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Adaptive antibacterial biomaterial surfaces and their applications

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ABSTRACT

Bacterial infections on the implant surface may eventually lead to biofilm formation and thus threaten the use of implants in body. Despite efficient host immune system, the implant surface can be rapidly occupied by bacteria, resulting in infection persistence, implant failure, and even death of the patients. It is difficult to cope with these problems because bacteria exhibit complex adhesion mechanisms to the implants that vary according to bacterial strains. Different biomaterial coatings have been produced to release antibiotics to kill bacteria. However, antibiotic resistance occurs very frequently. Stimuli-responsive biomaterials have gained much attention in recent years but are not effective enough in killing the pathogens because of the complex mechanisms in bacteria. This review is focused on the development of highly efficient and specifically targeted biomaterials that release the antimicrobial agents or respond to bacteria on demands in body. The mechanisms of bacterial adhesion, biofilm formation, and antibiotic resistance are discussed, and the released substances accounting for implant infection are described. Strategies that have been used in past for the eradication of bacterial infections are also discussed. Different types of stimuli can be triggered only upon the existence of bacteria, leading to the release of antibacterial molecules that in turn kill the bacteria. In particular, the toxin-triggered, pH-responsive, and dual stimulus-responsive adaptive antibacterial biomaterials are introduced. Finally, the state of the art in fabrication of dual responsive antibacterial biomaterials and tissue integration in medical implants is discussed.

1. Introduction

Long-term use of biomaterials in body has been threatened by the adhesion and proliferation of bacteria on implant surface, leading to biofilm formation in some cases. Formation of biofilms causes local infections and even implant failure, resulting in death of the patients in the worst case [1]. Currently, the implant-associated bacterial infections result in more than 100,000 deaths each year in the United States of America alone. Normally, the host immune system is very efficient in clearing the opportunistic pathogens that cause the tissue contamination. However, in the implant-associated infections, a local tissue response is triggered, leading to acute and chronic inflammation, foreign body reaction, and granulation tissue formation and thereby fibrous encapsulation. These events may finally drive the microbial colonization and infection of the implants. Hence, the implant infection is characterized by complex interactions between biomaterials and host, in particular, the host immune response [2].

Microbial contamination during surgery often leads to the prosthetic contamination after surgery, while infections developed with 3–24 months are called as subacute infections. The late infections usually take more than 24 month, and are asymptomatic. They become symptomatic when new infections occur due to the hematogenous spread at the implant site [3]. Gram-positive cocci are the most common organisms causing the implant infections, whereas aerobic Gram-negative organisms less frequently cause the infections, and anaerobes cause only 4% of implant infections. Moreover, the infections of implants depend very much upon the site of the implantation and time of the surgery. Early infections occur usually because of the virulent microorganisms at the time of surgery such as *Staphylococcus aureus*. Delayed infections are caused by low-virulent microorganisms such as coagulase-negative staphylococci, while bacteria that infect the skin, dental respiratory, and urinary tract cause the late hematogenous implant infections [4].

In this review, we shall discuss the mechanisms of bacterial adhesion and biofilm formation after the implants are inserted in the body. Release of different substances that contribute to the biofilm formation and infection at the implant site are briefly introduced. Different strategies to combat bacterial infections used previously, for example, stimulus-responsive biomaterials along with their limitations are also included. The main part of the review article is focused on the development of adaptive antibacterial surfaces which are currently being explored in the

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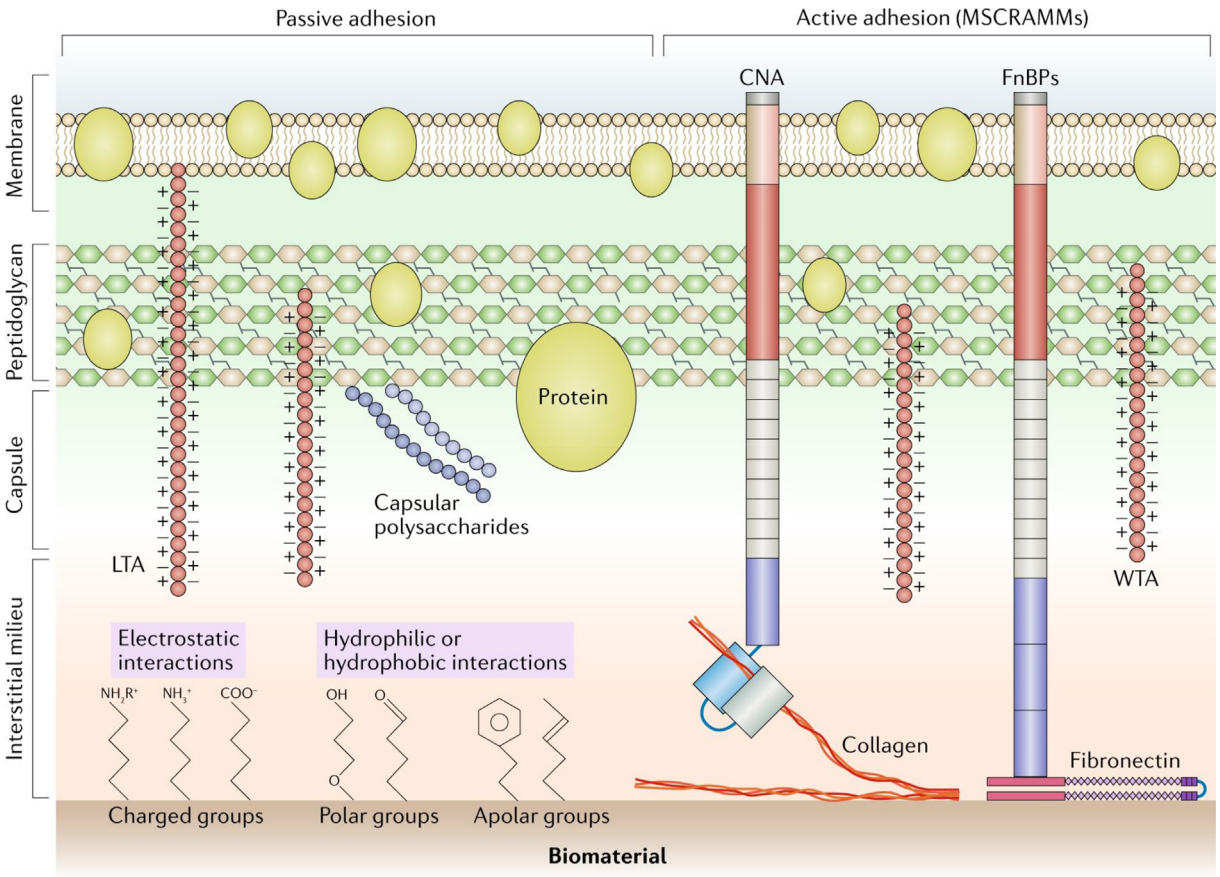

Fig. 1. Adhesion of *Staphylococcus aureus* to implant surface. Reversible passive mechanism and irreversible active mechanism both result in bacterial adhesion to biomaterial surface. Active mechanism occurs through adhesive matrix molecules, which bind through collagen and fibronectin. Reprinted from Ref. [17], Copyright (2018) with permission from Nature.

field. Tissue regeneration is an important aspect once the implants are used inside body. As regeneration and infection prevention at implant site goes side by side, the development of dual functional materials preventing the bacterial infection and promoting the tissue regeneration is finally summarized in this review.

2. Mechanisms of implant infection and antibiotic resistance

When being introduced in body, the material surfaces are readily covered with different extracellular matrix (ECM) and immune system proteins. Similarly, proteins from blood and interstitial fluids also rapidly coat the material surface within minutes. The surface chemistry and wettability of the materials play an important role in the attachment of different adhesins to the material surface [5].

2.1. Bacterial adhesion and biofilm formation

Bacterial interactions occur due to the adhesins present on the surface of the implants. Initial bacterial adhesion to abiotic surfaces is generally non-specific and is generated by unspecific forces such as van der Wall, acid base, and electrostatic interactions (Fig. 1). In these types of interactions, bacteria behave like colloidal particles [6–9]. The bacterial cell filamentous appendages such as pilli and nanofibres also act as adhesins and can lead to biofilm formation. Lectin-based adhesion also occurs, when the bare material surfaces are covered with ECM and immune protein components, resulting in implant infection. For example, binding of *S. aureus* and *Staphylococcus epidermidis* to abiotic surfaces is mediated by specific proteins autolysins AtlA and AtlE, respectively. These proteins play a role in the attachment of bacteria to the abiotic surfaces, and different biomolecules such as fibronectin and vitronectin also contribute to the formation of biofilms in *S. aureus* and *Enterococcus faecalis* [10–12].

Piliated and non-piliated bacterial adhesins are involved in the interaction of bacteria and ECM protein components. Bacterial adhesins also help in modulating the immune response and bacterial internalization. Collagen, fibronectin, and fibrinogen are the main matrix proteins functioning as the ligands for bacterial adhesins (Fig. 1). Collagen is the most abundant protein of bone matrix. Fibronectin promotes the adhesion and spreading of cells and influences the cytoskeleton assembly to maintain the shape of cells. Fibrinogen is made up of three pairs of non-identical chains synthesized by hepatocytes. These three proteins are mainly involved in the adhesion of different types of bacteria to the implant surface, leading to the implant-related infections [13–17].

