 1 to 2 cm [130,131]. The penetration depth of 915 MHz and 2.45 GHz microwaves in tissue is approximately 2 to 4 cm [132]. The tissue penetration depth of the US exceeds 10 cm [133,134]. From a historical perspective, designing corresponding exogenous smart response materials based on exogenous stimulation methods can achieve controllable release of signals from the outside to the inside. Take those researches as examples [135–137]. These nanoplatforms can release drugs in a controlled manner in response to various exogenous stimuli such as light, US, and magnetism [138]. The light-responsive biomaterial system consists of antibody prodrugs, dendritic macromolecules, and upconversion nanoparticles. Ultraviolet light and NIR can be used as stimuli to regulate the loaded drug with controlled release. US materials such as microbubbles, bubble liposomes, and nanogels can improve intracellular drug delivery efficiency and control the release rate of drugs by destroying cell membranes under US irradiation. Magnetically responsive biomaterial system was formed by using encapsulation, surface coating, or coupling to load drugs onto magnetic materials. The drug is released in situ to the target location under the stimulation of a magnetic field.

4. Current status of smart responsive antibacterial materials for antibacterial therapy

SRAMs can respond to various stimulus signals, and according to the way of giving stimulation factors, they can be divided into three categories: endogenous responsive antibacterial materials, exogenous responsive antibacterial materials, and multi-response antibacterial materials (Fig. 6 and Table 2). Under the stimulation of endogenous or exogenous signals, the structure and function of SRAMs will change, thereby releasing specific signals to achieve precise treatment of diseases in time and space. SRAMs could generate ROS, heat, leached ions, or so on upon particular stimuli (e.g., Redox species, pH, temperature, light, US, MW, and so on). Their antibacterial activity is mainly related to their bactericidal and bacteriostatic property. In recent years, developments in materials chemistry, biomolecular engineering, pharmaceutical science, micro-nano manufacturing, and other fields [139], as well as people's in-depth understanding of various biological reaction mechanisms, have further promoted the development and design of SRMs.

4.1. Endogenous stimuli-responsive antibacterial materials

The bacterial communities present at infection sites are intricate systems containing various types of bacteria and a distinct metabolic environment marked by acidic conditions, elevated local temperatures, high levels of reactive oxygen species, unique enzymes, and scarcity of nutrients[140–142]. Endogenous stimuli-responsive antibacterial materials often change their structure and properties to release antibacterial factors in direct physical contact with the stimuli. That part is mainly about the principle of designing endogenous stimuli-responsive antibacterial materials, including redox species-sensitive systems, pH-sensitive systems,

Fig. 6. 'Galaxy' of SRAMs. These materials rely on the way of releasing signals whether they need to be in contact with stimulation factors. The SRAMs mainly include endogenous responsive antibacterial materials (redox species, pH, temperature, and so on), exogenous responsive antibacterial materials (light, US, MW, and so on), and multistimuli-responsive antibacterial materials (pH and ROS, and so on).

Table 2
Summary of the SRMs for antibacterial application.

	Stimulus	SRAMs	Antimicrobial rates	Bacterial strains	Antibacterial mechanism	Reference
1	Redox species and NIR	MnO_2 hybrid (BMH) hydrogel	92.6 %	• MRSA	• ROS • Heat	Zhang et al. (2020) [287]
2	Redox species	TM/BHT/CuTA hydrogel	98.51 93.13 90.50	• *P. gingivalis* • *S. aureus* • *E. coli*	• •OH • $\bullet O_2^-$	Wang et al. (2023) [288]
3	NIR	g-C_3N_4@ Bi_2S_3 nanorods	99.20 % 99.60 %	• MRSA • *E. coli*	• •OH • $\bullet O_2^-$ • Heat	Wu et al. (2019) [289]
4	Visible light	PAM-PDA/Ag@AgCl hydrogels	99.97 % 99.91 %	• *S. aureus* • *E. coli*	• •OH • $^1O_2$ • Heat	Wu et al. (2019) [290]
5	660 nm + 808 nm	g-C_3N_4-Zn^{2+}@graphene oxide	99.10 %	• *S. aureus* • *E. coli*	• ROS • Heat	Wu et al. (2018) [291]
6	NIR (1064 nm) + pH	Ag/Bi_2MoO_6 (Ag/BMO) nanozyme	99.90 %	• MRSA	• Ag^+ • $\bullet O_2^-$ • Heat	Zhao et al. (2022) [292]
7	US	PCN-222-BTO	99.96 %	• MRSA	• $\bullet O_2^-$ • $^1O_2$ • Disturb electron transport chain	Tan et al. (2023) [212]
8	X-Ray	$Cs_3Cu_2I_5$@(Nisin + PEG-b-pCouNO)	96.00 %	• MRSA	• NO • $\bullet O_2^-$ • •OH • ONOO•	Zhang et al (2024) [268]
9	NIR	Ti-MoS_2-IR780-PDA-RGDC	98.99	• *S. aureus*	• $^1O_2$ • Heat	Wu et al (2019) [169]
10	NIR	Bi_2S_3/$Ti_3C_2T_x$	99.86 % 99.92 %	• *S. aureus* • *E. coli*	• ROS • Heat	Wu et al (2021) [42]
11	MW	$Ti_3C_2T_x$/ZnO–PPy	99.11 %	• MRSA	• $\bullet O_2^-$ • $^1O_2$ • Heat	Xiangmei Liu (2024) [293]
12	US	ZnO@ glucose-derived carbon spheres (HTCS)	99.788 %	• MRSA	• ROS	Xiangmei Liu (2024) [294]
13	MW	MoS_2/CNTs	99.97 %	• *S. aureus*	• Heat • $^1O_2$	Xiangmei Liu (2024) [295]
14	US	cationic starch@ curcumin nanoparticles	99.90 % 99.96 % 99.927 % 99.79 %	• MRSA • *S. aureus* • *E. coli* • MREC	• •OH • $^1O_2$ • Heat	Xiangmei Liu (2023) [296]
15	MW	Mn-doped porphyrin MOF loaded with calcium peroxide	99.71 %	• MRSA	• Heat • ROS	Xiangyu Zhang (2024) [297]
16	pH + NIR	PLNP@PANI-GCS	Over 99 %	• MRSA • *S. aureus* • *E. coli*	• Precise heat	Xiuping Yan (2020) [298]
17	US	Pd@Pt-T790	Nearly 100 %	• MRSA	• $^1O_2$	Nanfeng Zheng (2020) [266]
18	US	multiphase $BaTiO_3$	95 %	• *E. coli*	• •OH • $\bullet O^{2-}$	Xianzeng Zhang (2023) [299]
19	NIR	phosphorus/MnO_2 nanocomposite	Over 99.00 %	• MRSA	• •OH • Heat	Qinglin Kang (2023) [300]
20	NIR	MXene/SnS_2	89.50 % 95.40 %	• *S. aureus* • *E. coli*	• •OH • $\bullet O^{2-}$ • Heat	Yi Deng (2022) [301]
21	NIR + pH	CuFeOx/IR825@PCM	97.60 %	• *S. aureus*	• •OH • Cu^+ • Fe^{2+} • Heat	Yu Cai (2024) [302]
22	Enzyme	PEG-Schiff-Van@Van	86.70 %	• MRSA	• vancomycin	Baoqiang Cao (2020) [157]
23	NIR	TiO_2/TiO_{2-x}	96.88 % 97.56 %	• *E. coli* • *S. aureus*	• •OH • $^1O_2$ • Heat	Haobo Pan (2022) [303]
24	MW	Garcinia NPs	99.99 % 99.62 % 99.48 %	• *S. aureus* • MRSA • *E. coli*	• Heat • Gercinia	Shuilin Wu (2022) [88]

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Table 2 (*continued*)

	Stimulus	SRAMs	Antimicrobial rates	Bacterial strains	Antibacterial mechanism	Reference
25	US	RBC-HNTM-MoS_2	98.50 %	• MRSA	• $^1O_2$ • $\bullet O^{2-}$ • Mechanical force	Cao Yang (2022) [211]
26	US	PFP@Lip-Ce6/ metronidazole	99.99995 %	• *P. aeruginosa*	• $^1O_2$ • Metronidazole • Oxygen consumption	Lianhui Wang (2024) [259]
27	US	ZnTCPP@ZnO	99.73 %	• *Propionibacterium acnes*	• $^1O_2$	Kelvin W. K. Yeung (2023) [101]
28	US	MB-Pip	99.9993 %	• *Pseudomonas aeruginosa*	• •OH	Lianhui Wang (2023) [116]
29	H_2O_2 + NIR	Cu-POM	53.56 %	• *S. aureus*	• •OH • Heat	Chen Zhu (2023) [304]
30	NIR	SeC@PA	99.9996 %	• *S. aureus*	• NO • Heat • •OH • $^1O_2$	Xiaowei Zeng (2023) [305]
31	MW	Fe_3O_4/CNT/Gent	99.556 % 98.529 %	• MRSA • *E. coli*	• Gentamicin • Heat	Shuilin Wu (2020) [43]
32	NIR	GP-dAuNPs@Ce6	94.50 % 92.80 % 97.60 % 93.20 %	• *S. aureus* • *M. luteus* • *E. coli* • *P. aeruginosa*	• $^1O_2$ • Heat	Yao He (2022) [306]
33	US	Ver-PLGA@Lecithin	99.90 %	• *Helicobacter pylori*	• $^1O_2$	Lihua Yang (2024) [307]
34	US	MoS_2/Cu_2O	99.85 %	• *S. aureus*	• ROS • Cu ion	Xiangmei Liu (2023) [308]
35	H_2O_2 + US	PH-CpBT	99.90 % 99.95 %	• *S. aureus* • *E. coli*	• •OH • $^1O_2$ • Cu ion	Duan Wang (2024) [264]
36	H_2O_2 + NIR	$NP^{M123/Fc}$	91.42 % 94.54 %	• *S. aureus* • *P. aeruginosa*	• •OH • Heat	Dongsheng Zhou (2024)[309]
37	pH	ZnO-CuS microspheres	> 99 % > 99 %	• *MRSA* • *E. coli*	• •OH • Zn^{2+} • Cu^{2+}	Xianwen Wang (2024)[310]
38	NIR	TPA-Py@AuNCs ⊂ BSA	> 99 % > 99 %	• *S. aureus* • *E. coli*	• Ag^+ • Heat • ROS	Haitao Feng (2024)[311]
39	Light + US	Hf-based UIO-66 NPs	> 99 % > 99 %	• *S. aureus* • *E. coli*	• •OH • $\bullet O^{2-}$	Jianlin Shi (2024) [312]
40	808 nm	γ-PGA/PDA/GO_x/WO_x	> 99.99 % > 99.99 %	• *S. aureus* • *E. coli*	• •OH • Heat	Peng Li (2024) [313]
41	X ray	$Cs_3Cu_2I_5$@(Nisin + PEG-b-pCouNO)	> 99.99 %	• MRSA	• ROS • RNS	Duo Mao (2024)
42	US	$BiFeO_3$/Ti_3C_2	99.87 %	• *S. aureus*	• •OH • $\bullet O^{2-}$ • Heat	Shuilin Wu (2023) [314]
43	pH	copper−manganese NPs	> 99 %	• MRSA	• Cu^{2+} • Mn^{2+}	Min Zhou (2024) [315]
44	pH + NIR	PpIX-RSE	93.06 % 99.46 %	• *S. aureus* • *E. coli*	• NO • $\bullet O^{2-}$ • $ONOO^-$	Funeng Xu (2024) [316]
45	NIR	Bi_2MoO_6@sRuO2 @HA NPs	nearly 100 % nearly 100 %	• *E. coli* • MRSA	• •OH • $\bullet O^{2-}$ • $^1O_2$ • Heat	Yanan Liu (2024) [317]
46	H_2O_2	copper-doped carbon dots	nearly 100 % nearly 100 %	• *S. aureus* • *E. coli*	• •OH • $\bullet O^{2-}$	Xiaodong Xing (2024)[318]
47	H_2O_2	ZIF-8-pPt	99 % 99 %	• *S. aureus* • *E. coli*	• ROS	Dianping Tang (2024)[319]
48	NIR + pH	HPC/GPC/PFD hydrogel	nearly 100 % nearly 100 %	• *E. coli* • MRSA	• ROS • Heat	Baolin Guo (2024) [320]
49	T + pH	CS/NIPAM hydrogel	99 % 81.78 %	• *S. aureus* • *E. coli*	• Ga^{3+}	Xiaobin Jiang (2024)[321]
50	NIR	EGCG-Au NPs	99.94 % 96.62 % 99.98 %	• *S. aureus* • MRSA • *E. coli*	• ROS • Heat	Xiangchun Zhang (2024)[322]

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Table 2 (*continued*)