When an implant is inserted in the body for bone healing applications, there is competition between the host cells and pathogenic bacteria to adhere to the implant surface. The term 'race to the surface' is used for this phenomenon, as the fate of the implant will depend upon the types of cells attached. Therefore, rapid integration of the implant in the host tissue is very essential, which leads to bone apposition and osseointegration. Otherwise, the bacteria adhesion on the implant surface will lead to the failure of host defense system to prevent bacterial colonization and ultimate biofilm formation [7,18]. In the biofilms, there are bacteria aggregate encased in a matrix made up of extracellular polymeric substances (EPSs), tightly adhering to the implant surface (Fig. 2) [19]. Owing to the biofilm formation, bacterial infections become tenacious, resisting to therapy and also causing bacterial propagation to other body locations. Chronic inflammation occurs as the host defense system, and antimicrobial strategies become insufficient to eradicate the biofilms from the

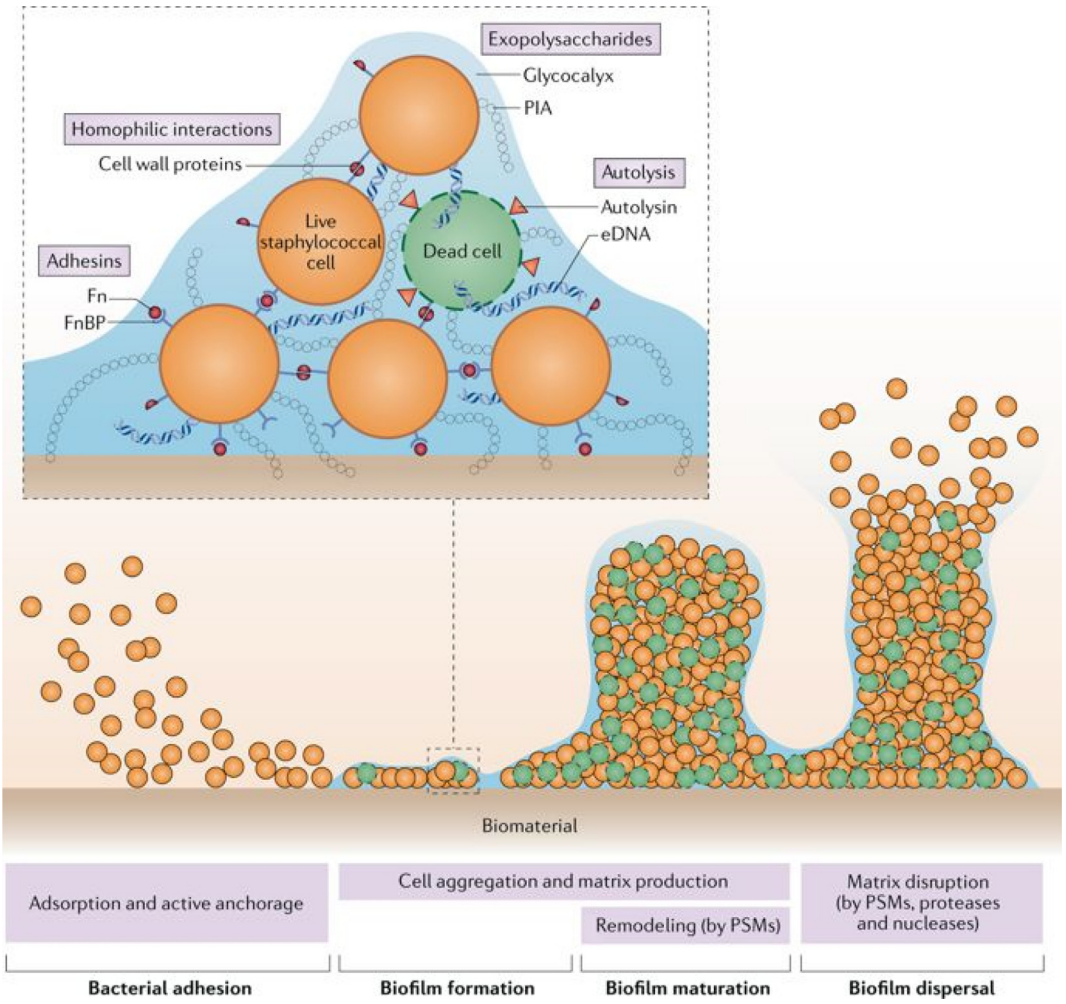

Fig. 2. Stages of biofilm formation. After adhesion, bacteria interact with each other to form microcolonies promoting bacterial aggregation. Large bacterial aggregates called as towers develop when polymeric matrix in biofilm progresses. PIA and eDNA expression in biofilm also contributes to the biofilm formation. Phenol-soluble modulins form characteristic water channels and are also involved in bacterial dispersal. Reprinted from Reference [17], Copyright (2018), with permission from Nature. eDNA, extracellular DNA; PIA, polysaccharide intracellular adhesin.

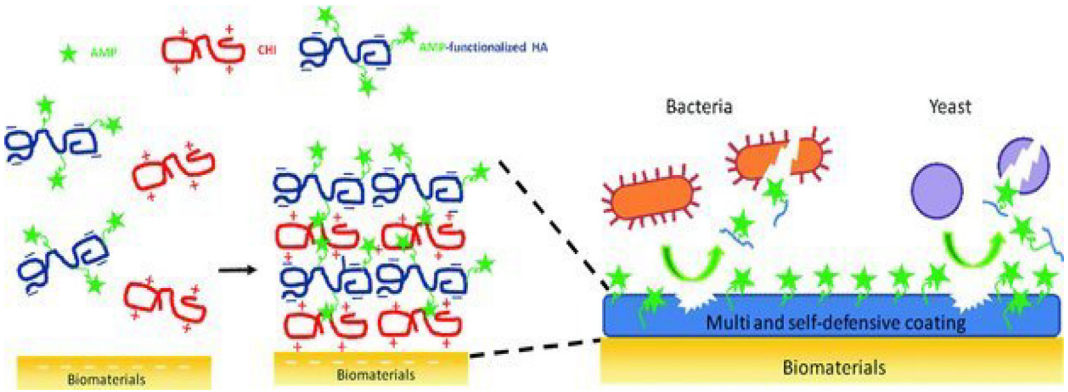

Fig. 3. Schematic representation of CHI/HA multilayers functionalized by an antimicrobial peptide (AMP) and their activity towards bacteria and yeasts based on the degradation of the film. Reprinted from Ref. [93] Copyright (2013), with permission from John Wiley and Sons. HA, hyaluronic acid; CHI, chitosan.

implant surface [20]. Biofilm formation starts with the adhesion of bacteria to the implants, leading to the formation of microcolony due to bacteria aggregation and EPS production. Further remodeling and maturation of bacterial microcolonies lead to the formation of macro colonies, followed by bacterial dispersal to the planktonic state. Bacteria adhere to each other and form biofilm matrix by producing the EPS during the biofilm development and maturation [21]. EPS is composed of proteins, extracellular DNAs, teichoic acid, exopolysaccharides, and lipoteichoic acid [22]. The main component of biofilm matrix in *S. epidermidis* and *S. aureus* is polysaccharide intracellular adhesin (PIA). Production of PIA is encoded by *ica*ADBC locus. Arciola et al. studied the antibiotic resistance in exopolysaccharide-positive and

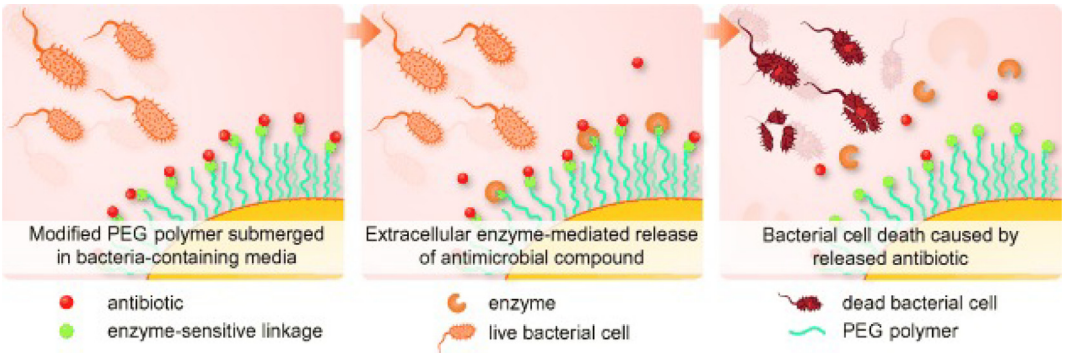

Fig. 4. The concept of bacteria-trigged enzymatic release of antibiotics from chemically modified polymers. Reprinted from Ref. [94] Copyright (2013), with permission from John Wiley and Sons.

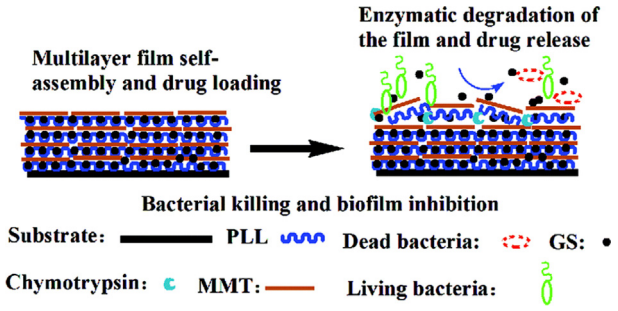

Fig. 5. Schematic representation of the self-assembled $(MMT/PLL\text{-}GS)_n$ multilayer films and the on-demand self-defense release of GS. Reprinted from Ref. [96] Copyright (2017), with permission from Royal Society of Chemistry. MMT, montmorillonite; PLL, poly-L-lysine.

exopolysaccharide-negative *S. epidermidis* strain isolated from orthopedic implants infection sites. They revealed that PIA-positive strains are more resistant to antibiotics especially aminoglycosides than the PIA-negative strains [23,24]. Environmental stress such as osmosis, ethanol, and heat also play an important role in the formation of increased PIA and subsequent biofilm formation in *S. epidermidis*. PIA production is also increased in the presence of sodium chloride, decreased nutrient and iron content, and lower oxygen levels. Production of PIA in the presence of sodium chloride is regulated by *rsb*U, which encodes the *Sig*B operon activator. *Sig*B is produced in Gram-positive strains, for example, bacillus and staphylococcus, which are responsible for quick adaptation and existence in stressful environment. Production of PIA in the presence of ethanol stress and subsequent biofilm formation are independent on the *rsb*U [25–29].

The bacterial behavior is also influenced by environmental shear stress caused by a fluid flow. It usually varies with the anatomical location of the implant being higher in blood vessels, cerebrospinal fluid shunts, and intravascular devices. Schaeffer et al. [30] isolated *S. epidermidis* from higher and lower shear stress areas. They showed that bacteria isolated from a higher shear stress are more likely to produce PIA-containing biofilms. Studies also show that increased production of PIA protects the bacterial biofilms from a higher shear stress. Kozitskaya et al. [31] explored the flexibility in adaptation of multiresistant *S. epidermidis* by studying the mutations in its genome. They found that insertion and excision of IS256 sequence in *ica*C can reversibly switch on and off the synthesis and expression of PIA in *S. epidermidis*. IS256 along with Tn4001 are responsible for antibiotic resistance in clinically isolated *S. epidermidis*.

Extracellular DNA (eDNA) in EPS is either produced by programmed altruistic death of bacteria or fratricide killing in which bacteria kill the target by releasing the killing factors while themselves are protected by particular immune proteins. Owing to versatility of eDNA, it plays an important role in stabilizing and strengthening the biofilm matrix, transfer of genes between cells, immune response modulation, and nutrients supply. eDNA released from the biofilm matrix can be a potential target for diagnosis and therapeutics. Teichoic acid and lipoteichoic acid have strong affinity to adhere bacteria to the biomaterial surface, resulting in biofilm formation [32–34]. The interaction between monospecies/multispecies

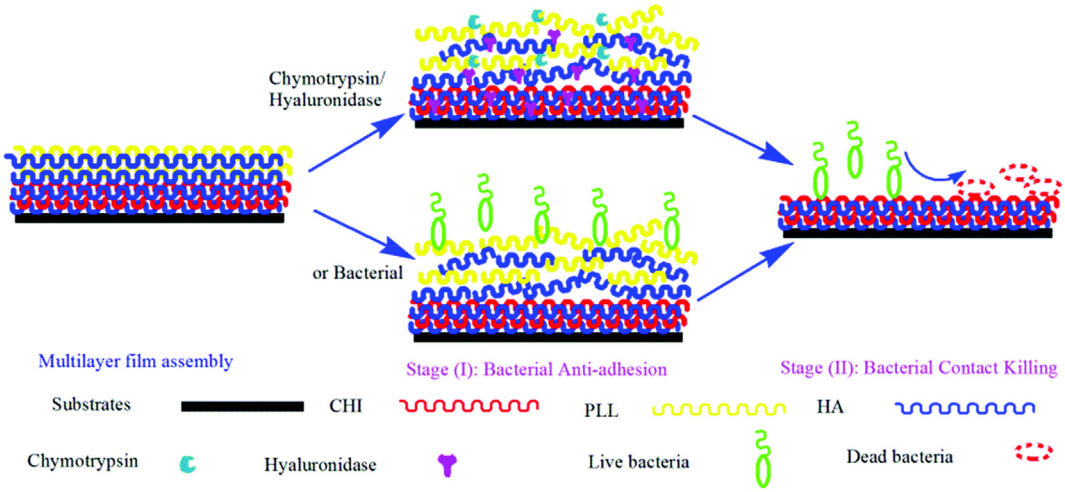

Fig. 6. Schematic representation of the $(HA/CHI)_n$–$(HA/PLL)_n$ self-assembled multilayer films and the enzyme-triggered and bacteria-triggered degradation of the films. Reprinted from Ref. [97] Copyright (2017), with permission from Royal Society of Chemistry. PLL, poly-L-lysine.

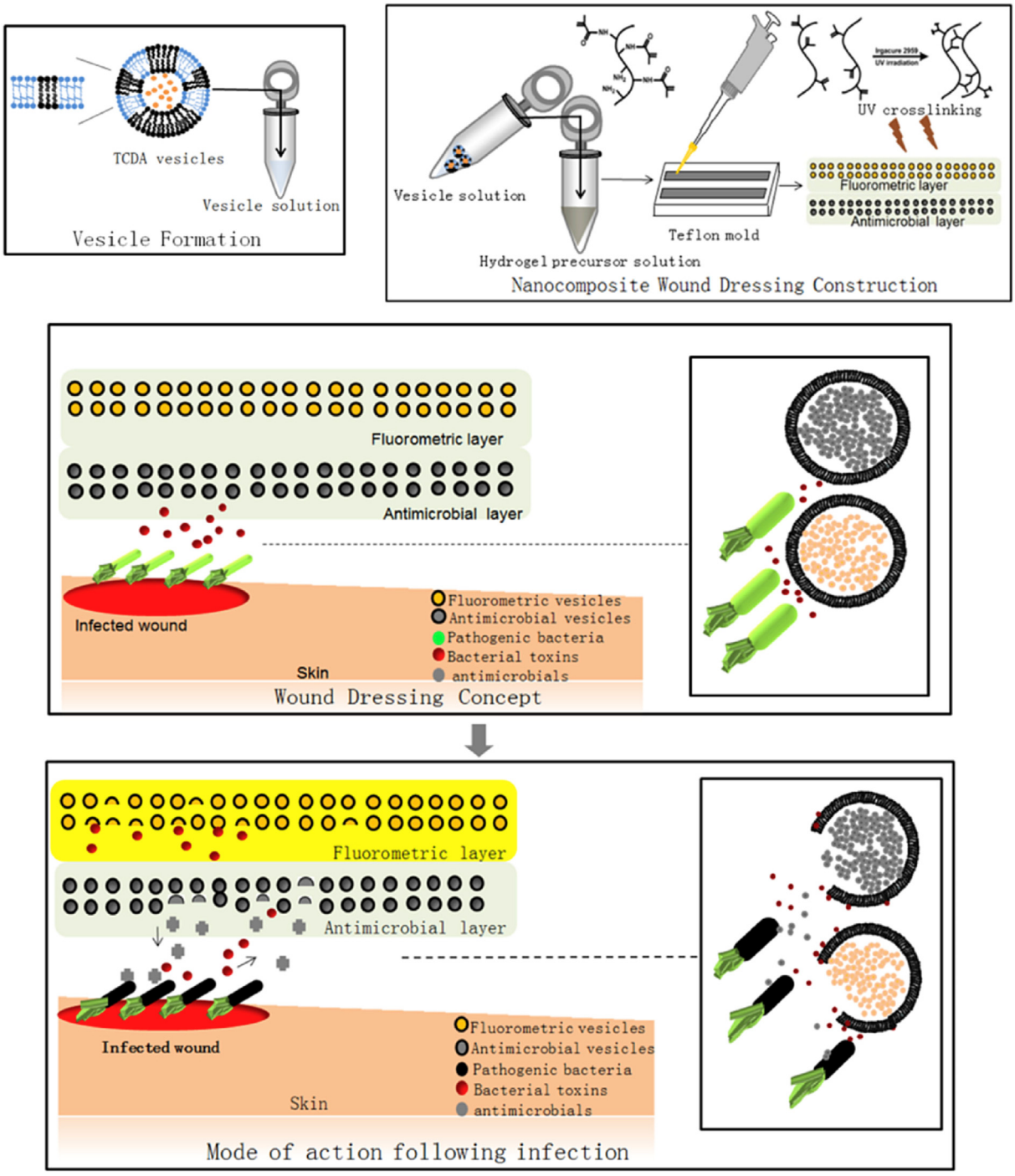

Fig. 7. Schematic of intelligent wound dressing construction and the mode of action following infection. The graphs illustrate that it can respond to the presence of pathogenic bacteria: gives a fluorimetric/colorimetric response, releases an antimicrobial agent to inhibit/kill growth of pathogenic bacteria, promotes and supports tissue growth. Reprinted with permission from Reference [98], Copyright (2018) from Elsevier.

bacteria within the biofilms, regulated by complex networks, is important to form and maintain the biofilms. Whenever bacteria colonize the material surface, there is a change in gene expression, indicating the importance of these genes for foreign body colonization and resulting in implant infections. Signaling system and subsequent gene expression in bacteria lead to production of different toxins, virulent factors, and formation of biofilms. The sensing system in bacteria also helps them disseminate to the blood stream, causing severe infections. Dispersal of bacteria to the surrounding body parts is caused because of the surfactant molecules, enzymatic degradation of EPS, and matrix production inhibition. Disruption of bacterial biofilms is mainly accompanied by different enzymes such as staphopain cysteine proteases, staphylococcal nuclease, and V8 glutamyl endopeptidase SspA and peptides toxins such as phenol soluble modulins (PSMs) (Fig. 2) [17,35]. PSMs are the main contributors to the biofilm dispersal in implant-associated infections. PSM production is regulated by Agr quorum sensing and is density dependent. It works by disrupting the non-covalent interactions between biofilm matrixes, resulting in increased formation of channels for nutrients delivery to deep

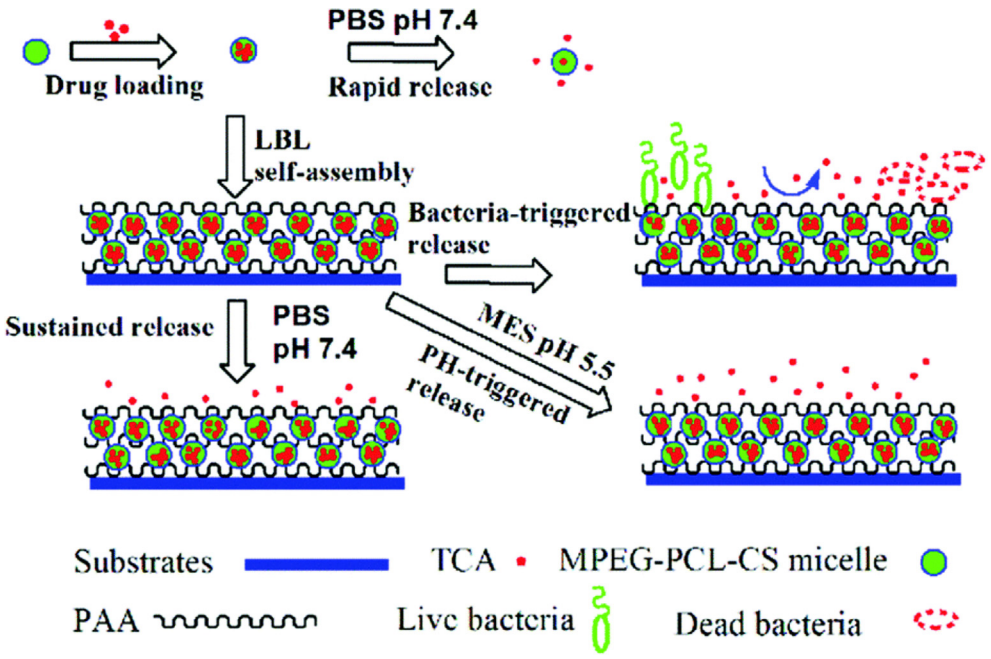

Fig. 8. Schematic representation of the (TCA/MPEG-PCL-CS)/PAA self-assembled multilayer films and the pH-triggered and bacteria-triggered release of the hydrophobic drug. Reprinted from Ref. [102] Copyright (2017), with permission from Royal Society of Chemistry. MPEG-PCL-CS, methoxy poly(ethylene glycol)-poly(ε-caprolactone)-chitosan; PAA, poly(acrylic acid).

biofilm layers. This, in turn, results in scattering of biofilm masses to the distal body parts [36].

2.2. Mechanisms of antibiotic resistance

Formation of biofilms on the medical implants usually leads to increase in antibiotic resistance. Several mechanisms are involved in the formation of resistance against antibiotics, either intrinsic or acquired. Owing to the inherent structural and functional characteristics, bacteria can be intrinsically resistant to antibiotics likely because of the absence of susceptible target for particular antibiotic. This intrinsic resistance varies from species to species because of the existence of various genes in one species being absent in other species. The acquired resistance occurs by various mechanisms such as poor penetration of antibiotic into the bacteria, resulting in lower intracellular concentration, effective efflux, genetic mutation, and posttranslational modification of the antibiotic target and/or inactivation of antibiotic by hydrolysis or other modifications [37].