	Stimulus	SRAMs	Antimicrobial rates	Bacterial strains	Antibacterial mechanism	Reference
51	NIR	levofloxacin-loaded polydopamine NPs (PDA@Levo)	87.4 % 68.7 %	• *S. aureus* • *P. aeruginosa*	• Levofloxacin • Heat	Daidi Fan (2022) [323]
52	pH + H_2O_2	Cu-TCPP	92 % 99 %	• *S. aureus* • *E. coli*	• ROS	Jindan Wu (2024) [324]
53	NIR + H_2O_2	GNR@CeO_2@GNPs	91.2 % 88.0 %	• *E. coli* • MRSA	• •OH • Heat	Ying-Wei Yang (2024)[325]
54	NIR + H_2O_2	C − Fe_3O_4	65.7 % 99.9 %	• *S. aureus* • *E. coli*	• •OH • Heat	Xufu Jian (2021) [326]
55	NIR	NFLA/CuS NHs	> 90 % > 90 %	• *E. coli* • MRSA	• NO • Cu^{2+} • Heat	Lei Liu (2024) [140]
56	NIR	ICG-Au_{15}NCs	99.94 %	• *S. aureus*	• •OH • $•O^{2-}$ • $^1O_2$ • Heat	Zhennan Wu (2024)[327]
57	pH + H_2O_2	ZnO-CuS/F127 Hydrogel	nearly 100 %	• *E. coli*	• •OH • Cu^{2+} • Zn^{2+}	Xianwen Wang (2024)[328]
58	MW	gentamicin loaded Fe_3O_4/PB NPs	99.90 % 99.90 %	• *S. aureus* • *E. coli*	• $•O^{2-}$ • $^1O_2$ • Heat • gentamicin	Xiangmei Liu (2024)[329]
59	NIR + H_2O_2	BGN-Fe-Ag_2S NPs	nearly 100 %	• *S. aureus*	• •OH • Heat	Yongxiang Zhao (2022)[330]
60	NIR + pH	LAMC/CD-C@M@P	nearly 100 % nearly 100 %	• *S. aureus* • *E. coli*	• Heat • ROS	Honglian Dai (2024)[331]
61	US	(CuMn)- quercetin	nearly 100 %	• MRSA	• Quercetin • $^1O_2$	Xiaobo Feng (2024)[332]
62	NIR	MXene/CaO_2 bio-HJs	nearly 100 % nearly 100 % nearly 100 %	• *S. aureus* • *E. coli* • MRSA	• Heat • Ca^{2+} • •OH • $^1O_2$	Yi Deng (2024) [333]
63	Redox species	Fe single-atom catalysts	nearly 100 % nearly 100 %	• *S. aureus* • *P. aeruginosa*	• •OOH • $•O^{2-}$	Jianlin Shi (2024) [334]
64	NIR + H_2O_2	SP/GOx/MnCO	nearly 100 % nearly 100 %	• *S. aureus* • *E. coli*	• Heat • CO • •OH	Kunneng Liang (2024)[335]
65	pH	rGO@FeS_2	nearly 100 %	• *Candida albicans*	• Biological extracts • •OH	Hui Wei (2023) [336]
66	T	tannic acid − loaded thermoelectric hydrogel	94 % 90 %	• *E. coli* biofilm • MRSA biofilm	• Tannic acid	Feng Yan (2024) [337]
67	H_2O_2	WS_2/WN	nearly 100 % nearly 100 %	• *E. coli* • MRSA	• •OH	Xin Yu (2024) [338]
68	NIR	TiO_2/Bi_2WO_6	99.03 % 99.11 % 98.31 %	• *E. coli* • MRSA • *P. gingivalis*	• ROS • Heat	Chuanbin Mao (2024)[228]
69	NIR	ferric iron/shikonin NPs-embedded hydrogels	nearly 100 %	• MRSA	• ROS • Heat	He Li (2024)[339]
70	NIR + H_2O_2	2TT-mC_6B@CeO_2@FA	> 99 % > 99 %	• *E. coli* • MRSA	• Heat • ROS	Ming Zhang (2024)[340]
71	H_2O_2	MOF/CGA@GP-CS	99.91 % 99.97 %	• *E. coli* • *S. aureus*	• CGA	Na Wang (2024) [341]
72	Infectious microenvironment	minocycline hydrochloride-loaded glycopeptide hydrogel	nearly 100 %	• *S. sanguinis* • *F. nucleatum* • *P. gingivalis*	• minocycline hydrochloride	Zujian Feng (2024)[342]
73	pH + NIR	CuFeOx/IR825@PCM	nearly 100 %	• MRSA	• •OH • Heat	Yu Cai (2024) [302]
74	H_2O_2	$CuCo_2O_4$ Nanoflowers	99.79 % 99.42 %	• *E. coli* • MRSA	• •OH • $•O^{2-}$ • Cu^{2+}	Xianwen Wang (2024)[343]
75	bacterial membrane components	oxygen vacancies-rich ZnO/ kaolinite	> 99 % > 99 %	• *E. coli* • *S. aureus*	• •OH • $•O^{2-}$ • $^1O_2$ • Zn^{2+}	Huaming Yang (2024)[344]
76	pH	carboxymethyl chitosan-oxidized dextran hydrogel	> 99 %	• *P. gingivalis*	• Embelin	Juan Xia (2024) [345]

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Table 2 (*continued*)

	Stimulus	SRAMs	Antimicrobial rates	Bacterial strains	Antibacterial mechanism	Reference
77	H_2O_2 + NIR	$CuFe_2S_3$@lactate oxidase	~99.99 % ~99.99 %	• *E. coli* • *S. aureus*	• •OH • $^1O_2$ • Cu^{2+} • $•O^{2-}$	Weizhong Yang (2024)[346]
78	OXD GSH	Copper-gallic acid-vancomycin nanoneedles	~95 % ~75 %	• MRSA • *E. coli*	• ROS • vancomycin • Cu^{2+}	Xianwen Wang (2024)[347]
79	H_2O_2	silver-enzyme nanogels	nearly 100 % nearly 100 %	• *E. coli* • *S. aureus*	• •OH • Ag^+	Chaobin He (2024)[348]
80	NIR	liquid metal@ polydopamine @Ag	nearly 100 %	• MRSA	• ROS • Heat • Ag^+ • Ga^{3+}	Xuyang Sun (2024)[349]
81	NIR + US	Ag-TiO_2-L-arginine	nearly 100 % nearly 100 %	• *E. coli* • *S. aureus*	• •OH • $•O^{2-}$ • NO • Heat	Lin Wang (2024)[350]
82	MW	Cu/C/Fe_3O_4-COOH	99.99 %	• *S. aureus*	• Heat • Cu ions • $•O^{2-}$	Xiangmei Liu (2024)[351]
83	ROS	cerium-alendronate supramolecular hydrogel	~89.7 % ~89.7 %	• *E. coli* • *S. aureus*	• Ce ions	Liang Cheng (2024)[352]
84	pH	peptide L5@LysSYL hydrogel	nearly 100 %	• *S. aureus*	• LysSYL	Xiancai Rao (2024)[353]
85	H_2O_2	CSHSs	nearly 100 % nearly 100 % nearly 100 %	• *E. coli* • *S. aureus* • *P. gingivalis*	• •OH	Zhen Liu (2024)[354]
86	US	ZnO@BT/HA	> 95 % > 95 %	• *E. coli* • *S. aureus*	• ROS	Guomin Wu (2025)[355]
87	Light	$TBSMSPy^+$	> 99 % > 99 %	• *P. gingivalis* • *F. nucleatum*	• redox imbalance	Benzhong Tang (2024)[356]
88	H_2O_2 + pH	$CuFe_5O_8$ nanocubes	nearly 100 % nearly 100 %	• *E. coli* • *S. aureus*	• •OH	Xianlong Zhang (2020)[142]
89	pH	DCPNAs	nearly 100 % nearly 100 %	• *S. aureus* • *Salmonella*	• Cu^{2+} • H_2O_2	Jianlong Wang (2021)[357]
90	pH	SSPMs		• *Staphylococci*		Linqi Shi (2020)[358]
91	Microenvironment	Gel/*L. reuteri*@FeTA	nearly 100 % nearly 100 %	• *E. coli* • *S. aureus*	• Biological extracts	Yong Sun (2023)[359]
92	US	Ti_3C_2-SD(Ti^{3+})	99.72 %	• MRSA	• Heat • $^1O_2$	Kelvin Wai Kwok Yeung (2023)[360]
93	US	AMV@NanoCip	99.99 %	• MRSA	• Ciprofloxacin • •OH	Gang Liu (2024)[361]
94	US	Ti-RP-SNO	nearly 100 %	• MRSA	• Heat • NO	Shuilin Wu (2021)[117]
95	US + NIR	CuS/Curcumin	99.56 % 99.48 %	• *S. aureus* • *E. coli*	• Heat • $^1O_2$ • •OH • $•O^{2-}$	Shuilin Wu (2021)[362]
96	US + NIR	Ti − S − TiO_{2-x}	99.995 %	• *S. aureus*	• Heat • $^1O_2$ • •OH	Shuilin Wu (2020)[232]
97	US	Fe_3O_4/TiO_2	99.50 %	• *S. aureus*	• •OH • $•O^{2-}$ • Disturb electron transport chain	Lan Zhang (2024)[363]
98	US	$BaTiO_{3-x}$/LA	nearly 100 %	• MRSA	• •OH • $ONOO^-$	Paul K. Chu (2024)[364]
99	US	PCN-224-coated MnO_2-hydrangea NPs	nearly 100 %	• *E. coli* • MRSA	• ROS	Chen Zhu (2024)[263]
100	US	lattice-strain-rich Ti_3C_2	99.77 %	• MRSA	• •OH • $^1O_2$	Xiangmei Liu (2023)[365]
101	US	BODN-NP	nearly 100 % nearly 100 %	• *S. aureus* • MRSA	• •OH • $^1O_2$	Wenliang Li (2024)[366]
102	US	CuO_2/TiO_2	>99.9999 % >99.9999 %	• MRSA • *P. aeruginosa*	• $•O^{2-}$ • Cu^{2+}	Zhiling Zhu (2023)[367]

(*continued on next page*)

Table 2 (*continued*)

	Stimulus	SRAMs	Antimicrobial rates	Bacterial strains	Antibacterial mechanism	Reference
103	US	IBV-TENG	nearly 100 % nearly 99 %	• *S. aureus* • *E. coli*	• voltage • current	Sang-Woo Kim (2023)[368]
104	pH/lipase	MSCO@PPEL	99.4 % 99.2 %	• *E. coli* • MRSA	• H_2O_2 • NO • Cu^{2+}	Baolin Guo (2024) [369]
105	pH	MPH NPs	98.5 % nearly 100 % 98.4 %	• *S. aureus* • *E. coli* • MRSA	• $•O^{2-}$ • •OH	Huayu Tian (2024)[370]
106	MW	MoO_2/WO_3	99.27 % 99.23 %	• *S. aureus* • MRSA	• Heat • ROS	Shuilin Wu (2022) [371]
107	MW	Au/Cu–BTA	99.998 % 99.966 % 96.871 %	• *S. aureus* • MRSA • *P. aeruginosa*	• Heat • $•O^{2-}$ • Cu^{2+}	Shuilin Wu (2024) [372]
108	MW	$BaSO_4/BaTi_5O_{11}$@PPy	99.61 %	• *S. aureus*	• Heat	Xiangmei Liu (2023)[373]
109	MW	Mn0.1PCC	99.71 %%	• MRSA	• Heat • •OH	Xiangyu Zhang (2024)[297]
110	US	2DMOF-TiO_2	93.99 %	• MRSA	• extracellular and intracellular electron transfer • ROS	Shuilin Wu (2024) [374]
111	US	2DMOF-MoS_2	99.56 % 98.12 % 95.80 %	• *P. gingivalis* • *F. nucleatum* • *S. aureus*	• Zn^{2+} • ROS	Xiangyu Zhang (2024)[375]
112	MW	M−Fe_3O_4/Au	99.98 %	• *S. aureus*	• Heat • $•O^{2-}$	Shuilin Wu (2021) [215]

temperature-sensitive systems, enzyme-sensitive systems, and other-sensitive systems.

4.1.1. Redox species-sensitive systems

Endogenous stimuli-responsive antibacterial materials are activated by redox substances, which can undergo redox reactions with redox substances in the physiological environment [70]. During redox reactions, the primary chemical groups include disulfide bonds, organometallic complexes, viologens, and tetrathiafulvalene [143]. Under normal physiological metabolism, cells or bacteria will produce some redox substances through normal metabolic processes, such as ROS, cysteine, MDEs, thiol proteins, and other reducing secretions [70]. The content of extracellular and intracellular redox substrates has noticeable differences, which can be used to design redox-responsive materials. For example, Lo's group [144] constructed ROS and GSH dual-responsive micelles by copolymerizing ROS-responsive structure (diethyl sulfide (Des)) and GSH-responsive structure (disulfide-containing cystamine (Cys)). The contents of ROS and GSH are low in normal physiological environments, and the micelle structure can remain stable, so the Camptothecin (CPT) is not released. In the pathological microenvironment, there is a high content of ROS and GSH, and the micelles gradually swell and rupture, releasing the CPT, thereby achieving sound treatment effects. Cheng's group [145] used the bacterial metabolites (Poly(3,4-

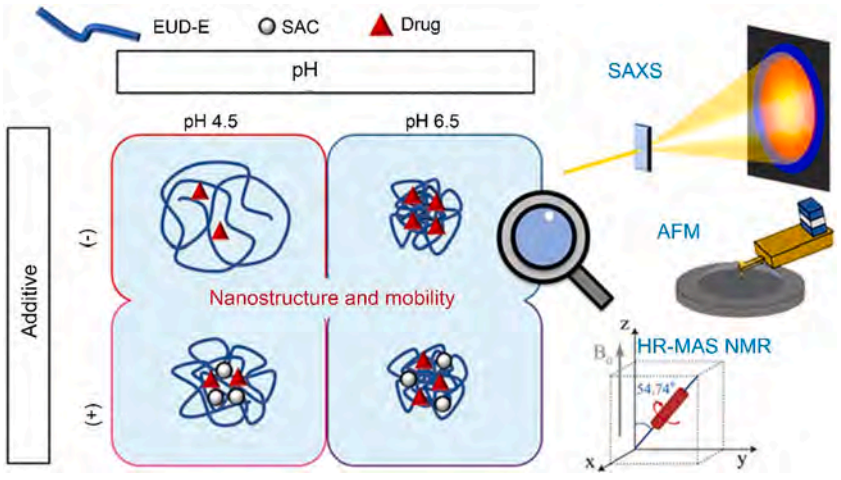

Fig. 7. Structural transformation diagram of EUD-E at different values of pH.[149] Adapted with permission. Copyright 2021, American Chemical Society.

propylenedioxythiophenalt-3,4-ethylenedioxythiophene) copolymer, PPE) to detect Gram-positive and Gram-negative bacteria. The oxygen in the environment would oxidize PPE into its oxidation state (ox-PPE), causing a fading reaction. The oxidized ox-PPE reacts chemically with reducing substances (such as cysteine and GSH) produced during bacterial metabolism, and the color of the solution changes.

4.1.2. pH-sensitive systems

Because of anaerobic fermentation and the ensuing inflammation, bacterial infections are typically characterized by very low pH levels [146]. pH-responsive smart materials are materials whose structure changes at a specific pH, such as expansion, contraction, dissociation, degradation, fusion, or rupture, thereby regulating subsequent biological reactions [146,147]. The primary causes of a material's pH sensitivity are ionizable groups' protonation or cleavable bonds' breakdown in acidic environments. Aminoalkyl methacrylate copolymer and methyl methacrylate copolymer are two typical pH-responsive polymers [148]. Aminoalkyl methacrylate copolymer is a U.S. Food and Drug Administration-approved cationic polymer that has enhanced solubility in acidic environments at pH < 5. Polymers made from acrylic acid, methacrylic acid, maleic anhydride, and N,N-dimethylaminoethyl methacrylate are classic examples. The structure of those materials would be changed at different pH. The small-angle X-ray scattering (SAXS), atomic force microscopy (AFM), and high-resolution magic-angle spinning nuclear magnetic resonance (HR-MAS NMR) are used to assess the influence of pH on the structure of aminoalkyl methacrylate copolymer (EUD-E) [149]. In detail, the aminoalkyl methacrylate copolymer (EUD-E) has a partially folded structure at a high value of pH (pH 5.5 ~ 6.5). It changes into a partially folded structure when the pH value is lowered (pH 4.0 ~ 5.0). It is a random coil structure (Fig. 7). This property of EUD-E gives this polymer excellent application prospects in treating infectious diseases. In addition, methyl methacrylate copolymer (Eudragit®-E100) is another typical pH-responsive material with low solubility at neutral pH and high solubility at low pH value. It can exist stably in cell culture media. When it is taken up by cells and enters lysosomes, the lower pH value in lysosomes can be used to promote the release of loaded drugs [150].

4.1.3. Temperature-responsive systems

Temperature-responsive smart materials are generally polymer materials with the lowest critical solution temperature (LCST). These polymers are naturally sensitive to physiological temperatures since the LCST falls between ambient and body temperatures [139]. LCST-containing polymers typically experience an abrupt phase change close to the LCST. This may be accomplished by changing the proportion of hydrophobic to hydrophilic components or swapping out the polymer's end groups [151]. Homopolymers and copolymers of poly(N-isopropylacrylamide) (PNIPAM) are currently the most studied thermosensitive polymers [151]. The LCST of the PNIPAM copolymer is about 32 °C. The LCST can be adjusted to close to body temperature by adding comonomers or hydrophilic groups [152]. As shown in Fig. 8**a**, the macroporous polyvinyl alcohol formaldehyde network grafted N-isopropylacrylamide to synthesize a PNIPAM-based hydrogel, whose phase transition temperature is 30 ~ 34 °C [153]. The hydrogel has an interconnected porous structure. The sample reaches expansion equilibrium within 80 s below 27 °C. However, when the sample is exposed to a relatively high temperature (48 °C), the polymer hydrogel undergoes a phase transition and quickly reaches expansion equilibrium within 40 s. Elastin-like polypeptides (ELPs) are another type of thermosensitive complex currently attracting attention [139]. By controlling the composition and length of the peptides in the polymer, the thermal response temperature of ELPs can be tuned from 0 °C to 100 °C [154]. The monomethoxy poly(ethylene glycol) (mPEG) is another temperature-responsive material (Fig. 8**b**) [155]. When the temperature is increased, the hydrogel is formed by gelation.

4.1.4. Enzyme-sensitive systems

A variety of enzymes (e.g., gelatinase [156], serine protease-like B enzyme [157], hyaluronidase [158], lipase [159], and so on [160]) in the microenvironment of bacteria can be used as stimulus factors to design enzyme-sensitive systems. The poly(ε-caprolactone) (PCL) and Pro-Leu-Gly-Val-Arg-Gly (PLGVRG) are generally standard enzyme-activatable peptide linkers, which could be cut

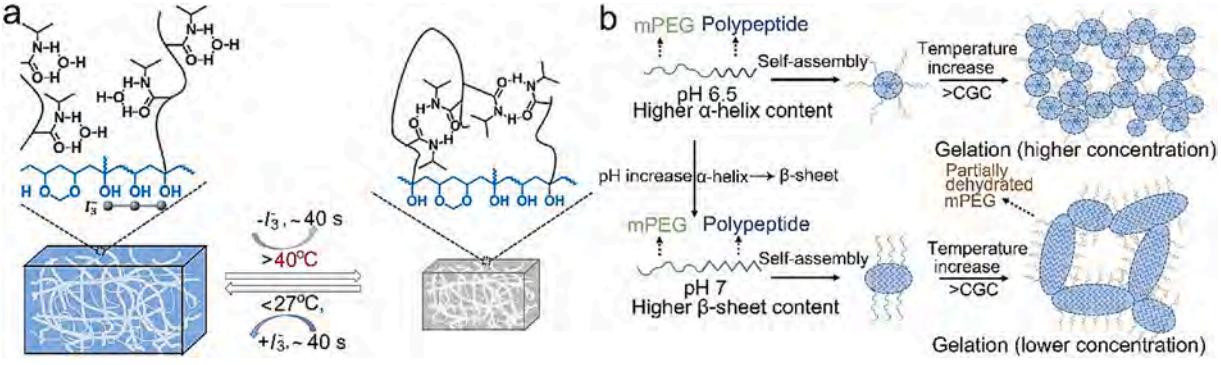

Fig. 8. The illustration of (a) the structure of PNIPAM-based hydrogel in different temperature[153] Adapted with permission. Copyright 2018, American Chemical Society. and (b) the structure of Polypeptide-based hydrogel in different temperature[155]. Adapted with permission. Copyright 2023, Wiley-VCH.

by lipase [161] and gelatinase [162], respectively. They act as cleavage sites to control the release rate of nanoparticles or drugs. For example, biocidal quaternary ammonium groups were linked by bioresponsive PCL segments in the middle to form triblock copolymers named reverse micelles (RM). Lipase produced by bacteria would enzymatically hydrolyze the PCL blocks of RMs. The biocidal agents, quaternary ammonium groups, was released in control to kill *S. aureus* in situ (Fig. 9**a**). The detailed structure of PLGVRG is as shown in Fig. 9**b**. Ppa-PLGVRG-Van included pyropheophorbide-α (Ppa) as a signaling molecule, Pro-Leu-Gly-Val-Arg-Gly (PLGVRG) as an enzyme-responsive peptide linker, and vancomycin (Van) as a antibiotic. The gelatinase secreated by bacteria would cut the PLGVRG linkers to control the release behavior of Van, bringing great antibacterial effects (Fig. 9**c**) [156].

4.1.5. Other-sensitive systems

Endogenous stimuli-responsive materials include redox-sensitive, pH-sensitive, temperature-sensitive, and enzyme-sensitive smart-responsive materials. Other stimuli include adenosine triphosphate (ATP) [163], ions [164], glucose [165], bacterial toxins [166], and so on. They are currently mainly used in the controlled release of drugs. Compared with non-responsive materials, responsive materials can interact with stimuli in the physiological environment and regulate their biological functions controllably. Many stimuli-responsive antibacterial systems can also target the infected region and further augment the bactericidal effect of materials.

Multiple stimuli-responsive antibacterial systems use various responsive materials to accomplish a wide range of necessary antibacterial tasks flexibly and on-demand, including bacterial biofilm infections and intractable drug-resistant bacterial infections. Without human assistance, dual bacterial metabolite stimuli may precisely identify an infected location and regulate bactericidal capabilities [70]. Antibacterial systems that respond to several stimuli are more intelligent, have multiple roles, and can kill drug-resistant bacteria and bacteria in biofilms and stop biofilm growth. Multiple stimuli mainly included bacterial metabolites and physical factors.

4.2. Exogenous stimuli-responsive antibacterial materials

External source-responsive smart materials are mainly involved with additional medical equipment. According to the tissue's penetration depth by the stimulation source, external stimulation is primarily divided into light, US, and MW. Based on this, researchers have designed a series of materials that can interact with different external stimuli such as light, US, and microwaves and have therapeutic functions [167]. Exogenous stimulation signals achieve non-invasive and remote controllability of materials and use the photoelectric properties of materials to generate ROS and heat in situ, which can be used to treat antibacterial and other diseases.

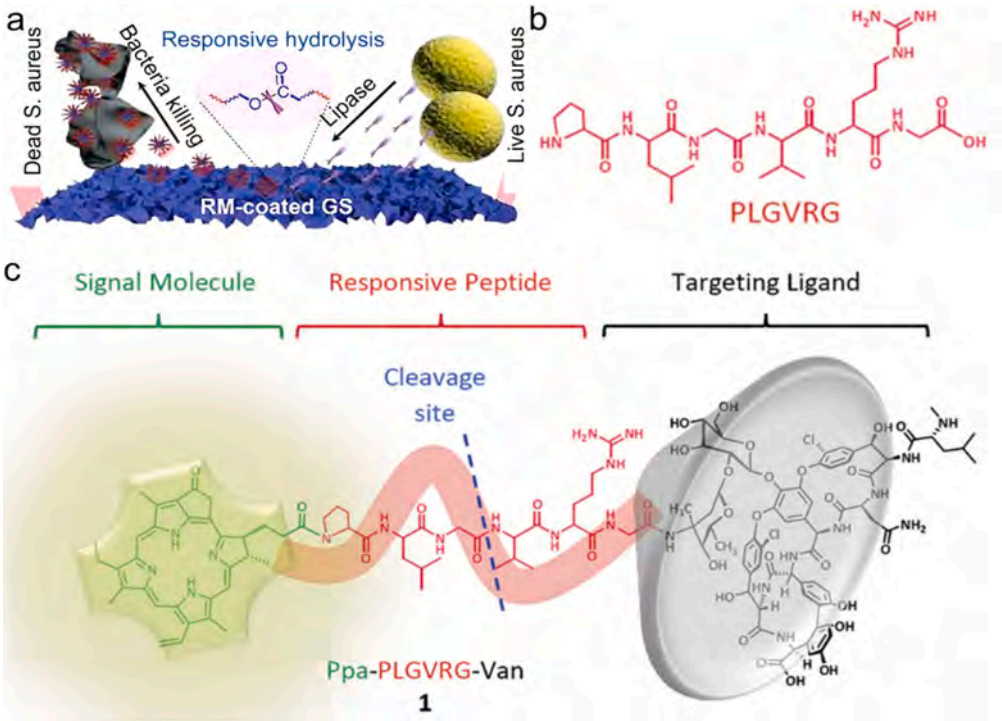

Fig. 9. (a) Schematic illustration for the mechanism of bioswitchable self-sterilization in bacterial infection site.[161] Adapted with permission. Copyright 2021, Wiley-VCH. (b) The molecular structure of PLGVRG. [156] Adapted with permission. Copyright 2015, Wiley-VCH. (c) The illustration of the forming mechansim of gelatinase-responsive materials.[156] Adapted with permission. Copyright 2015, Wiley-VCH.

4.2.1. Light-sensitive systems

Light-activated external source-responsive smart materials are irradiated by light of specific wavelengths, including ultraviolet light from 100 to 400 nm, visible light from 400 to 760 nm, and NIR light from 760 to 1350 nm, which can generate photoacoustic electrons and photogenerated holes to achieve subsequent photocatalytic and photothermal processes [168]. Recently, since bacteria can be somewhat killed by heat or the ROS they create when exposed to light, photoresponsive biomedical materials are intriguing substitutes for antibiotic-free treatment of bacterial illnesses [42,169].

Due to the differences in material structures, inorganic and organic photosensitizers (PS) exhibit completely different photoresponse processes. The following takes the photocatalytic process of titanium dioxide (TiO_2) as an example to explain the specific photocatalytic mechanism of the inorganic PS [170]. It is mainly divided into the following processes: (1) TiO_2 absorbs photons from the light, and when the energy of the photons exceeds the band gap of the photocatalyst, carriers are generated; (2) Some carriers recombine; (3) At the Ti(IV) site Capture conduction band electrons to generate Ti(III); (4) Surface titanol groups capture holes in the valence band; (5) Holes trigger oxidation reaction; (6) Photogenerated electrons trigger reduction pathway; (7) Further thermal reaction (such as hydrolysis or reaction with ROS) and photocatalytic reaction to generate ROS.

The photoreaction of the light-responsive functional groups, such as photoisomerization and photodimerization, provides the basis for the photochemical effect in polymers. Photochemically reactive compounds will create photoreversible covalent crosslinking spots in polymers when exposed to a specific wavelength and frequency of light. The cross-linking and de-crosslinking process of the polymer network then results in a reversible photochemical reaction [171]. Upon photoactivation, the organic PS is activated from the ground singlet state to the excited singlet state and then to the excited triplet state through intersystem crossing: for the type I PDT, the PS in T1 is involved in an electron transfer process to react directly with the triplet oxygen ($^3O_2$) or biological substrate for producing $\bullet O_2^-$ and $\bullet$OH, respectively; In type II PDT, cytotoxic $^1O_2$ is generated as a result of a transfer of energy between the PS in T1 and the surrounding $^3O_2$ [172]. For nanomaterials, it is generally accepted that the interfacial redox reactions of electrons and holes, which are produced when the semiconductor catalyst is exposed to the light of sufficient energy, are the main reactions that cause the photocatalytic effect, even though the precise mechanism of photocatalysis varies depending on the pollutants [173]. Few fundamental studies are conducted on the first and often extremely quick photocatalytic processes within and at the semiconductor surface when a photon with energy greater than the photocatalyst's bandgap energy is absorbed. However, knowing these processes is crucial for better designing photocatalytic and photothermal materials.

4.2.2. Ultrasound-sensitive systems

The tissue penetration depth of UV and visible light is limited due to the absorption of light by biological tissues [174]. US frequencies are higher than human hearing and range from 20 kHz to several gigahertz [175]. Its tissue penetration depth can reach several centimeters, which is significantly higher than the penetration depth of light, and it can solve the problem of the limited penetration depth of light-responsive smart materials. US waves can propagate with low loss in opaque or complex media, can be localized in small areas in space and time, and can be tuned in frequency over 12 orders of magnitude to couple to objects at different time and length scales efficiently. In addition, US can freely adjust the tissue penetration depth by changing the frequency, duty cycle, and exposure time, making it suitable for treating diseases at different depths [146]. The role of US in biological tissues can be divided into the interaction between US and liquid and between US and solid materials. Under ultrasonic waves, bubbles are generated in the liquid environment, resulting in bubble cavitation. The rapid and nearly adiabatic bubble collapse causes the internal temperature of the bubble to increase rapidly, accompanied by intense energy, resulting in luminescence (sonoluminescence) and triggering a series of chemical reactions (sonochemistry) [176]. The cavitation effect has two forms: stable and inertial cavitation. The process depends on surface tension, pressure, and frequency. Stable cavitation is caused by the oscillation of bubbles, a process that creates microfluidics (a fluid that moves and shears extremely fast). Inertial cavitation (such as microbubbles, nanodroplets, nanobubbles, etc.) mainly enhances the therapeutic effect. When the pressure difference in the liquid reaches a specific value, the bubbles expand rapidly and eventually collapse. Shear stress and shock waves generated by bubble collapse generate extremely high pressures and temperatures up to 5000 K at the cavitation point. The ultrasonic cavitation effect can further interact with materials to boost the generation of ROS. In addition, the ultrasonic catalysis and acoustic perforation increase the permeability of cell membranes, and has excellent therapeutic effects on bacterial infections.