The biofilm formation on the implants is the major source of antibiotic resistance because of the failure to penetrate deep inside the biofilms and slow or non-growing ability of cells [38]. Suci et al. [39] observed the transport impedance of fluoroquinolone antibiotic ciprofloxacin to the *Pseudomonas aeroginosa* biofilms. Hoyle et al. [40] observed the same results for piperacillin. The reason for such impedance is the existence of different compounds, in particular the polymeric compounds within the biofilms [41–44]. The anionic polymeric compounds such as alginate can bind to various types of cationic antibiotics, leading to the failure of penetration into the biofilms. However, some antibiotics have been shown to diffuse through the biofilms but failed to eradicate the infection, revealing the existence of other mechanisms. Three forms of heterogeneity exist within the biofilms including spatial, response, and cell heterogeneity [45]. In particular, there are certain regions of high and low cell growth within the biofilms, possibly due to the depletion of bacteria nutritive compounds or the accumulation of inhibitory compounds. Those antibiotics targeting cell wall synthesis work well on bacteria in the growing stages. However, they are inefficient to eradicate the biofilms having the non-growing bacteria. This implies that the bacterial response to antibiotics is non-uniform within the biofilms [46]. Huang et al. studied the effect of biocide monochloramine on killing *Klebsiella pneumonia* and *P. aeruginosa* biofilms on stainless steel. They observed the loss of bacterial respiratory activity near biofilm fluid interface, while those lying deep in the biofilms have persisted respiratory activity [47]. Similarly, Korbar et al. observed elongation of the *Pseudomonas fluorescens* cells after treatment with fluoroquinolone fleroxacin lying near the biofilm interface [48]. Polymicrobial biofilms represent another hurdle to the antibiotic treatment as there are mutually beneficial relationships between different bacterial species within these biofilms, leading to different responses to antibiotics and ultimately poor response [49,50]. Environmental factors such as oxygen, pH, stress, osmosis, and so on also play an important role in antibiotic efficacy. Another factor that contributes to the antibiotic resistance is the transfer of genetic information between different bacterial species. Plasmid conjugation is an important process for the transfer of genetic traits, which is facilitated in the complex diverse environment within biofilms, resulting in the transfer of antibiotic resistance characteristics among different bacterial species [45].

2.3. Release of antibiotics from the antibacterial surfaces

The release of antibiotics at the infection site has been extensively studied to kill bacteria, in particular, in a dose-dependent manner. For example, hydroxyapatite has been used to load different types of antibiotics including gentamicin and tobramycin, cephalothin sodium, amoxicillin, vancomycin hydrochloride, and so on. [51,52]. Chitosan has good antibacterial properties against different bacteria. Chitosan/alginate multilayers on cotton have been prepared using layer-by-layer (LBL) assembly. The multilayers decrease the growth of bacteria [53]. Chitosan and hyaluronic acid (HA) have been used with silver-doped bioactive glass nanoparticles to reduce the bacterial growth [54]. Polymethylmethacrylate has been used to load levofloxacin along with lactose (as stimulator molecule) to check antibacterial activity against *S. aureus*; 2.5% levofloxacin is most capable of reducing the biofilm formation within 48 h [55]. To avoid the corrosion problem and to get antibacterial property, different materials loaded with antimicrobial drugs are used to coat the titanium implants. For example, vancomycin-loaded poly(ethylene glycol) (PEG) hydrogels coated on

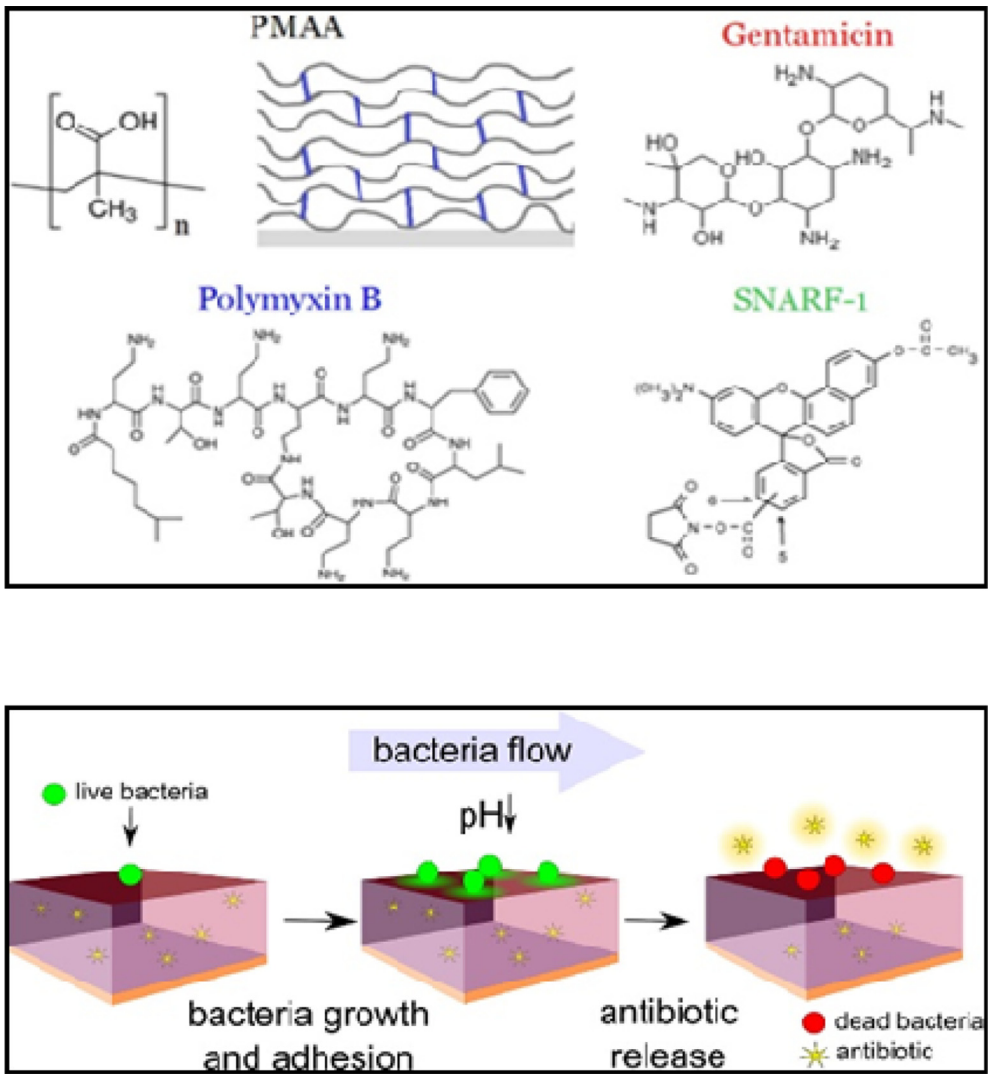

Fig. 9. Chemical structures and schematic presentation of poly(methacrylic acid), PMAA, hydrogel-like coating with crosslinking segments (indicated in blue), two antibiotics (gentamicin and polymyxin B), as well as a reactive label (SNARF-1 carboxylic acid, acetate, succinimidyl ester). Reprinted from Ref. [103] Copyright (2017), with permission from Elsevier.

titanium can release vancomycin in muscle tissues in a sustained manner, which is attributed to the slow swelling of hydrogel with blood and tissue fluid at the site of infection [56]. Plasma electrolytic oxidation–modified titanium substrate was coated with rifampin loaded in ordered mesoporous magnesium silicate through electrophoretic deposition. After a burst release within 7 h, the release of rifampin was slowed down until 96 h [57]. Vancomycin hydrochloride–loaded poly(vinyl alcohol) borax microgels were coated on titanium by using electrospray technique. The size and density of the pores control the drug release from the gel as they are exposed to the saturated ethanol vapor that ultimately leads to good antibacterial effect [58]. The effect of vancomycin hydroxide and tobramycin-loaded calcium sulfate beads (CS-B) was investigated to eradicate the biofilm formation on orthopedic materials. 1 and 7 log reduction in bacterial growth in the biofilms of *P. aeruginosa Xen41* and *S. aureus SAP231* was observed, respectively [59]. Another antibacterial drug, cefazolin was loaded into polycaprolactone (PCL) scaffold having micro and macro porous structure by using 3D printing and fused deposition modeling (FDM) techniques. The increased surface area and microporosity of the scaffold help load this heat labile drug efficiently. The microporous scaffold shows the dose-dependent release of antibiotic with a burst release in the first a few hours and then slow release for up to 7 days [60].

2.4. *Effective strategies to fight biofilm colonization*

To treat the implant-associated infections, various surface modification techniques have been used recently. The molecular to microscale topological features of the implant surface have been controlled by advancing the development of certain nanofabrication tools. The important aspect after the implant insertion in the body is the successful integration with host tissues while avoiding the pathogenic bacteria to adhere to the implants. So far, two types of materials have been developed, that is, antifouling surface that resists the adherence of bacteria to the implant and bactericidal surface that kills the bacteria in contact with the implants.

The microbe-resistant surface can be constructed by using certain antifouling substances to coat the implant surface. The strategies include superhydrophobic, non-charged, or highly hydrated surfaces, which do not favor the attachment of bacteria [61,62]. PEG and zwitterionic polymers can effectively resist bacterial attachment because of the dynamic motion and steric repulsion of the hydrated polymer chains [63,64]. Heparin coatings can inhibit the bacterial attachment by increasing the hydrophilicity of the surfaces. Surface topography can also be used as an important parameter to inhibit bacteria adherence. For example, the superhydrophobic surfaces having the microstructures and

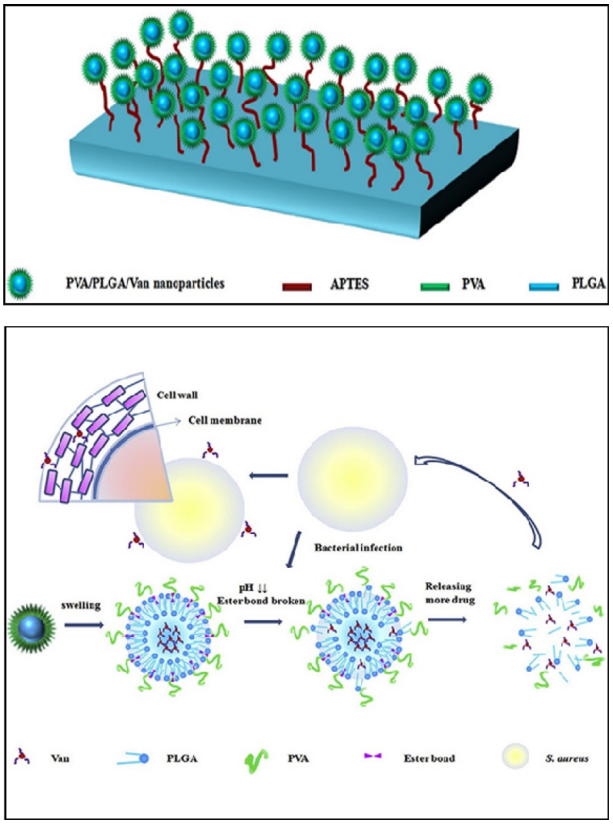

Fig. 10. Schematic illustration of fabrication process of hybrid PVA/PLGA/Van NPs grafted on titanium and schematic illustration of drug release from hybrid PLGA NPs with the decrease of pH and antibacterial mechanism of Van. Reprinted from Ref. [106] Copyright (2017), with permission from Elsevier.

nanostructures can avoid the bacterial attachment to some extent [65]. Design of antifouling surfaces is rather complex because the microorganisms have complex mechanisms to enable their attachment to the surfaces [66,67].