4.2.3. Microwave-sensitive systems

Compared with visible light and NIR, microwaves, like US, also have deeper tissue penetration capabilities, so they have received more and more attention in treating deep tissue diseases. MW-activated external source-responsive smart materials can generate heat or ROS under MW irradiation. The wavelength of microwaves is between 1 mm and 1 m, and the corresponding frequency range is 0.3 ~ 300 GHz (between infrared and radio frequency) [177]. The Federal Communications Commission has reserved frequencies of 2.45 GHz and 915 MHz for use by industrial and residential MW ovens to prevent interference with telecommunications equipment. The frequency of microwaves currently used in medical applications is generally 2.45 GHz [178]. Microwaves are a new tool used in the biomedical field [179]. MW heating is very different from traditional heating methods. The conventional heating process involves a heat conduction process. That is, energy is slowly transferred from the external to the internal environment, and finally, the material is heated. The heating method requires more energy to achieve the purpose of heating the material. MW heating mainly drives the dipoles in the material to undergo rapid reciprocating motion (billions of times/second), generating 'friction heat' to achieve a uniform and fast heating of the material. In addition, microwaves can heat MW-responsive materials in a targeted manner without heating the surrounding ambient temperature to that level, which is relatively fast and energy-saving. According to the effect of the interaction between microwaves and materials, MW-responsive materials can be divided into two major categories: MW heating agents and MW

catalysts. The capacity of the materials to absorb and convert MW radiation into heat makes MW heating possible. Materials can be classified as conductors (metals, graphite), insulators (quartz glass, porcelain, ceramics), and dielectrics (water, carbon, Fe_3O_4) according to the various interaction modes. Most MW radiation that strikes a conductor is reflected off its surface. On the other hand, MW radiation can pass through the insulator without causing any loss. Heat generation is not a good use for these two kinds of materials. Dielectric heating is the process by which dielectric materials absorb MW radiation and produce heat. Two key characteristics of dielectrics are (1) a low number of free charge carriers and (2) the presence or generation of a dipole moment. Selective heating of heterogeneous catalysts has been experimentally demonstrated as "hot spots" in MW catalytic reactions, which is beneficial to producing ROS triggered by MW. The primary mechanism behind MW catalytic reactions was based on plasma radiation in liquid. The emergence of light during the process could generate electrons and react with oxygen to produce ROS [178].

4.2.4. *Other-sensitive systems*

There are also other sensitive systems, such as enzyme-sensitive systems, self-regulated systems, and so on. In pathological situations, certain enzymes (such as proteases, phospholipases, or glycosidases) have altered expression profiles. Most drug delivery methods that included enzymes took advantage of the extracellular environment's enzymes. Drug distribution can be self-regulated via systems that can react to variations in the concentration of particular analytes. This is especially crucial for the non-invasive treatment of diabetes, which calls for a mechanism that uses blood glucose levels to determine when to release insulin.

4.3. *Multistimuli-responsive antibacterial materials*

The antibacterial effect can be further enhanced by sensitivity to many stimuli. Only systems that react concurrently are included here. Because an oxidative environment and a pH gradient coexist in some clinical circumstances, the oxidative substrate could further act as the substrate in the following catalytic reaction. pH and light responsiveness can be employed to design doubly responsive smart materials. For example, as shown in Fig. 10**a**, the G1 micelle included NO-releasing moieties/Pd-based photocatalyst (PC) and tertiary amine (TA) residues/Pd-based PC. The responsive mechanism is shown in Fig. 10**b**. The deprotonated TA moieties enabled them to scavenge $^1O_2$ to prevent oxygen quenching of the Pd-based PC and promote NO release in high pH and normoxic environments, such as those in the periphery of biofilms. However, these TA moieties are positively charged in response to the inner layer of biofilms' local acidic pH, which improved the micellar nanoparticles' ability to penetrate the deeper biofilms. Under hypoxic circumstances, photoredox catalysis occurred within the inner layers of biofilms, resulting in the subsequent release of NO [180].

In summary, SRMs have the static properties of traditional materials and the dynamic properties of responding to stimulus factors. This dynamic property is manifested in both space and time. SRMs can react to surrounding environmental stimuli by releasing appropriate signals through structural and functional changes. With a deeper understanding of materials design principles and physiological processes, SRMs can output signals that can be directly matched to specific environments or conditions. When SRMs are triggered by endogenous or exogenous stimuli, the mechanical properties of some materials change to adapt to different support performance needs [138]. Some materials can also change their structures through chemical reactivity to load and release different doses of drugs [181]. Some materials form microrobots, using light to remotely control the robot's movement [182]. SRMs use controllable physical and chemical properties to selectively release signals, bringing new ideas to material design, introducing new functions to materials, and laying the foundation for future precision treatments.

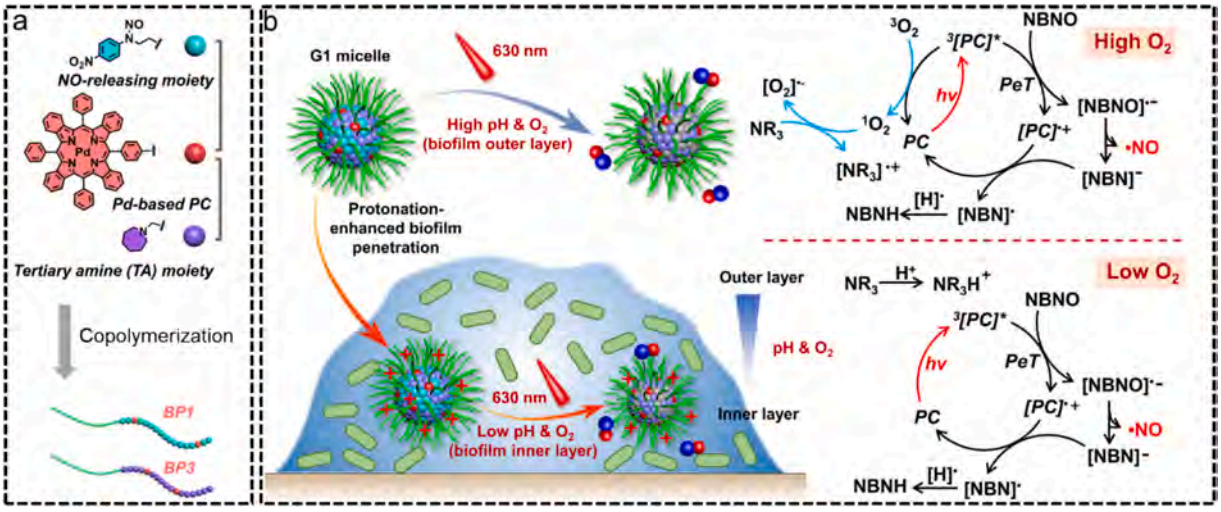

Fig. 10. The illustration of the (a) synthesis and (b) responsive mechanism of biofilm microenvironment and NIR light. Plausible mechanisms of red light-mediated NO release from G1 micelles in heterogeneous biofilms.[180] Adapted with permission. Copyright 2023, Jian Cheng et al.

5. Application of smart responsive biomaterials against bacterial infection diseases

The infectious microenvironment exhibits distinct physicochemical characteristics compared to healthy tissues, including localized acidosis (reduced pH), hyperthermia, and elevated concentrations of pathogen-derived virulence factors such as toxins, metabolic byproducts, and hydrolytic enzymes (e.g., gelatinase, lipase, hyaluronidase, and phospholipase) [183]. These pathological features have been strategically exploited in developing endogenous-responsive smart biomaterials that enable spatially and temporally controlled treatment of diseased areas. Such smart materials have the benefits of enhanced therapeutic effects and minimized adverse reactions, making them particularly promising for treating bacterial infectious diseases [184]. However, they also have certain limitations.

Exogenous stimulation, including light, US, and microwaves, can be a 'switch' for antibacterial therapies. Most responsive therapeutic platforms have been developed based on the controllability of exogenous responsive smart biomaterials for managing bacterial infectious diseases [185]. For instance, phototherapeutic agents can generate ROS and localized hyperthermia upon light irradiation, enabling efficient pathogen eradication [186]. Thermosensitive platforms allow on-demand antibiotic release in response to thermal stimuli, which further improves the therapeutic effect of antibiotics [187], etc. Engineering these remotely controllable responsive switches into SRMs is a common strategy in building smart responsive therapeutic platforms. SRAMs are widely used against planktonic bacteria and biofilms.

This section will systematically examine the therapeutic application of SRAMs for managing various diseases, including acute lung infection, bacterial osteomyelitis, implant-associated infection, periodontitis, chronic lung infections, implant-associated biofilms, etc.

5.1. Acute lung infection

Bacterial pneumonia represents a prevalent acute respiratory infection characterized by inflammatory damage to alveolar structures and distal bronchial airways. Bacterial pneumonia is one of the infectious diseases with high morbidity and mortality worldwide, constituting a significant threat to public health systems worldwide [188]. Community-acquired pneumonia (CAP) and hospital-acquired pneumonia (HAP) are the two main categories of the illness [5]. One significant kind of HAP is ventilator-associated pneumonia (VAP) [5]. Epidemiological data from the Global Burden of Disease Study (2019) reveal that lower respiratory tract infections, including pneumonia and bronchiolitis, affect approximately 489 million people worldwide [189]. Globally, mortality rates remain alarmingly high, particularly for healthcare-associated cases, ranging from 20 % to 30 % for HAP and 20 % to 50 % for VAP, respectively [190,191]. The causative microorganisms differ greatly between CAP and HAP. CAP's most common causative microorganisms are *Streptococcus pneumoniae*, *Haemophilus influenzae*, whereas the most common microorganisms in HAP are *Staphylococcus aureus*, *P. aeruginosa*, *Acinetobacter*, etc [192,193].

5.1.1. pH sensitive systems

Bacterial pneumonia often causes acute and severe pathological lung injury and uncontrollable cytokine storm [194]. Effective treatment of bacterial pneumonia usually requires efficient clearance of pathogens colonizing the lungs, alleviation of oxidative stress, and regulation of inflammatory responses [194]. Taking advantage of the unique microenvironment of the lesion area, a series of endogenous smart response materials have been developed to treat bacterial pneumonia [195]. For example, Shi's group [196] employs block polymers (Poly(ethylene glycol)-poly(ε-caprolactone), (Poly(ethylene glycol)-block-poly(ε-caprolactone), PEG-b-PCL) and block polymers (poly(ε-caprolactone)-poly(aminoester), (Poly(ε-caprolactone)-block-poly(amino ester), PCL-b-PAE) self-assembled

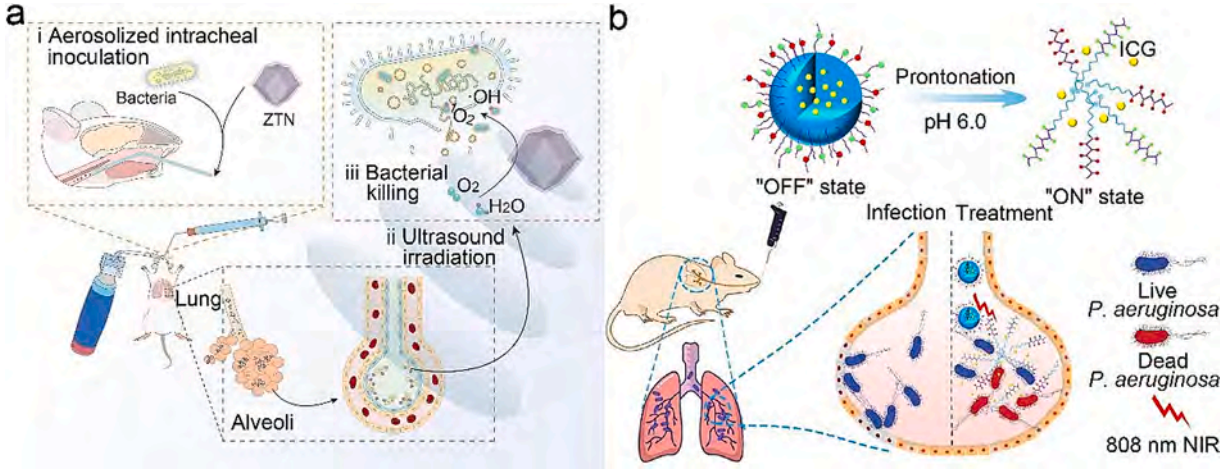

Fig. 11. (a) Schematic illustration of ZTNs for Sonodynamic therapy of bacterial lung infections.[197] Adapted with permission. Copyright 2022, Wiley-VCH. (b) The illustration of GFNPs for targeted delivery of phototherapy agent against bacterial pneumonia.[198] Adapted with permission. Copyright 2019, American Chemical Society.

and combined with DNase (DNase) to obtain pH-responsive nanomicelles (PEG/PAE-DNase particles). Under physiological conditions (pH not lower than 6.4), the coupling of DNA and PAE protects the deoxyribonuclease in the micelles (DNase), while PEG prevents the adsorption of blood-borne proteins to the micelles. PAE is positively charged when the pH is lower than 6.4 and can target biological membranes. At the same time, the hydrophilicity of PAE increases, and DNase is released to degrade organisms. The eDNA in the membrane matrix destroys the integrity of the bacterial biofilm structure. When loaded in the micelles, antibiotics can also effectively kill bacteria and ultimately provide a good treatment for bacterial pneumonia caused by *S. aureus*.

5.1.2. Exogenous stimuli responsive systems

The exogenous auxiliary treatments for bacterial pneumonia mainly focus on sound therapy and phototherapy mediated by sonosensitizer [197] and photosensitizer [198]. For example, Zhou's group [197] utilizes ZIF-8-derived carbon@TiO_2 nanoparticles (ZTNs) to develop inhalable inorganic sonosensitizers for treating bacterial pneumonia. As shown in Fig. 11**a**, ZTNs are accurately delivered to the lung infection site through intratracheal atomization. Under US irradiation, ZTNs are activated to produce ROS, mainly $^1O_2$ and ·OH, thereby quickly killing Gram-negative multi-drug-resistant bacteria colonizing the lungs. It is highly biologically safe and has a good therapeutic effect on bacterial pneumonia. Zhang's group [198] prepared pH-responsive photosensitizer-loaded gadofullerene nanoparticles (GFNPs) for efficient phototherapy of bacterial pneumonia. As shown in Fig. 11**b**, the shell of the nanocarrier is composed of a heteropolyvalent sugar-mimetic shell, which is enriched on the bacterial surface by targeting bacterial surface lectins (LecA and LecB), while the core of the nanocarrier is composed of pH-sensitive polymers composition of matter. Under physiological conditions (pH = 7.4), the photosensitizer is not released from the nanocarrier, while in an acidic microenvironment (pH = 6.0), the polymer can be released from hydrophobicity to hydrophilicity through protonation. The photosensitizer generates ROS and heat under NIR laser irradiation, which has a significant inhibitory effect on bacterial growth and biofilm formation and can inhibit the development of bacterial resistance. In addition, the nanocarrier has excellent biocompatibility and has no side effects on normal tissues. It shows excellent therapeutic effect on pneumonia induced by *P. aeruginosa*.