The bactericidal surface can kill bacteria when they come into contact with the implant surface [68–70]. The coated biomaterials including certain antimicrobial peptides, metals, nitric oxide, and quaternary amines are immobilized on the surface to inhibit bacterial attachment but not released into the surrounding environment [68–78]. Antimicrobial metals such as silver, aluminum, cobalt, zinc, and copper have been widely used to kill the bacteria. However, they are toxic to the body because of the released metal ions when they are corroded in physiological environment. This may lead to the decreased cell viability and host tissue integration failures [79,80]. Nanoparticles have also been used as bactericidal materials to kill the bacteria. The exact mechanism of action of nanoparticles is not clearly understood, but it may involve the production of reactive oxygen species that damage the cell membrane. The nanoparticles also have certain drawbacks such as apoptosis induction, genome destruction, and transport to the distant tissues and cells, leading to systemic effects [61,81]. These strategies are not much successful because the bacteria produce resistance to these antimicrobials as well [82].

The response of body to external stimuli varies largely and is often unpredictable. The macromolecules or the parts of cells machinery such as enzymes, proteins, nucleic acids, and/or polysaccharides respond differently to different types of stimuli, that is, they may remain stable with a wide range of changes in external stimuli or have great conformational changes along narrow variation of external stimuli. To circumvent the problem of irregular antibiotic release and antibiotic resistance, stimulus (light, pH, temperature, biomolecules, electrical pulses, etc)-responsive polymer coatings that can release antibiotics in response to some stimuli are being produced. [83], which can inhibit the attachment of bacteria on the implant surface and to kill them upon attachment of bacteria [66]. For example, chitosan/phosphate thermosensitive gels functionalized with greenly synthesized Ag or Ag@Pd show bactericidal activity against Gram-positive *S. aureus* and Gram-negative *P. aeruginosa* [84]. Yu et al. prepared poly(β-substituted methyl carboxybetaine acrylamide) brushes on a substrate using surface-initiated atom transfer radical polymerization (SI-ATRP) polymerization. These brushes show superhydrophilic and pH responsive characteristics, and have greater anti fouling property against many bacterial species [85].

3. Development of bacteria-adaptive biomaterials for antibacterial applications

Nonetheless, some limitations in the use of stimulus-responsive biomaterials still exist: the microenvironment at the site of infection is accompanied by different bacteria and conditions such as pH, temperature, oxidative stress, enzyme *etc*. Therefore, the stimuli-responsive biomaterials could not kill the pathogens effectively at some cases. Complex external factors in the body affect the working of these biomaterials, leading to low release accuracy and some other side effects [86]. One of the recent approaches is the development of antibacterial biomaterials that release antimicrobial agents upon attachment of specific bacteria to the surface. These so-called self-defensive antibacterial coatings respond to bacteria on demand, and thus attract great attention because they are highly efficient and can be specifically targeted.

3.1. Virulence factor–triggered adaptive antibacterial materials

Although the pathogenic bacteria pose great threat to human's health and life, there are still many non-pathogenic bacteria that are good for our health. The difference between these two kinds of bacteria strains is that a majority of pathogenic bacteria can secret virulence factors such as toxins and enzymes (hyaluronidase, proteases and lipases) which damage or lyse cell membrane and affect the function of host tissues, while the non-pathogenic bacteria do not [87]. Based on these differences, many adaptive antibacterial materials have been developed in the form of nanocapsules [88,89], surface coatings [90], and multilayer films [91]. Most of these materials are composed of enzymatically or toxically degradable polymers, which can only respond to the infected microenvironment induced by pathogenic bacteria. The decomposition of these materials and thus release of drugs is triggered by the virulence factors secreted by pathogenic bacteria, avoiding the overuse of antimicrobials and the occurrence of antimicrobial-resistant bacteria.

3.1.1. Antimicrobial-releasing biomaterials

Release of antimicrobials from material matrix immediately after infection is a direct strategy to kill the bacteria at an early stage. The approach to design this kind of materials is based on loading antimicrobial agents into the substrate or conjugating drugs to matrix via responsive linkages. For example, cross-linked hyaluronic acid (HA)-based nanocapsules loaded with polyhexanide, a kind of antiseptic agents, were developed via an inverse miniemulsion technique. The secretion of hyaluronidase by gram-positive *staphylococcus* bacteria destroys the nanocapsules, followed by the on-demand release of polyhexanide [92]. The nanocapsules exhibit high stability in different mediums and have long-term action at bacterial infection sites. In another study, a polysaccharide coating with embedded antimicrobial peptides against both bacteria and yeasts was prepared by using hyaluronidase as a stimulator. Antimicrobial peptides (AMP)-functionalized HA and chitosan (CHI) multilayers were prepared using LBL assembly. The release and activation of AMP is triggered by the enzymatic degradation of HA by hyaluronidase secreted by the pathogens (Fig. 3). The films can fully inhibit the growth of gram-positive *S. aureus* bacteria and *Candida albicans* yeasts. Moreover, the adhesion of fibroblasts is rather poor on the multilayer film, highlighting its medical application to

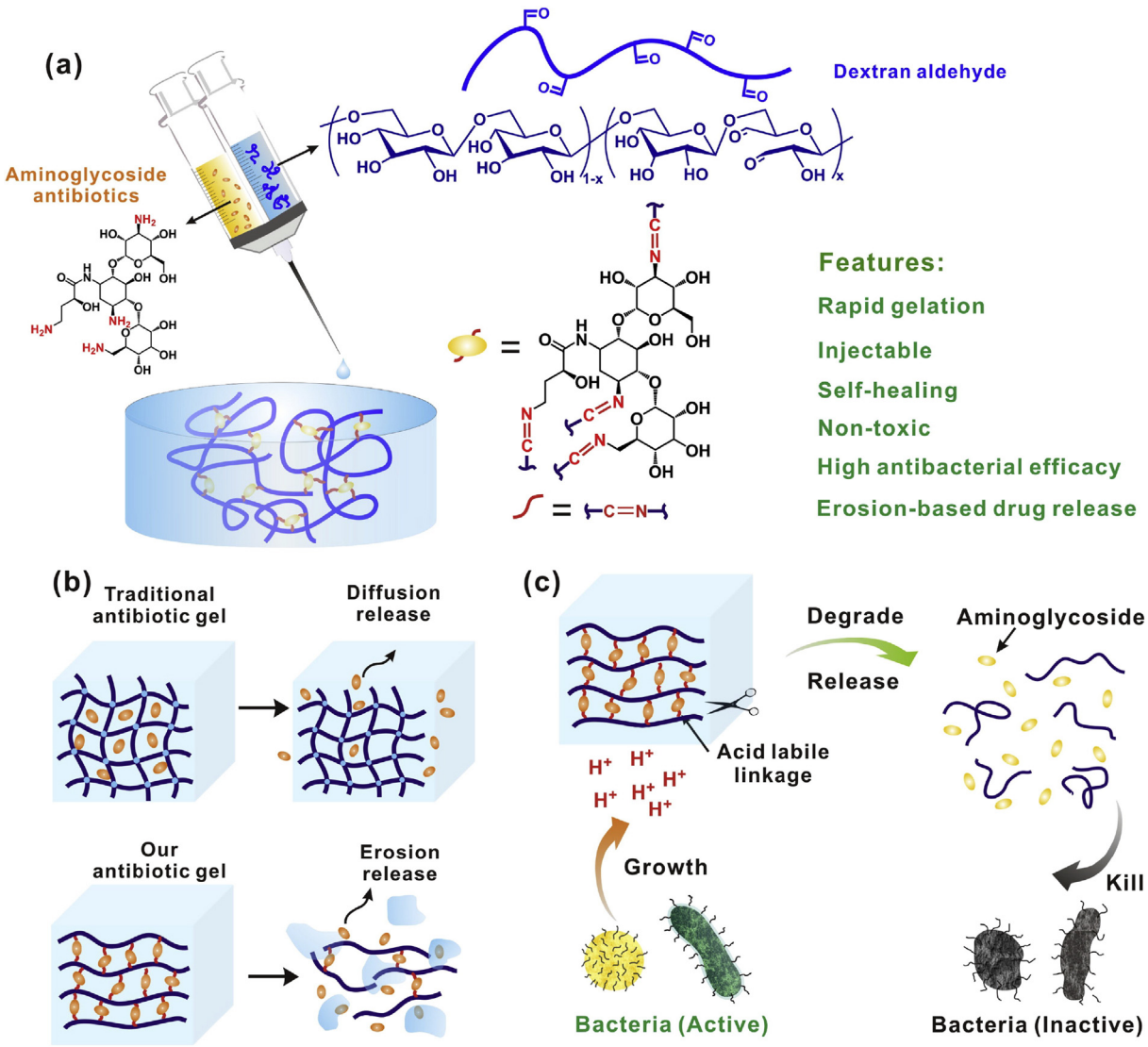

Fig. 11. Concept of the smart aminoglycoside hydrogels. (a) Preparation of aminoglycoside hydrogels by mixing oxidized polysaccharides with aminoglycosides via the formation of acid-labile linkages. (b) Illustration of the diffusion-based and erosion-based drug release from antibiotic hydrogels. (c) Mechanism of the responsive aminoglycoside hydrogel in the treatment of bacterial infections. Reprinted from Ref. [107] Copyright (2017), with permission from Elsevier.

prevent infections on catheters or tracheal tubes where fibrous tissue encapsulation is undesirable [93]. The microenvironment at bacterial infection sites is also particularly abundant in extracellular lipases [1]. Bioactive compounds (antimicrobial drugs and quorum sensing [QS] signals) were grafted on a PEG-based polymeric surface through a standard solid-phase synthesis technique by utilizing lipases-sensitive linkages such as anhydride bond [94]. At the infection sites, the extracellular lipases can catalyze hydrolysis of the anhydride bond and thus release the antibiotics to control the bacterial populations and signaling molecules to modulate the quorum sensing (Fig. 4). This system provides a method for linking a wide range of active molecules to chemically modified surfaces and releasing them in a controlled way, which is helpful for constructing adaptive antibacterial coatings on implants in the future.