5.1.3. Combined stimuli responsive systems

Synergistic therapeutic approaches yield superior therapeutic efficacy compared to monotherapy. The combined strategies include pH synergistic antibiotic stimulation [199], MW synergistic antibiotic stimulation [88], etc. For example, Feng's group [199] created PMB@TMOS@ZIF-8@MSCm-UBI29-41 (PMZMU) NPs, specifically designed for the targeted delivery of antimicrobial drugs and sonodynamic therapy. Polymyxin B (PMB)-loaded TCPP-doped mesoporous organo-silica (TMOS) nanoparticles are sealed with the acidity-responsive gatekeeper metal–organic framework ZIF-8 and further disguised with UBI29-41 peptides modified MSC membrane (MSCm), which can target inflammation and evade the immune system. ZIF-8 stayed stable and successfully stopped PMB leakage from the TMOS in neural tissues. The MOF broke down quickly once it entered the bacterial milieu, allowing PMB to be released under control. After being activated by US, the leftover TMOS caused TCPP-mediated SDT to eradicate bacteria and biofilms. It also accomplished self-degradation by interacting with GSH in the bacterial microenvironment through its disulfide bond (—S—S—).

5.2. Bacterial osteomyelitis

Bacterial osteomyelitis is a disease associated with bone destruction mediated by pathogenic bacteria [200]. The infection site can be limited to part of a single bone or involve multiple areas, including bone marrow, cortical bone, periosteum, and surrounding soft tissue [201].

Osteomyelitis is a deep-tissue infection that can be life-threatening in severe cases [43]. The incidence of bone infection after an open fracture exceeds 30 %. In the United States, the average cost of hospitalization for osteomyelitis is US$105,043 (2013 to 2016), increasing yearly [202]. *S. aureus* is the most prevalent and devastating pathogen in osteomyelitis infections [4]. Clinically, bacterial osteomyelitis is treated with long-term and high-dose systemic antibiotics, which are challenging to treat [203,204]. In addition, many patients with bacterial osteomyelitis have limited therapeutic effects after antibiotic treatment and require surgical debridement. After combined surgical debridement and systemic antibiotic treatment, the failure rate is still as high as 20 % [205].

Taking bacterial osteomyelitis caused by *S. aureus* infection as an example, there are many reasons for the failure of antibiotic treatment in bacterial osteomyelitis, including (1) widespread antibiotic resistance; (2) changes in bacterial metabolism or biofilm formation. Leading to bacterial resistance to antibiotics; (3) antibiotics are unable to penetrate infected and damaged bone tissue; (4) bacterial colonization in bone tissue with the help of cells (intracellular bacteria) leads to the ineffectiveness of antibiotics [206].

5.2.1. Enzyme sensitive systems

Currently, antibiotics are commonly used clinically to treat bacterial osteomyelitis, and the treatment time is often longer than six weeks [207]. For chronic osteomyelitis, the treatment period is more extended [208]. To shorten the treatment cycle and improve treatment efficiency, researchers use the characteristics of the infectious disease microenvironment in the process of bacterial infectious osteomyelitis to design new antibacterial agents, control the release rate of antibiotics/antimicrobial peptides, and increase the number of antibiotics/antimicrobial peptides in the damaged bone tissue, etc. For example, Vallet-Regí's group [209] takes advantage of the characteristics of the infectious microenvironment to construct antibiotic-loaded mesoporous silica nanoparticles (MSN) that can target bone tissue to treat bacterial osteomyelitis in situ. Moxifloxacin and rifampicin are loaded into MSN to avoid chemical interactions between antibiotics. At the same time, the surface of MSN loaded with antibiotics is coated with gelatin and colistin coatings. The gelatin can be degraded by enzymes in the infection microenvironment, thereby controlling the release of antibiotics. Colistin can break down biofilms, destroying their structural integrity. Free bacteria can be effectively killed by moxifloxacin

and rifampicin. In addition, MSN was further modified with aspartic acid hexapeptide and targeted to bone tissue to improve the retention time of nanoparticles in the lesion area. This targeted nanocarrier has good bactericidal effects *in vitro* and *in vivo* and can remove biofilms, thereby effectively treating bacterial infectious osteomyelitis.

5.2.2. Exogenous energy responsive systems

Osteomyelitis caused by *S. aureus* is a persistent deep-tissue infection affecting bone tissue. The current main method for treating osteomyelitis is the systemic use of high-dose antibiotics, which brings many challenges, including antibiotic resistance, systemic toxicity, and multiple recurrences leading to reoperation. Exogenous SRMs have received increasing attention as an effective means to overcome the limitations of antibiotics and biosafety issues. At present, there have been studies on the treatment of bacterial osteomyelitis by external means such as light and US. For example, Liao's group [210] synthesized hydrogel microspheres by combining ionically cross-linked sodium alginate and genipin-cross-linked gelatin with tannic acid and Cu^{2+}, named SA-Gel@TA-Cu^{2+} (SGTC2). As shown in Fig. 12, SGTC2 microspheres have excellent photothermal treatment capabilities and can be injected into the lesion area through needle injection. The Cu^{2+}, ROS, and heat released under NIR irradiation can effectively remove *S. aureus*. Infect. At the same time, SGTC2 microspheres can regulate the immune microenvironment, regulate immune responses, and promote bone regeneration. Under the synergistic effect of these functions, SGTC2 has a good therapeutic effect on bacterial osteomyelitis. Yang's group [211] constructs a piezoelectrically enhanced sonosensitizer (RBC-wrapped HNTM-MoS_2) composed of porphyrin-based hollow metal–organic framework (HNTM), molybdenum disulfide nanosheets, and red blood cell (RBC) membrane. Porphyrin has acoustic response properties. Adding MoS_2 nanosheets further enhances the piezoelectric effect, enhances the ability of HNTM to generate ROS under US, and improves the composite material's sonodynamic therapy (SDT) antibacterial ability. In addition, a layer of RBC membrane is modified on the surface of HNTM-MoS_2, and RBC membrane proteins can neutralize toxins remaining in the bone marrow. The nanoparticles have a good therapeutic effect on MRSA-induced osteomyelitis under US irradiation. Tan Lei et al [212] design a US-activated piezoelectric responsive heterojunction of PCN-222-BTO (PCN: porous coordination network) that can alter the electron transfer pathway at the abiotic and abiotic–biotic interfaces under the US to provide a 99.96 % bactericidal effect quickly (15 min). A built-in electric field created by US-induced polarization of BTO encourages the transfer of excited electrons from PCN-222 to BTO at the PCN-222-BTO interface, raising the formation of ROS. In particular, the MRSA-BTO interface also activates the biological electron transport from the bacterial membrane to BTO. Compared to clinical vancomycin therapy, our US-responsive dual-interface system exhibits a greater therapeutic impact when treating the MRSA-infected osteomyelitis model.

5.2.3. Multi-stimuli responsive system

Living systems' complex functions are determined by their innate ability to work together in response to various environmental stimuli, which causes dynamic changes in their physicochemical characteristics [213]. The combined stimuli include pH-responsive and enzyme-responsive synergistically [214], MW-responsive and bacterial protein-responsive synergistically [215], and so on. For example, Chao He et al [214] design a bone mesenchymal stem cell membrane-constructed nanocell (CFE@CM) with chemodynamic therapeutic effectiveness, bone marrow targeting, hydrogen peroxide self-supplying, acid-responsiveness, and cuproptosis induction.

5.3. Implant-associated infection

Bacterial infection of implant surfaces is one of the most common infectious diseases associated with biomaterial surfaces [216] WHO statistics show that device-related infections account for 25.6 % of all medical infections in the United States [217]. Among them, *S. aureus* is the most common pathogen in total joint arthroplasties in the United States [218]. Implants can serve as a base for bacterial colonization after being implanted. Once infection occurs later, almost all prosthetic devices must be replaced, causing chronic or

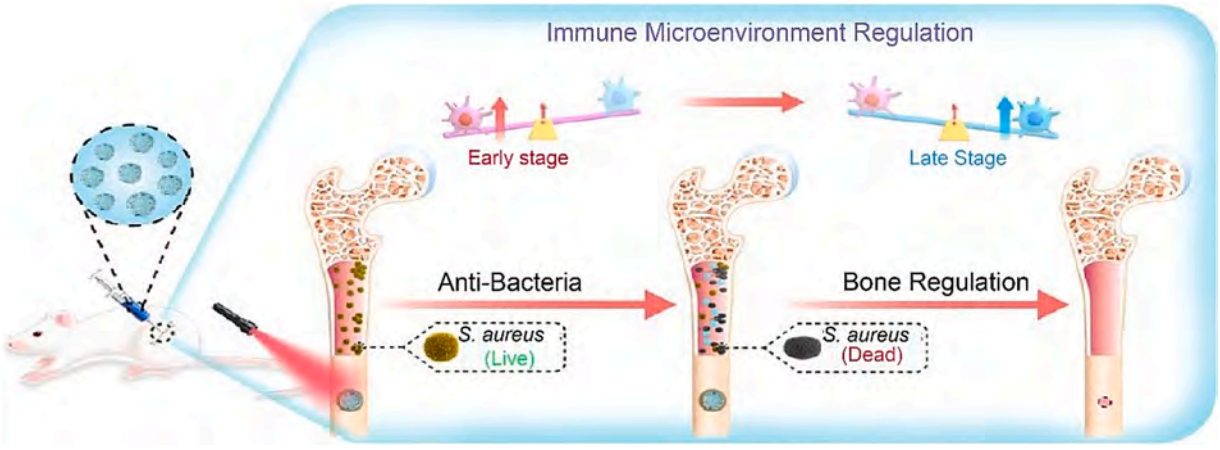

Fig. 12. Schematic diagram of the mechanisms utilizing SGTC2 microspheres for treatment of acute osteomyelitis under the irradiation of NIR light. [210] Adapted with permission. Copyright 2024, American Chemical Society.

recurrent diseases and even requiring amputation in severe cases [219,220]. Implant infections involve complex interactions among pathogens, implants, and hosts. Local tissue reactions triggered by implants include acute and chronic inflammation, foreign body reaction, granulation tissue formation, and fibrous encapsulation [221]. It often creates an immunosuppressive niche [222], making implants susceptible to colonization by pathogenic bacteria [216]. In addition, the implant's surface is prone to bacterial adhesion, and biofilm formation is also a major reason for implant failure.

5.3.1. *Endogenous responsive systems*

Bacterial infections on implant surfaces often share standard features of the infectious microenvironment [223]. Researchers often combine the above factors to design self-smart response materials to combat bacterial infection on the implant surface. Among these, the most widely studied endogenous stimulant is the abnormal pH at the infection site [224]. Temperature differences are another common irritant [183]. For example, Chen et al [225] construct porous hydroxyapatite (HA) implants with smart responsive drug release properties to treat bacterial-infected bone defects. As shown in Fig. 13**a**, ethylenediamine-functionalized polyglycidyl methacrylate brushes are synthesized through surface-initiated atom transfer radical polymerization and gentamicin sulfate (GS), followed by an acid reaction. Carbine linkages were combined with an ethylenediamine-modified poly(glycidyl methacrylate) backbone to produce adaptive and sustainable antibacterial HA implants (HA-GS). The structure of HA-GS is stable in the absence of bacterial infection. Once a bacterial infection occurs, the GS in the 3D structure can be released and kill the bacteria, thereby treating bacterial-infected bone defects. Yeung's group [226] removed bacterial infection on metal surfaces by constructing a temperature-responsive tungsten doped vanadium dioxide (VO_2: W) film. Specifically, as shown in Fig. 13**b**, the VO_2: W film will transform from the metallic phase to the semiconductor phase at 37 °C. When bacteria adhere to the surface of the VO_2: W film, the electrons in the bacterial electron respiratory chain will be transferred to the surface of the VO_2: W film instead of being transferred to the surrounding oxygen to form water, causing the bacterial respiratory chain to become turbulent and causing excessive production of ROS in the bacteria. ATP synthesis is inhibited, etc., effectively clearing bacterial infection on the metal surface and inhibiting the formation of bacterial biofilm.

5.3.2. *External stimuli triggered systems*

In recent years, phototherapy and sonotherapy have been used because of their excellent spatiotemporal controllability, rapid antibacterial properties, and resistance to drug resistance in treating bacterial infections on the surface of implants. It has received widespread attention for its pathogenicidal effect [117,227–229]. Furthermore, compared with traditional antibiotic treatment, long-term use of SRAMs rarely leads to the emergence of drug-resistant mutants [183]. Exogenous responsive materials-based therapy has been widely used to treat implant-related infectious diseases [117,230]. During the SRAT process, the exogenous responsive materials convert light energy into heat energy and ROS under the stimulation of light, US, and so on, thereby inactivating pathogenic bacteria. For example, Zhang et al [231] synthesize a graphdiyne (GDY) composite TiO_2 nanofiber to solve the problem of bacterial infection on the implant surface through photocatalysis and long-term antibacterial ability. As shown in Fig. 14**a**, under UV irradiation, the free electrons in photo-excited TiO_2 are transferred to the GDY surface, and the recombination rate of photo-generated electrons and holes slows down, generating more ROS and showing a good therapeutic effect on bacterial infections on the implant surface. Wu et al [232] develop a NIR/US synergistic therapy strategy for treating bacterial infections on implant surfaces. As shown in Fig. 14**b**, S doping TiO_2 (Ti-S-TiO_{2-x}) increases the oxygen vacancy content in the TiO_2 coating. Under the joint irradiation of NIR and ultrasonic waves, the

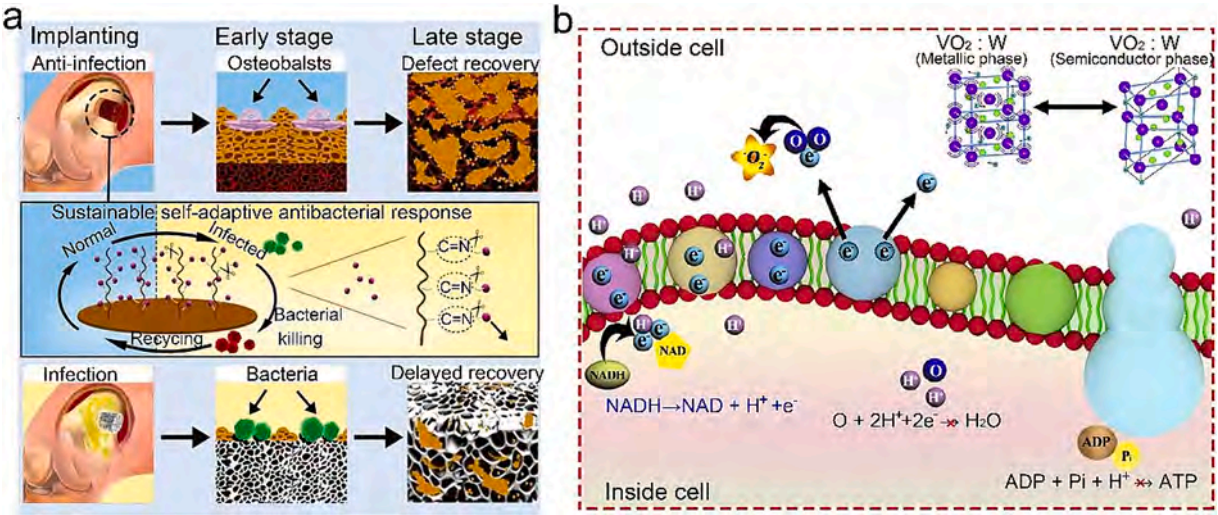

Fig. 13. (a) Schematic illustration of the effects and acting mechanism of the self-adaptive antibacterial HA-GS implant with sustainable responses. [225] Adapted with permission. Copyright 2019, Wiley-VCH. (b) Schematic illustration of the mechanism of VO_2: W film against bacterial infections.[226] Adapted with permission. Copyright 2018 Jinhua Li et al. Published by Elsevier Ltd.