3.1.2. *Antifouling materials*

Once bacteria attached on substrates are killed by antibiotics and released thereof, the dead bacteria may become the sites for biofilm formation [95]. Therefore, it is important to construct films that can release dead bacteria and prevent biofilm formation in the long run. For example, Wang and co-workers designed a series of self-cleaning films for eradication of bacterial infection. In a first approach, they constructed films by combining organic and inorganic materials. Self-assembly was used to fabricate an antibiotic-loaded multilayer film composed of montmorillonite (MMT) and poly-L-lysine (PLL) [96]. Once bacterial infection occurred, PLL could be degraded by chymotrypsin in microenvironment, leading to on-demand release of antibiotics from the films. Moreover, the peeling of the layers from surface releases bacterial corpses and debris and thus inhibits biofilm formation (Fig. 5). To avoid the overuse of antibiotics, antibiotics-free multilayer films composed of PLL, HA, and CHI as polymeric matrix were developed in the second approach, which are responsive to two types of enzymes, hyaluronidase and chymotrypsin (Fig. 6) [97]. The top $(HA/PLL)_n$ multilayers are totally enzymatically degradable, possessing excellent antiadhesion properties. The bottom $(HA/CHI)_n$ multilayers exhibit antibacterial properties because of the antimicrobial function of CHI [97]. These two kinds of films have adaptive antibacterial and antifouling capacities at the same time, providing a potential method for fabricating antibacterial surfaces for long-term use.

3.1.3. *Theranostic materials*

Bacterial infections easily occur at the wound site or on the surface of indwelling devices, the diagnosis and treatment of which is crucial [88].

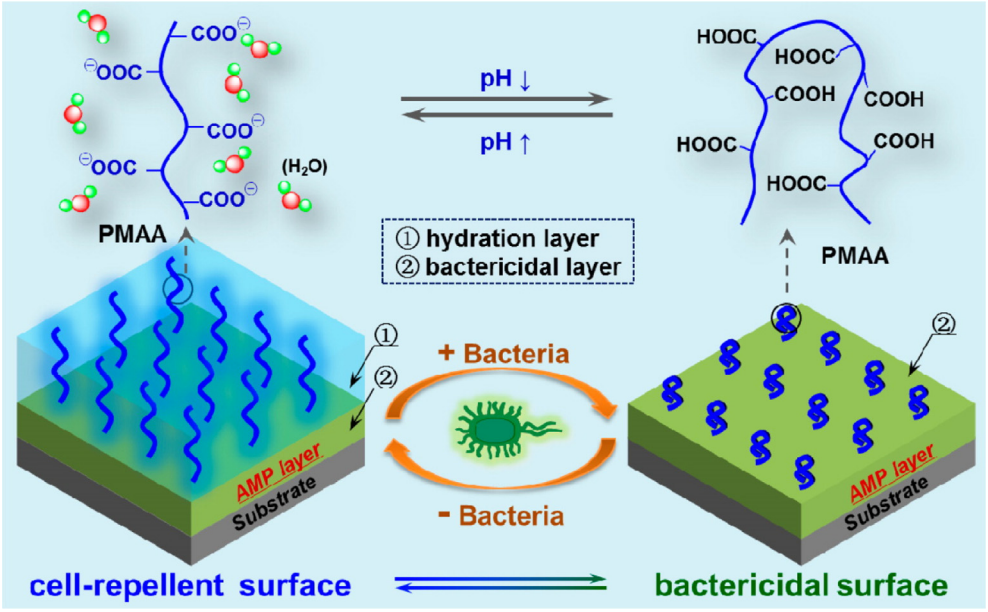

Fig. 12. Schematic diagram of the bacteria-responsive hierarchical antibacterial surface. Reprinted from Ref. [108] Copyright (2016), with permission from American Chemical Society.

An intelligent theranostic wound dressing composed of ultraviolet-crosslinkable methacrylated gelatin (GelMA) was designed. This dressing had two GelMA layers, in which vesicle-encapsulated antimicrobials and carboxyfluorescein were embedded in the lower and upper layers, respectively (Fig. 7). The shell of vesicles was composed of a phospholipids bilayer which is similar to eukaryotic cell membranes and can be destructed by toxins or enzymatic factors secreted by pathogenic bacteria, leading to the release of antimicrobial and carboxyfluorescein. The released fluorescein is diluted and 'switched on' and thus gives a visual color change. Therefore, the dressing not only inhibits bacteria growth but also has given a visual warning of infection. This design provides a natural defense against infection, which can help reduce the overuse of antibiotics and diagnose the occurrence of infection [98].

3.2. *pH-triggered adaptive antibacterial materials*

Studies have shown that pH is a particularly relevant stimulus for antibacterial coatings, because many bacteria metabolically acidify their local environment as a result of the secretion of acidic substances such as lactic or acetic acid [99–101], which triggers the release or exposure of antimicrobial agents. So far, many kinds of pH-triggered adaptive antibacterial materials have been fabricated; most of which are composed of positively or negatively charged polymers such as poly(acrylic acid) (PAA) and chitosan.

3.2.1. *Retention and release of antimicrobials via electrostatic force*

Different types of acids produced by bacteria can trigger the release of loaded antimicrobial agents at the local infection site, when the charge balance within the film or between the material and antimicrobials is broken. Using this approach, LBL multilayer films were constructed by using hydrophobic triclosan-loaded cationic micelles and negatively charged PAA [102]. The micelles were composed of a methoxy poly(-ethylene glycol)-poly(ε-caprolactone)-chitosan (MPEG-PCL-CS) block polymers. The PAA layer prevents the rapid release of triclosan loaded in micelles under normal physiological conditions, thus reducing the incidence of drug-resistant bacteria. As the pH value decreases, the permeability of the film increases because of the pH-responsive properties of both chitosan and PAA, leading to the release of antibiotic triclosan (TCA) (Fig. 8). Although this method allows the retention of hydrophobic molecules, there is a sustained release of these molecules in the normal medium.

To overcome the sustained release of antibiotic under normal physiological environment, S. A. Sukhishvili and co-workers designed a series of adaptive materials through LBL technique, in which the antibiotics were directly combined with the substrates via electrostatic force [103–105]. For example, using chemically cross-linked poly(methacrylic acid) (PMAA) as a matrix, they prepared a kind of antibiotic-loaded hydrogel polymer coating (Fig. 9) [103]. PMAA has a high content of carboxylic groups, which are capable of loading large amount of positively charged antibiotics through electrostatic force and release antibiotics in response to pH decrease induced by the bacteria adhesion. This hydrogel-like coating could effectively kill *S. aureus* and *E. coli* under static, small volume conditions and fluid flow in buffered conditions. In addition, hydrogel-like nanocomposite LBL films composed of like-charge polymers (PAA) and inorganic MMT clay nanosheets were also constructed [104]. This kind of nanocomposite significantly enhances the retention of positively charged antibiotics under physiological conditions for up to 45 days, because the coating release PAA-bound antibiotic at lower pH induced by bacteria, whereas the MMT-bound antibiotic remains within the coating for long-term antibacterial protection. Furthermore, they reported another antibacterial coating constructed by direct assembly of natural polyphenol molecule tannic acid (TA) with several cationic antibiotics [105]. Compared with the LBL films of linear polymer molecules, TA could retain more antibiotics for as long as one month because of its hydrogen bonding and electrostatic interactions with antibiotics. The low pH of the pathogenic bacteria environment triggers an antibiotic burst release from TA/antibiotic coatings because of a change in charge balance within the TA/antibiotic complex. This film is capable of retention and release of antibiotics in a controlled manner, providing applications in designing adaptive films and assembled materials.

3.2.2. *Retention and release of antimicrobials via pH-responsive linkages*

Apart from loading antibiotics into the substrate through electrostatic force, pH-sensitive linkages can also be used to fabricate adaptive antibacterial materials. For example, Liu et al. fabricated a pH-responsive surface drug delivery system composed of hybrid poly(vinyl alcohol)/poly(lactide-co-glycolide)/vancomycin (PVA/PLGA/Van) nanoparticles on biomedical titanium (Fig. 10). Based on the decrease of pH at the local bacterial infection sites, ester bonds between PVA and PLGA can be

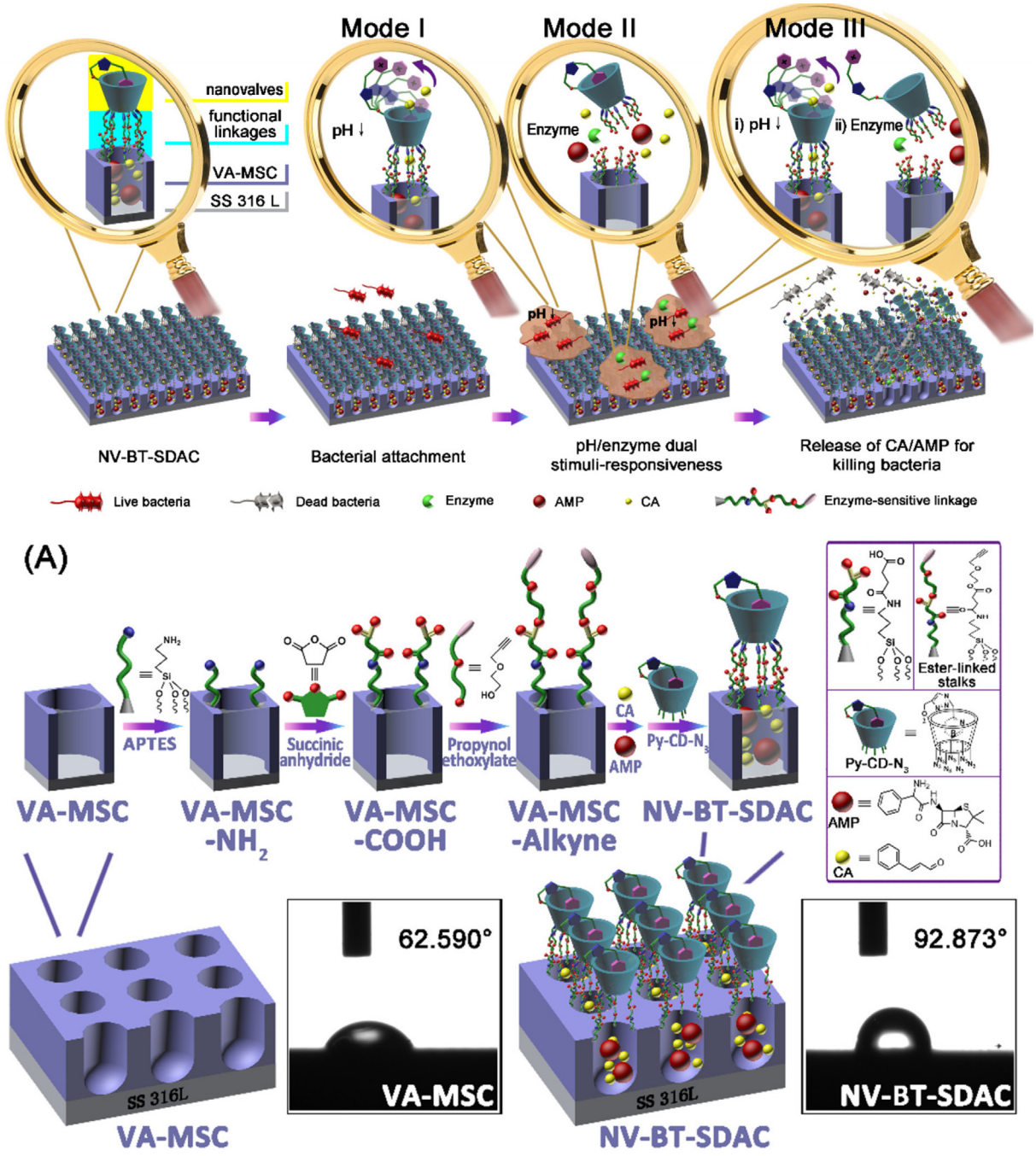

Fig. 13. Schematic representation of structure and working mechanisms for nanovalves-based, bacteria trigerred self defensive antibacterial coating (NV-BT-SDAC) deposited on SS [109]. Reprinted from Reference [109] Copyright (2017), with permission from American Chemical Society. SS, stainless steel.

broken, leading to Van release from nanoparticles. In addition, the surface has special hierarchical nanoscale microstructure which can facilitate the osteoblasts attachment and proliferation on implants. This work offers an idea for designing coatings on metallic implants which can improve cell attachment and antibacterial activity [106]. Hu et al. [107] designed a new type of aminoglycoside hydrogels by cross-linking oxidized polysaccharides using aminoglycosides as cross-linkers. Bacterial infection improves the acidity, which can cleave the Schiff base linkage between aminoglycosides and polysaccharides to release aminoglycoside antibiotics and further kill the bacteria by targeting bacterial ribosomes and inhibiting protein synthesis (Fig. 11). This release pattern avoids burst release of drugs and allows the drug release to synchronize with gel degradation.

3.2.3. *Renewable materials*

The aforementioned pH-responsive adaptive antibacterial materials are not renewable and may become inefficient when antibiotics are released completely or the matrix is degraded. Therefore, it is essential to design a kind of materials that exert their adaptive antibacterial activities without additional reloading of antimicrobial agents. In one of such studies, the surface-initiated photoiniferter-mediated polymerization (SIPIMP) strategy was used to prepare the hierarchical antibacterial surface consisting of an AMP-tethered bactericidal background layer and a pH-responsive poly(methacrylic acid) (PMAA) outer layer (Fig. 12)

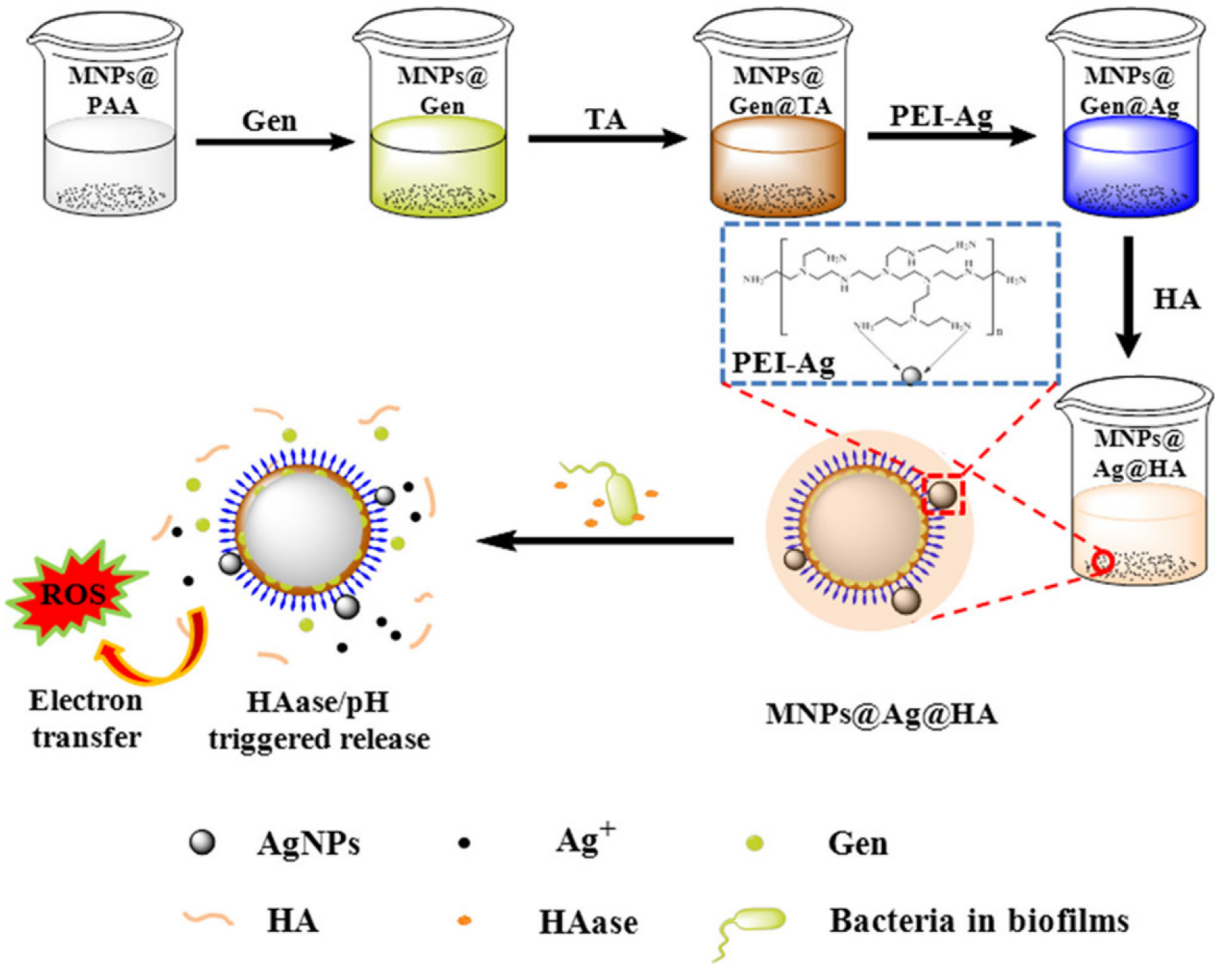

Fig. 14. Schematic of preparation of MNPs@Ag@HA via electrostatic interaction and mechanisms of antibacterial capacities. Reprinted from Ref. [110] Copyright (2018), with permission from American Chemical Society.

[108]. Under normal physiological conditions, the PMAA hydration layer can significantly inhibit the initial bacterial adhesion and the underlying AMP is shielded, rendering the hierarchical surface biocompatible. When bacterial colonization and biofilm formation occurs on the surface, the local environment becomes acidic, leading to the collapses of the PMAA chains and thereby exposure of the underlying AMP, ultimately activating the bactericidal functions. In addition, the dead bacteria and debris on the surface will be released by returning PMAA to its negatively charged state, making the surface renewable.

3.3. Dual stimuli-responsive adaptive antibacterial materials

The aforementioned adaptive antibacterial materials can release antibiotics and kill the bacteria in response to bacterial infections and possess great sterilization function. However, in most cases, the high levels of virulence factors such as enzymes and decrease of pH simultaneously exist at the sites of infections. Therefore, it is necessary to fabricate adaptive antibacterial materials sensitive to two or more stimuli simultaneously.

Fu et al. reported a novel vertically aligned mesoporous silica coating (VA-MSC) on the surface of stainless steel (SS) [109]. The coating was composed of VA-MSC as nanoplatforms loaded with antibiotics (cinnamaldehyde [CA] and ampicillin [AMP]). Nanovalves were installed on the exterior surface of VA-MSC coating via enzymatic sensitive linkages (Fig. 13). CA and AMP were sealed in the pore of VA-MSC to prevent the slow leakage under normal physiological environments. Once bacteria are attached, the surface can quickly respond to the environmental changes, including transition from self-complexation to self-dissociation of nanovalves with pH decrease, hence breaking the linkage triggered by lipase. Therefore, the coating can respond to pH/enzyme dual stimuli and release the antibiotics in three release modes: separate release of CA, corelease, and sequential release of CA and AMP. In addition, the synergistic interactions between CA and AMP enable this coating with excellent antibacterial efficacy in a controlled manner. In another study, antibiotic gentamicin (Gen), TA, and silver nanoparticles were coated on magnetic nanoparticles (MNPs) via electrostatic interactions, whose surface was capped with biodegradable HA molecules (Fig. 14). The overexpressed hyaluronidase and acidic environment at infection sites promote the degradation of the outermost HA layer and the release of bactericidal active Gen, Ag^{+}, and reactive oxygen species (ROS). Moreover, because of the excellent super paramagnetism of MNPs, the nanocomposites can penetrate in the deep layers of biofilms under external magnetic field. Therefore, the nanoparticles exhibit excellent properties of sterilization and biofilm disruption [110].

4. Antibacterial property and tissue integration of medical devices: dual function adaptive biomaterials

Successful biomedical devices and development of tissue engineering have gained success because of the use of biomaterials. These biomaterials have unlocked the regenerative innate potential of cells/tissues and help restore the normal body functions by repairing the damaged cells/tissues. Successful implants require well integration in surrounding tissues to avoid microbial colonization that may occur because of