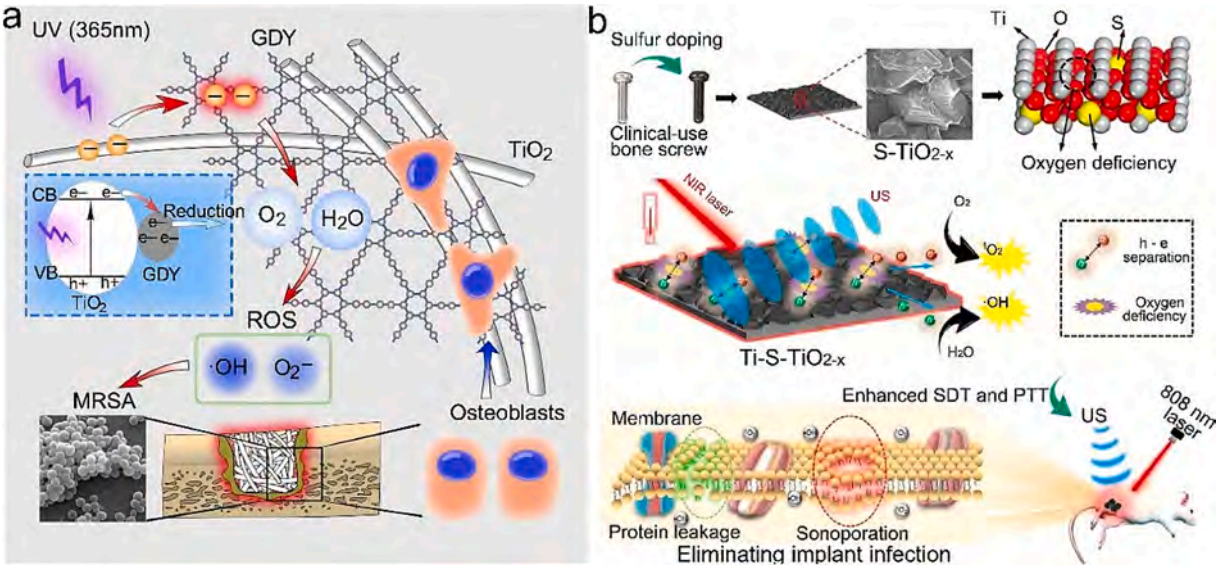

Fig. 14. (a) Schematic of the dual function of TiO_2/GDY in orthopedic implant infection.[231] Adapted with permission. Copyright 2020, Springer Nature, Rui Wang et al. (b) Schematic illustration of the mechanism of Ti-S-TiO_{2-x} for bone infection therapy under NIR light and US irradiation. [232] Adapted with permission. Copyright 2020, American Chemical Society.

electron transfer efficiency of the Ti-S-TiO_{2-x} coating is significantly improved due to the nanostructure and oxygen vacancies. The recombination efficiency of the generated photo-generated electrons and photo-generated holes is reduced, but the photothermal conversion ability is promoted. In addition, enhancing the sonodynamic effect encourages the production of $^1O_2$ and ·OH, resulting in a good therapeutic effect on bacterial infections on the implant surface under the synergistic effect of sonodynamic force, light, and heat.

5.3.3. *Hybrid systems*

Regeneration and repair of bone tissue is a dynamic, long-term process, and its complexity significantly rises when disease-causing factors arise and evolve. Combination therapy is frequently used to address complex clinical situations. Similar to this, several studies have shown multiple stimuli-responsive strategies that have the potential to respond to various internal or external triggers at the same time and have numerous pro-regenerative or therapeutic effects [233]. For example, Bin Tang et al [234] prepare Cu-doped TiO_2 (TiO_2-Cu) films on Ti by magnetron sputtering and annealing (Fig. 15). The combined effects of hyperthermia and Cu ions produce good antibacterial activity against *Streptococcus mutans* on Ti under the irradiation of 808 NIR. Xudong Wang et al [233] construct a three-dimensional (3D) printing akermanite scaffold (AKT-Fe_3O_4-CaO_2) by co-loading calcium peroxide (CaO_2) and iron oxide (Fe_3O_4) nanoparticles into the 3D scaffold. The loaded CaO_2 nanoparticles produce calcium ion (Ca^{2+}) pools to promote bone regeneration and serve as H_2O_2 sources to accomplish H_2O_2-self-sufficient nanocatalytic osteosarcoma treatment catalyzed by coloaded Fe_3O_4

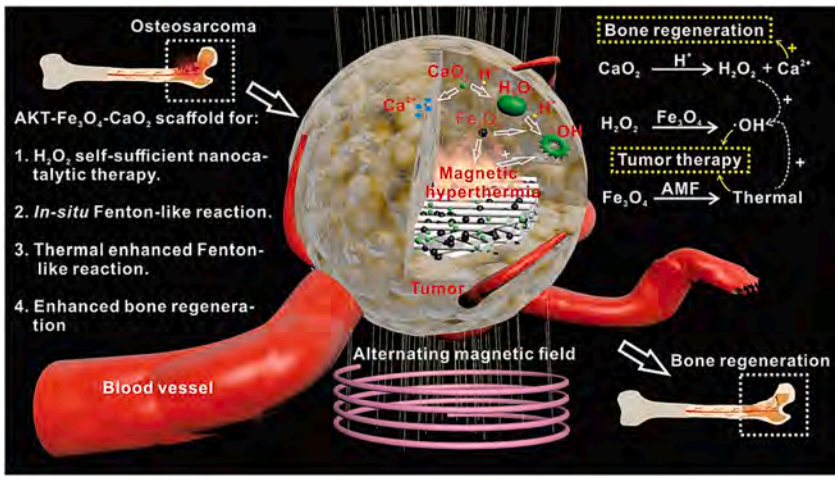

Fig. 15. Schematic illustration of the cancer-therapeutic performance and bone-regeneration bioactivity of 3D-printing scaffolds co-loading with Fe_3O_4 and CaO_2 NPs (AKT-Fe_3O_4-CaO_2).[233] Adapted with permission. Copyright 2019, Wiley-VCH.

nanoagents. Both magnetic hyperthermia, which is made possible by Fe_3O_4 nanoparticles under different magnetic fields, and a hyperthermia-enhanced Fenton-like nanocatalytic process that produces very toxic hydroxyl radicals work together to provide the synergistic osteosarcoma-therapeutic effect.

5.4. Periodontitis

The results of dynamic interactions between microorganisms, their host, and the host's food are best shown by oral infectious illnesses, which include microbial colonization of oral surfaces and the formation of pathogenic biofilms (also known as dental plaque) [235]. The oral cavity is a significant site for biofilms. Dental plaque is a biofilm first put forward over 120 years [236]. One cubic millimeter of dental plaque contains about 100 million bacteria [237]. Many bacteria were in the oral biofilm, including *Streptococcus gordonii*, *Streptococcus mitis*, *Streptococcus oralis*, *Streptococcus sanguinis*, etc [238]. The acidic niches these embedded bacteria create, with pH values near 4.5, provide an acidic milieu promoting ongoing biofilm formation [239]. Meanwhile, the acidic microenvironment of dental biofilms (plaque) destroys tooth enamel, causing dental caries [240]. Meanwhile, dental biofilms will also cause many systemic illnesses, such as immune system disorders, diabetes, and cardiovascular diseases [241,242]. Therefore, preventing or treating pathogenic oral biofilms is challenging, and treating oral biofilms is crucial for overall health management.

5.4.1. pH responsive systems

Using the very acidic oral biofilm milieu, NP-based approaches have been employed to treat illnesses linked to oral biofilms. *Porphyromonas gingivalis* oral biofilms have been treated with the antibiotic doxycycline using liposomes coated with quaternary ammonium-modified chitosan [243]. Chitosan's residual amines produce pH-responsive groups that undergo protonation in acidic environments, resulting in pH-dependent action. Similarly, nanocarriers fabricated with pH-responsive block copolymers that can bind to negatively charged hydroxyapatite have been used to deliver farnesol [244] and chlorhexidine [245] for treating dental caries. For example, Gu's group [246] anchored low-dose Ag NPs/Ag^+ ions on the surface of GDY, resulting in the formation of GDY/L-cys/Ag (GLA) enzymes through an L-cysteine (L-cys) and GDY driven coordination-reduction strategy. GLA exhibits activated POD-like activity upon Ag^+ loading in acidic plaque biofilms, specifically converting low-dose H_2O_2 (200 μM) into very hazardous •OH. Concurrently, GLA exhibits on-demand acidic plaque biofilm-responsive Ag + release, promoting more ROS production. By increasing the bacterial membrane's susceptibility, ROS facilitates the destruction of *S. mutans* and the elimination of plaque biofilms from human teeth by combining the effects of catalysis and Ag^+ release.

5.4.2. US triggered systems

The exogenous responsive materials against oral biofilms mainly focused on generating ROS and heat [247]. SRAMs' produced hyperthermal action has the potential to permanently harm bacterial and biofilm structures, enabling effective biofilm removal without producing resistance [248]. However, most pathogenic bacteria in oral illnesses are anaerobic or facultatively anaerobic, limiting ROS-mediated SRAMs' antibacterial efficiency. In contrast, the generation of ROS in SRAMs is predominantly influenced by the oxygen content in the surrounding environment. The highly reactive $^1O_2$, •OH, $•O_2^-$, and other reactive species can conduct antimicrobial activities [247]. For example, Cui Huang et al [249] construct a US-activated microbomb by encapsulating perfluorohexane (PFH) and iron-tannin-modified calcium peroxide (CaO_2-TA-Fe) in poly(lactide-co-glycolide) (PLGA) vesicles as the ROS-generating reactors for dental biofilm elimination. Following the ultrasonic toothbrush's US irradiation, the quickly vaporized PFH can both blast the tight biofilm for efficient delivery of the lethalhydroxyl free radicals (•OH) caused by degradative Fe^{3+} from the iron-tannin network and quickly explode the PLGA shell to aid in the generation of H_2O_2 from CaO_2. This process then proceeds with

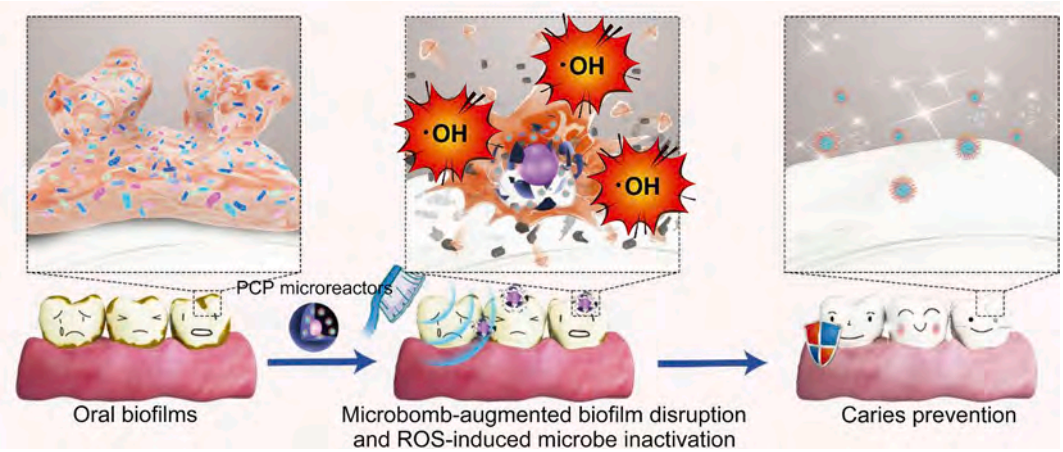

Fig. 16. The illustration of PCP microreactors against oral biofilms under US irradiation by US-activated ROS generating microbombs.The US-triggered microbombs clear dental biofilm by self-suppling H_2O_2, accelerating Fe(III)/Fe(II) conversion, and enhancing ROS generation in the cascade reactions.[249] Adapted with permission. Copyright 2023, Wiley-VCH.

cascade catalysis to eradicate the biofilm (Fig. 16).

5.4.3. Combined strategies for persistent biofilms

The physiological environment is complex; some platforms were designed to respond to multiple stimuli. For example, Cui's group [250] designed chlorhexidine (CHX)-loaded, silver-decorated mesoporous silica nanoparticles (Ag-MSNs@CHX) with a systematic pH- and GSH-responsive release profile of CHX and silver ions, demonstrating effectiveness against *Streptococcus mutans* (*S. mutans*) and its biofilm. Zhang's group [251] developed a biofilm microenvironment-induced PEG sheddable light-activated nanoplatform (PS-NP@(C + I)), formulated from dual block copolymers of polyethylene glycol-b-poly(2-acrylamide glucopyranose) (PEG-b-PAGA) and poly(3-acrylamide phenylboronic acid)-b-poly(2-(5,5-dimethyl-1,3-dioxan-2-yloxy) ethyl acrylate) (PAAPBA-b-PDMDEA) with co-encapsulation of CIP and IR780. The removable PEG shell is thought to enhance EPS penetration, facilitating effective medication delivery to lesions affected by biofilms. Upon penetrating oral biofilms, the dynamic borate linkages within the platform's interlayer dissolved under mildly acidic conditions (pH 6.5), thereby re-exposing boric acid ligands to anchor specifically to bacterial targets. In the meantime, the coassembly undergoes the dissociation that starts the quick drug release because of the brief hydrolysis of DMDEA

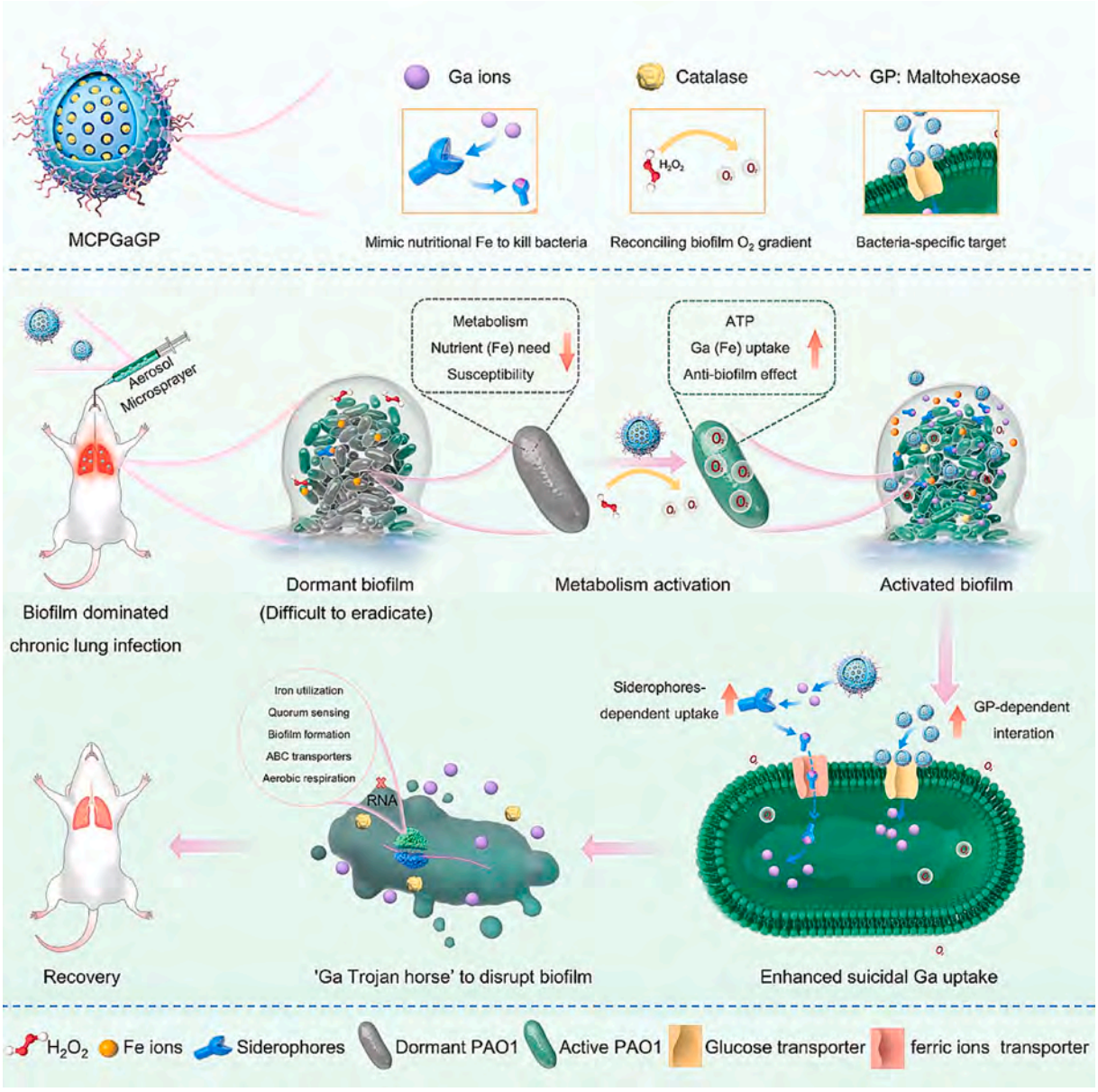

Fig. 17. The illustration of metabolism substrates-responsive MCPGaGP for clearing biofilm in chronic lung infections.[258] Adapted with permission. Copyright 2024, Elsevier B.V.

moieties submerged in the acidic oral biofilm focal milieu (pH 4.7). Therefore, when exposed to 808 nm NIR light, the released IR780 is activated, producing cytotoxic ROS and local hyperthermia that work with CIP to destroy oral biofilms.

5.5. Chronic lung infections

About 60 % of people with cystic fibrosis (CF) die within five years due to chronic lung infections, which are a primary source of morbidity and mortality in these patients [252–254]. One of the most common causes linked to persistent lung infections in CF patients has been identified as the development of *P. aeruginosa* biofilms [116]. The lives and health of individuals worldwide are impacted by chronic lung infections brought on by opportunistic microorganisms such as *P. aeruginosa*, particularly those ill or immunocompromised [255,256].

5.5.1. Redox sensitive systems

Biofilms associated with persistent lung infections are generally embedded in very viscous mucus or resilient sputum rather than directly adhering to epithelial cell surfaces. Furthermore, antibiotics or encapsulated nanomedicines cannot penetrate the complex biofilm structure. Biofilm-microenvironment-responsive nanoparticles have been produced to address this issue, representing a promising technique for reducing biofilm infection [257]. These biofilm-microenvironment-responsive NPs are developed against biofilm. The biofilm oxygen heterogeneity is the main feature of the biofilm metabolism state. For example, Min Zhou et al [258] take advantage of a maltohexaose (GP)-modified catalase and gallium ions co-loaded polydopamine-coated mesoporous silica (MCPGaGP) nanosystem to wake up *P. aeruginosa* (PAO1) biofilm by converting endogenous hydrogen peroxide to oxygen to activate the metabolism of dormant bacteria inside biofilms. Activated PAO1 would release more ferric ion-acquisition tools, including siderophores, improving the suicidal absorption of dietary iron-mimicking gallium. Additionally, the delivery of MCPGaGP to regions of chronic lung infections caused by biofilms and the targeted release of gallium into bacteria is made possible by intratracheal aerosolized administration and modification of the bacterium-specific transporter maltohexaose, resulting in better therapeutic effects towards chronic lung infections (Fig. 17).

5.5.2. US triggered systems

Exogenous responsive materials have also shown promise for treating chronic lung infections. For example, Lianhui Wang et al

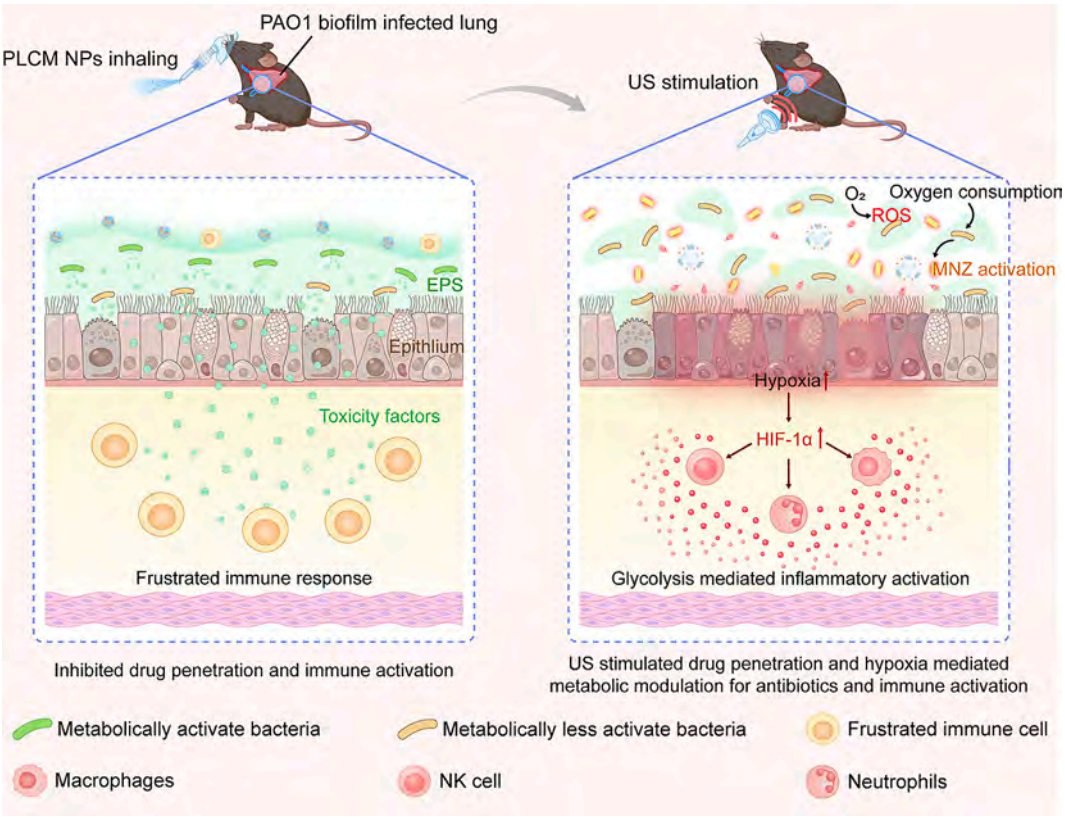

Fig. 18. The illustration of metabolic modulation-mediated antibiotic and immune activation to efficiently treat chronic lung infection induced by PA biofilms. OXPHOS: oxidative phosphorylation.[259] Adapted with permission. Copyright 2024, American Chemical Society.

[259] construct PFP@Lip-Ce6/MNZ nanoparticles (PLCM NPs) by loading with perfluoropentane (PFP), sonosensitizer (chlorin e6, Ce6), and antibiotic (metronidazole, MNZ) with liposome (Lip) nanoparticles against biofilm-associated chronic lung infections under US assistance. Under US stimulation, PLCM NPs could generate microbubbles for PA biofilm disruption and facilitate the penetration of Ce6 and MNZ within biofilms. Besides, Ce6 can generate ROS to kill PA by consuming the surrounding oxygen under US stimulation, which activates the MNZ and immune cells for biofilm elimination. On the one hand, the oxygen depletion by Ce6-mediated sonodynamic therapy modulates the bacterial metabolic state into anaerobic respiration, induces the overexpression of nitroreductase in PA, and prompts the MNZ reduction to antibacterial fragments. In mouse models, this metabolic modulation approach showed effective therapeutic efficacy for persistent lung infections caused by *P. aeruginosa* biofilm (Fig. 18).

5.5.3. Hybrid strategies for biofilm eradication

Significant efforts are made to design combined responsive materials against chronic lung infections based on the microenvironment in the lung and the external factors released by SRMs. For example, Wang's group [116] designed the nanocatalyst-shelled MBs with US-responsive catalytic properties could effectively treat chronic lung infections caused by *P. aeruginosa* biofilms by simultaneously destroying the biofilms chemically and physically and causing macrophages to polarize into a pro-inflammatory phenotype. By catalyzing H_2O_2, the Fe_3O_4 NPs with peroxidase-like catalytic activity can produce free radicals and break down the biofilm matrix. Through physical shear stresses, the MB-Pip may break apart biofilms under US stimulation, allowing Fe_3O_4 NPs to penetrate and pipinto (Pip) the deep layer of *P. aeruginosa* biofilms. Infected tissues' overexpressed H_2O_2 can be catalyzed by Fe_3O_4 NPs to create hydroxyl radicals (•OH), which chemically break down biofilms and eliminate the bacteria they contain. In addition, the exposed *P. aeruginosa* can be effectively rendered inactive by the penetrating Pip.

5.6. Implant-associated biofilms

Bacterial adhesion is the first step in implant-related infection. Bacteria adhere to the implant's surface and produce micro-colony aggregates, slowly forming a biofilm. Biofilms have a natural shielding effect on antibiotics and host immune cells. Therefore, bacterial adhesion and biofilm formation play a key role in the pathogenesis of implant infection [260]. The bacterial biofilm formation on the implant surface could be summed up to several stages: bacterial adhesion (early attachment of bacteria to the implant surface), biofilm formation, and maturation (bacterial aggregation, bacterial extracellular polymerization The formation of microcolonies due to the production of organisms and the formation of microcolonies due to further remodeling and maturation), the spread of biofilms (after the biofilm is partially dispersed, the bacteria return to a planktonic lifestyle and the infection spreads) [216]. In biofilm formation by *S. aureus*, fibronectin-binding proteins first bind to fibronectin molecules to form bridges and promote their aggregation. Then, bacterial extracellular polymers (a signature product of biofilm maturation) gradually form, adhere tightly to the substrate, and proliferate to produce larger bacterial aggregates, producing more bacterial extracellular polymers. In addition, the development of polysaccharide intercellular adhesins and the release of extracellular DNA from dead host cells and bacterial autolysis are two processes that contribute to the creation of biofilms. The diffusion of biofilms is completed by phenol-soluble modulins, proteases, and nucleases [216].

Because of their high likelihood of recurrence and the establishment of medication resistance, implant-associated biofilm infections brought on by multidrug-resistant bacteria have become an unsolvable therapeutic dilemma [216]. Implant-adherent bacteria that live in biofilms, such as MRSA and *E. coli*, are highly resistant to host immune responses and drugs, leading to chronic biofilm infections that negatively impact public health and the global economy [261]. An alternative to conventional surgery and antibiotics that could more readily produce superior therapeutic results is a source of increasing worry [17].

5.6.1. pH triggered systems

Peri-implant infections typically share infection-microenvironment traits [183]. Bacterial biofilms, for instance, cause an acidic environment to build at the infectious site. Additionally, following a pathogen infection, the lesion's temperature rises. Furthermore, the infections' toxins, hydrolases (including phospholipase, lipase, hyaluronidase, and gelatinase), and other metabolites alter the infected location's milieu compared to normal tissues. These characteristics are used in developing endogenous stimuli-responsive implant surfaces, which enable the targeted activation and regulated release of medicines to treat infections associated with implants. For example, Xu's group [225] formed the porous hydroxyapatite (HA) implants conjugated by gentamicin sulfate (GS, a kind of aminoglycoside antibiotic in clinics) through ethylenediamine-functionalized poly(glycidyl methacrylate) (PGED, acid-responsive) brush (HA-CS). HA–GS was stable in normal tissue but could release GS to eradicate bacteria when a bacterial infection (acidic environment) occurred.

5.6.2. NIR triggered systems

Apart from the compounds generated within or around biofilm infection sites, several external energy sources can also initiate the release of drugs from intelligently engineered SRMs. Because artificial external stimuli are provided in these situations, the response behavior of SRMs is more accurate and controlled. For example, Lin Wang et al [262] design an antibacterial phototherapeutic system by combining polydopamine (PDA)-black phosphorus nanosheets (BP NSs)/ZnO nanowires (NWs) on titanium (Ti) substrates. A remarkable photothermal treatment (PTT) capacity was achieved, and the Zn^{2+} was released from ZnO, resulting in the breakdown of the biofilm and excellent antibacterial properties. For example, Wu's group [169] designed a titanium implant modified with MoS_2/IR780/ arginine–glycine–aspartic acid–cysteine (RGDC) coating. The MoS_2 and IR780 could produce thermal effects and ROS under the irradiation of NIR, resulting in a great impact in eradicating bacteria and biofilm on the implant surface.

5.6.3. Hybrid systems for biofilm eradication

H_2O_2 in biofilm is abundant [104], and additional metabolic byproducts of aerobic bacteria will break down into oxygen and water, producing antimicrobial components under certain catalytic effects. And the above stimulus combined with exogenous stimulus against bacterial infections for a better therapeutic effect. For example, Chen Zhu et al.[263] designed porphyrinic MOF-based heterostructured nanoparticles (MnO_2@PCN@Mem, MnPM). The MnPM can catalyze the conversion of H_2O_2 into oxygen within the biological microenvironment. And then, the produced oxygen can enhance oxygen-dependent SDT to kill bacteria by disrupting bacterial homeostasis (e.g., Mn ion excess, oxidative stress malfunction, cell membrane integrity deficit, quorum sensing (QS) system disorder, etc.). Wang's group [264] designed a multifunctional nanoreactor by combining piezoelectric barium titanate with polydopamine and copper. Cu^+-catalyzed chemodynamic processes created hydroxyl radicals, and ROS was synthesized through piezoelectrics. Lastly, the increased ROS leads to DNA damage and weakening of the bacterial membrane structure. By disrupting bacterial membrane homeostasis caused by increased ROS levels and promoting intracellular transit of Cu^+ into bacteria, the PH-CpBT scaffold demonstrated good antibacterial activity against *S. aureus* with US stimulation.

5.7. Other infections

Muscle bacterial infections are comparatively rare. Contiguous infection sites, traumatic trauma, vascular insufficiency, or hematogenous spread can all cause myositis. The mechanism of disease is connected to the infecting organism [265]. There were also many strategies involved with SRAMs. For example, Nanfeng Zheng et al [266]. designed a platform of Pd@Pt-T790, which was prepared by bridging enzyme-catalytic Pd@Pt nanoplates with the organic sonosensitizer *meso*-tetra(4-carboxyphenyl)porphine (T790). The nanozyme activity was successfully restored to catalyze the breakdown of endogenous H_2O_2 into O_2 after exposure to US radiation. Such "blocking and activating" enzyme activity has the potential to provide active, controlled, and disease-loci-specific nanozyme catalytic behavior and was especially crucial for reducing the possible toxicity and adverse effects of nanozymes on healthy tissues. Using the US-switchable enzyme activity, exceptional accumulation at infection areas, and superior biocompatibility,

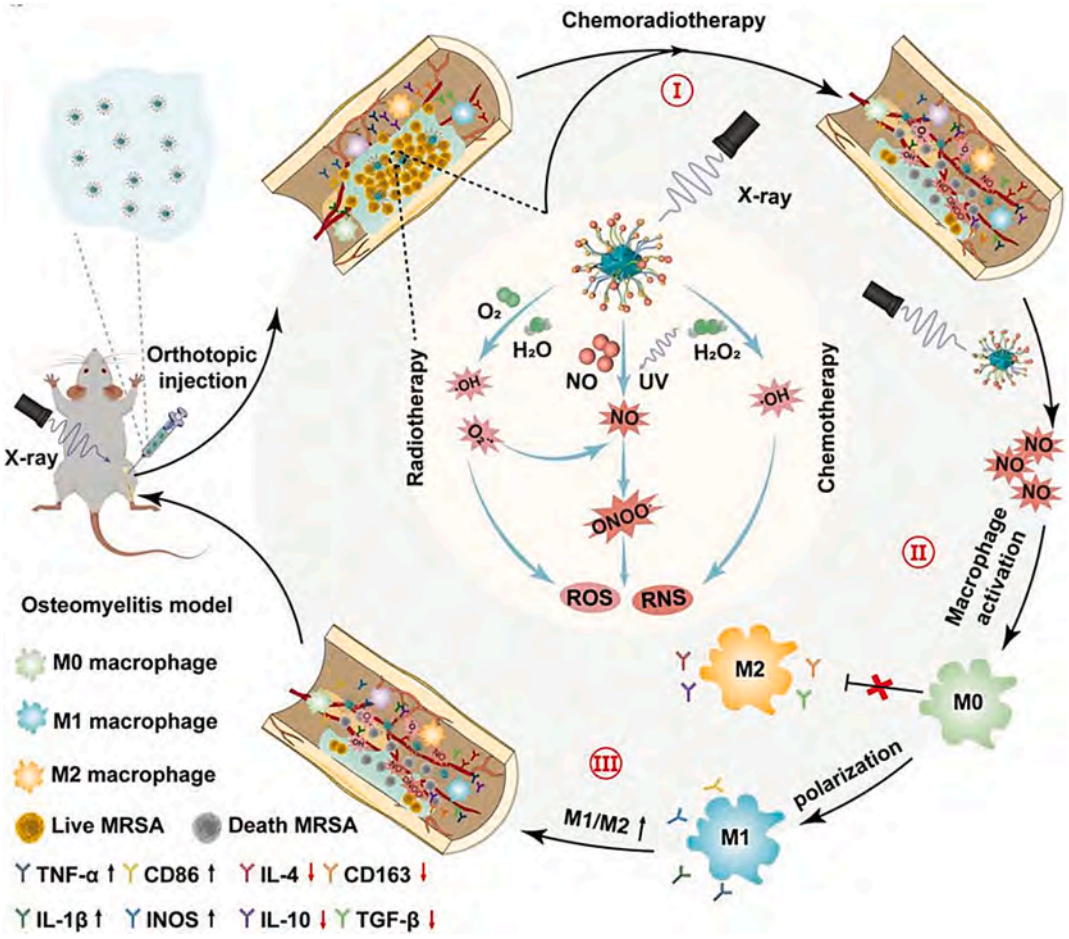

Fig. 19. Schematic illustration of the design of SNP nanoradiosensitizer and their anti-biofilm and inflammatory regulation functions to treat osteomyelitis.[268] Adapted with permission. Copyright 2024, Wiley-VCH.

the Pd@Pt-T790-based SDT system effectively eliminated myositis caused by MRSA.

On the other hand, the illnesses linked to biofilms are usually slow-developing, chronic infections that the immune system seldom ever cures. There are also other bacterial infections, such as cardiac valve [267], osteomyelitis [268], and so on. Many SRAMs were also used against other bacterial biofilm-related infectious diseases. For example, Xinge Zhang et al [268] designed $Cs_3Cu_2I_5$ nanoscintillators functionalized with polyethylene glycol (PEG)-based photosensitive nitric oxide donors (PEG-b-pCouNO) and an antimicrobial peptide (Nisin), designated as $Cs_3Cu_2I_5$@(Nisin + PEG-b-pCouNO) (SNP). When exposed to X-ray radiation, the suggested polymer-reinforced nanotherapeutic produced reactive nitrogen and oxygen species. These species could penetrate biofilms and bind particularly to MRSA for improved chemoradiotherapy treatment. This study showed how effective a synergistic chemoradiotherapy and immunotherapy approach might be in treating osteomyelitis caused by MRSA biofilm (Fig. 19).

6. Limitations and challenges

The endogenous response smart material treatment strategy utilizes the pathological microenvironment of infectious diseases as a regulatory factor. Although it can also effectively utilize antibiotics, the specific pharmacokinetics are still unclear [240]. Also, endogenous stimulation signals are often difficult to control and vary depending on individual patients. For bacterial pneumonia, current treatments mainly focus on using antibiotics to inhibit the establishment of bacteria in lung tissue, with minimal attention being paid to lung flora. As for bacterial infection on the implant surface, its main limitation lies in the difference between the bacterial material interface and the cell material interface, and the characteristics of materials and organisms are not fully understood; for bacterial infectious osteomyelitis, the main disadvantage is the extensive use of antibiotics, which affects autoimmunity. Systemic immune response has a certain inhibitory effect.

Exogenous means are easier to control than endogenous means. However, the design mechanism of exogenous smart response materials is still unclear. The theoretical support for the energy absorption and conversion process using materials is minimal. In addition, some external sources used by exogenous methods have significant limitations in treating deep-seated infections. Treatment options for deep tissue infections, such as bacterial infections on the implant surface and osteomyelitis, are limited. The development of sonosensitizers, MW heating agents, and MW catalysts is minimal. In addition, there are limited studies on suitable deep infection animal models combined with clinical trials to verify the clinical feasibility of exogenous materials.

6.1. Development of chronic infection animal models

Chronic infectious diseases are not only debilitating for affected individuals but also impose a significant financial burden on healthcare systems. For example, approximately 15 % of individuals with diabetes develop foot ulcers [269], which are a common site for chronic infections. The characterization of chronic infectious diseases is different from that of acute injuries. However, many animal models for chronic infectious diseases are based on acute injuries, representing the primary clinical etiology of chronic illnesses. These models are crucial for understanding chronic infection and tissue repair mechanisms. However, no model is without limitations. Developing chronic infection animal models can identify more accurate prognostic indicators and therapeutic targets, essential for treating chronic infectious diseases. These are also very important for designing SRAMs to promote recovery. It is a challenge for the SRAMs to release the on-demand signals in response to the changing physiological environment in chronic infectious diseases.

6.2. Approaches to reduce the development of resistance

Addressing antimicrobial resistance (AMR), particularly bacterial AMR, has become a critical global health challenge, threatening the effectiveness of infection prevention and treatment strategies [270]. It is imperative to develop and implement innovative approaches to minimize the development of resistance.

6.3. Beyond conventional antibacterial therapies

The rising rates of antimicrobial resistance, coupled with the slower pace of new antibiotic discovery, have significantly undermined the effectiveness of traditional antibiotics in treating bacterial infections. As a result, multidrug-resistant, extensively drug-resistant, and even pan-drug-resistant bacterial strains are becoming increasingly prevalent. This alarming trend has fueled concerns about a potential 'post-antibiotic era,' in which many bacterial infections may become untreatable. To address this urgent threat, exploring alternative, safe, and efficient therapeutic strategies is imperative to ensure a robust pipeline of effective treatments remains available to clinicians [271].

6.4. Current status of clinical translation of SRAMs

The clinical translation of SRAMs is complex from the bench to the bedside, and nontrivial optimizations and improvements are necessary. In particular, individual differences make it difficult to control endogenous responsive smart materials. The exogenous responsive SRAMs are more promising. However, the selection of SRAMs based on external energy conversion currently lacks established clinical guidelines. The tissue penetration ability, side effects, and hardware availability should be evaluated when applying external stimuli [71].

Different SRAMs have different advantages and disadvantages. Up to now, the most technologically mature platform is light-activated materials. But the limited tissue penetration and phototoxicity restrict its clinical application [71]. Even for 808 nm NIR laser, safety standards of intensity restrict to less than 0.33 W cm^{-2} to prevent cutaneous damage in PDT and PTT [81], resulting in PDT and PTT mainly suitable for superficial wound infections rather than deep-tissue (eg. bone infections) infection *in vivo*. In contrast, magnetic-responsive systems offer superior tissue penetration (up to 15 cm) with excellent biosafety [82], but require complex field-generating infrastructure and lack precision in material targeting. In addition, the US also has clinically verified penetration ability and biosafety [83]. But the insufficient tissue accumulation, poor bioavailability, stability, and rapid immune clearance limited the clinical application of sonosensitizers [84]. Those problems are still the limitation in translating SRAMs into clinical.

6.5. Regulatory landscape in taking scientific research to clinics

The regulatory landscape towards antibacterial agents is not a critical concern due to the antibiotic resistance crisis. In response to the urgent clinical need for effective therapies against multidrug-resistant organisms, regulatory agencies—including the European Medicines Agency and the U.S. Food and Drug Administration—have recently accelerated updates to their guidelines for antibacterial drug development, particularly for infections with high unmet medical need [272–274]. However, SRAMs remain largely unexplored in clinical trials. The key challenges lie in technical and regulatory hurdles, even for a biomaterial used independently [275]. In addition, as biomaterials grow increasingly complex, there is a challenge for regulators to keep the balance between the potential advantages of new materials and the little additional risk to the public offered by already approved materials [275].

7. Conclusions and future perspectives

Bacterial infectious diseases pose a considerable threat to the life and health of people worldwide. Developing safe and efficient therapies to treat bacterial infectious diseases with the help of smart responsive biomaterials is an effective solution. At the same time, there are still some research gaps in smart antibacterial materials. The mechanisms of clearing planktonic bacteria and biofilms and recent advances in the design of SRAMs in response to the internal/external stimuli are outlined. Meanwhile, we also summarize the latest progress in the development of SRAMs. Properties of both internal- and external-stimuli-responsive smart antibacterial materials are analyzed, and we also discuss the potential features required for antibacterial applications of various infectious diseases. It also discussed the challenges and future directions, including the clinical translation of smart materials.

For smart response materials, their evaluation indicators mainly come from two aspects. The first aspect is the basic performance of smart response materials – response efficiency. SRMs often require high selectivity, high sensitivity, and timely responsiveness. Another aspect is the clinical transformation potential, which often requires smart response materials to have good stability, excellent biocompatibility, and industrialization potential. Specifically, the future challenges of intelligently responding to antibacterial materials mainly include the following points:

(1) The ultimate goal of smart responsive biomaterials is to maintain response efficiency and stability in the complex environment of the body. For example, in treating bacterial infections, the potential physiological toxicity and immune stimulation of materials often cause a lot of concerns. For this problem, it is necessary to have an in-depth understanding of the behavior of SRMs in the body. One good solution is to determine how materials interact with the biological environment by implementing monitoring or imaging techniques.
(2) Develop high-performance smart responsive antibacterial materials based on new response mechanisms. For example, in the current treatment process of bacterial infections, there is insufficient integration with analytical chemistry and no bridge between metabolites and antibacterial detection. For this problem, further research on the cascade reaction of smart response materials is essential. For example, skin sensitivity to moisture can be used as a new source of stimulation. The skin will relax and contract under the action of water molecules. Combined with piezoelectric materials, it has the potential to achieve efficient antibacterial effects on the skin.
(3) Inter-individual differences hinder their further clinical translation for endogenously responsive smart antibacterial materials. The expression levels of endogenous signals in animals often differ greatly from those in humans. For this condition, the signal amplifier is a feasible solution. Different signal levels can be effectively adjusted using signal amplifiers.

In summary, there are more and more studies about SRAMs due to in-depth analyses and the fulfillment of additional functional requirements. Nonetheless, we are only one step closer to practical clinical applications, and many hurdles remain. We expect that this review of the literature on SRAMs in biomaterials will help to design and develop new SRAMs for clinical applications in the future.

CRediT authorship contribution statement

Jieni Fu: Conceptualization, Writing – review & editing, Methodology, Data curation, Validation, Formal analysis, Writing – original draft, Investigation. **Chaofeng Wang:** Data curation, Methodology. **Xiangmei Liu:** Funding acquisition, Project administration, Conceptualization, Supervision, Validation, Data curation, Writing – review & editing. **Shengli Zhu:** Investigation. **Yufeng Zheng:** Investigation. **Zhaoyang Li:** Validation, Software. **Zhenduo Cui:** Software, Validation. **Yu Zhang:** Funding acquisition, Methodology, Software. **Hui Jiang:** Conceptualization, Methodology, Software. **Yongping Cao:** Supervision, Validation. **Paul K Chu:** Validation, Formal analysis, Software. **Shuilin Wu:** Data curation, Writing – review & editing, Validation, Funding acquisition, Project

administration, Conceptualization, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

No data was used for the research described in the article.

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