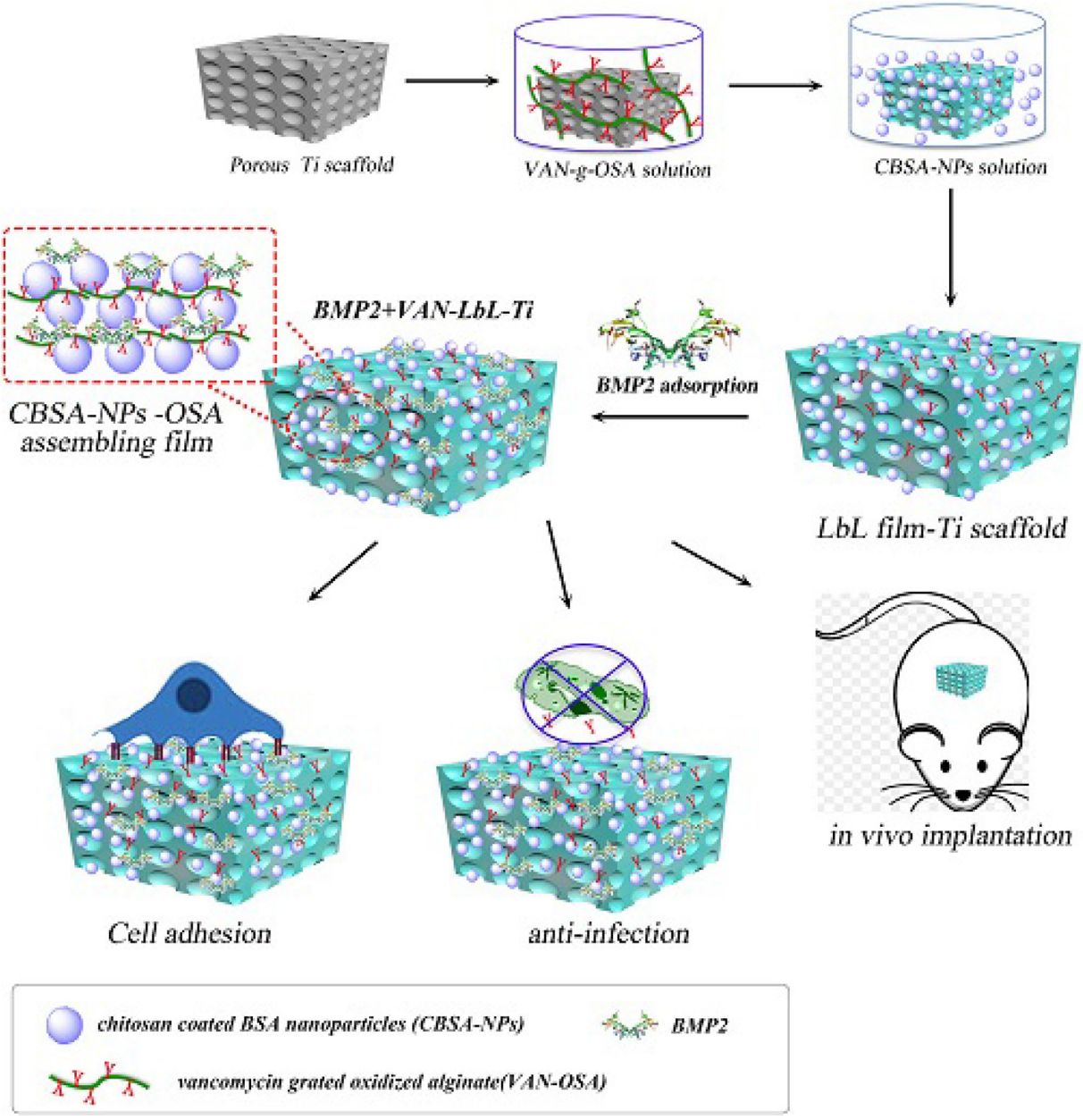

Fig. 15. Schematic of modification of porous titanium scaffolds by assembling chitosan–BSA NPs and Van-grafted oxidized alginate for dual functions of bone regeneration and antiinfection. Reprinted from Ref. [113] Copyright (2017), with permission from John Wiley and Sons. NP, nanoparticles; Van, vancomycin.

invasion of epithelial and mucosal barriers. Owing to bacterial infections, the integration of implants with surrounding tissues is hindered, causing severe immune response. The adhesion of surrounding host cells, on one hand, increases the tissue-material integration and, on the other hand, helps avoid the bacterial colony formation and prevent the implants infection. Therefore, to achieve the long-term effects, it is important to consider both the tissue integration and infection prevention. Surface modification of the implant biomaterials is an effective way to decrease the microbial infection and increase the tissue integration simultaneously.

Li et al. [111] constructed a biointerface having dual response, that is, detection of bacterial infection and promotion of tissue regeneration. The peptide surface having the ability for self-assembly consisted of three layers, that is, cell-adhesive peptides (Arg-Gly-Asp), infection-responsive peptides (G-1,G-2,G-3/C-1,C-2,C-3) and an antifouling layer of hexaethylene glycol (HEG). The cell-adhesive peptides have the ability to bind with cellular integrin, promoting the cell adhesion and spreading. The middle layer can be cleaved in response to infection by different types of bacteria, exposing the HEG layer that can detect the biofilm formation. Responsive behavior of the peptides is confirmed by comparing the retention time of proteolysis fragments and untreated peptides. Retention time of the treated peptides is shifted or disappeared. By contrast, the retention time of control peptides (G-ctrl/C-ctrl) is not changed significantly compared with the treated peptides, confirming the action of enzymes. The HEG layer of peptides G-1 and C-1 have shorter fragments and a better cleavage ratio, so these two peptides are chosen for further studies named as HEG-G-1, HEG-C-1, HEG-G-ctrl, and HEG-C-ctrl. Cell adhesion is increased on the responsive interface, being driven by the affinity of arginylglycylaspartic acid (RGD) peptides to cell surface receptors (integrin). The extension and growth of cells is increased because of the contact of unfurled lamella shape and the filopodia-substrate contact on the modified surface. The modified interface shows good biocompatibility for adhesion, spreading, and proliferation of cells. The modified biointerfaces have good antifouling property,

inhibiting the bacteria attachment, formation of biofilm, and nutrients deposition as compared with the controls. *In vivo* studies show that RGD peptides are able to promote the macrophage recruitment, reducing the inflammation, and promoting angiogenesis.

Lim et al. [112] prepared a multimaterial coating by using silicon-substituted hydroxyapatite (SiHA), silver-substituted hydroxyapatite (AgHA), and hyaluronic acid (HA). SiHA and AgHA are used in 1:1 ratio, which can impart bioactivity and have antibacterial properties, and a bioactive layer made up of HA is used to enhance the osseointegration. Log reduction assay demonstrated the inhibition of bacterial adhesion on the implant surface, leading to prevention of bacterial biofilms. The delay in exponential growth of bacteria was observed because of oligodynamic effect of Ag^{+}, AgHA, and SiHA-AgHA/HA that are useful to prevent the early infections. Formation of bound silicate network on SiHA is enhanced due to the presence of Si, leading to enhanced interaction with the cell integrins. This interaction results in formation of cell-specific signals, leading to better cell attachment. Presence of Si^{4+} ions in the layers increases the bioactivity as revealed by the enhanced gene expression and cell signaling pathways in bone forming cells.

Han et al. [113] improved the biocompatibility and biofunctionality of titanium (Ti) surface by using chitosan-coated bovine serum albumin (BSA) nanoparticles (CBSA NPs) and oxidized alginate (OXA). The LBL assembly technique was used to coat these materials on Ti surface (Fig. 15). CBSA NPs and OXA possess many functional groups, enabling the chemical and physical interactions of BMP2, leading to its steady and effective immobilization. Grafting of vancomycin on OSA was achieved by reaction between the aldehyde group of OSA and the amino group of vancomycin. The LBL films, even without the BMP2, enhance the adhesion and proliferation of cells. The high affinity of LBL components and nanostructure of LBL film on the microporous structure of Ti leads to better adhesion and proliferation of bone marrow cells (BMCs) *in vitro* and ectopic bone formation *in vivo*. Furthermore, vancomycin loaded on

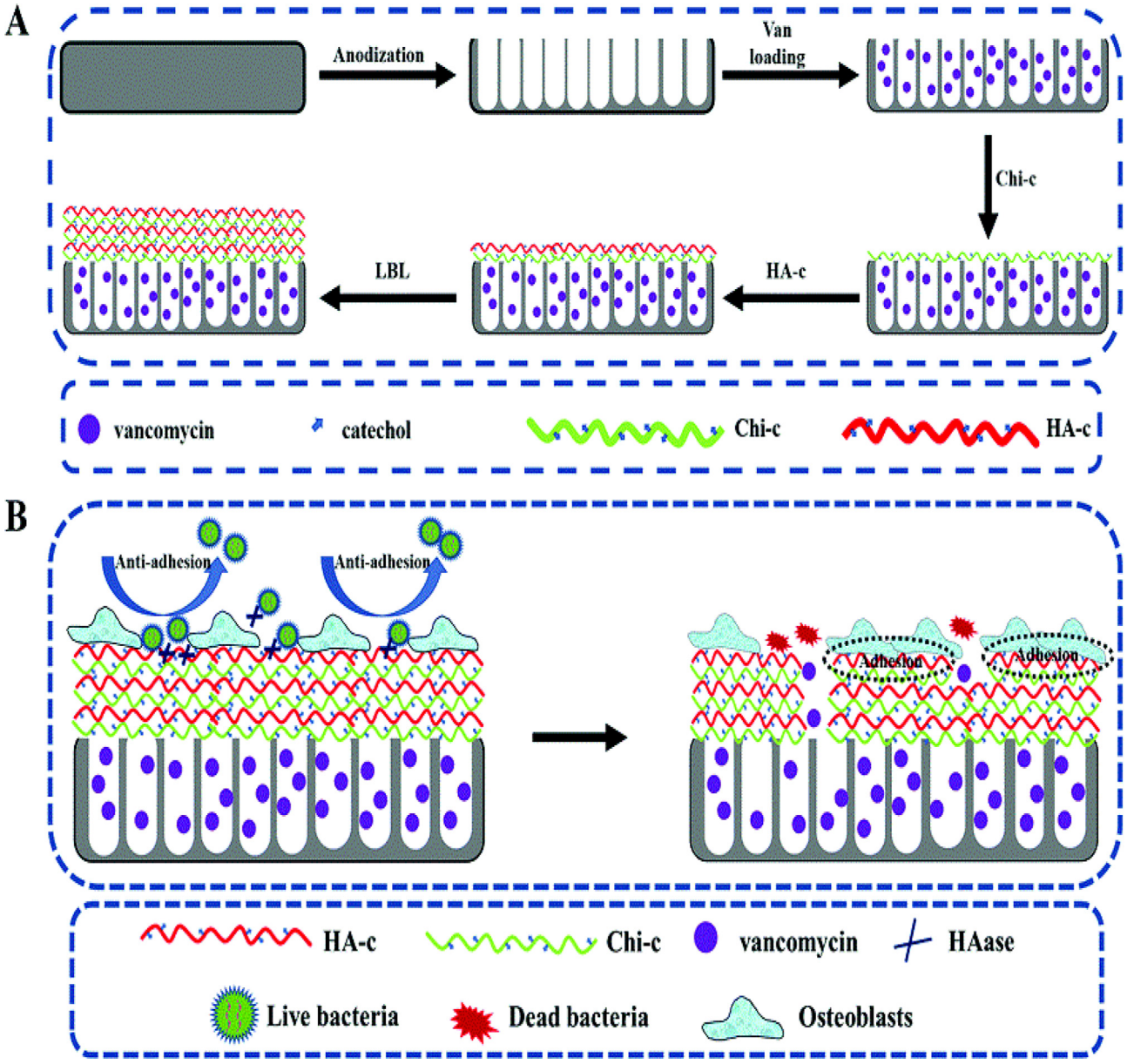

Fig. 16. (A) Schematic of the fabrication of catechol-functionalized multilayer films on Van-loaded titanium nano tubes (TNTs) array-modified Ti substrates. (B) Schematic of the inhibition of bacteria growth arising from the dual effects of antiadhesion ability and bacteria-responsive release of Van toward the infected area, simultaneously enhancing osteoblast adhesion due to the positive effects of numerous catechol groups on the modified Ti substrates. Reprinted from Ref. [114], Copyright (2018), with permission from American Chemical Society.

the LBL component results in effective antibacterial effect.

Yuan et al. [114] modified HA-c/CHi-c multilayer films with catechol, which were further assembled on vancomycin-loaded titanium substrates (Fig. 16). The amount of loaded vancomycin is blocked by these multilayer films. This system is bacteria responsive, which can release vancomycin on demand in the infection microenvironment. During the infection, hylauronidase (HAase) released by the bacteria will degrade the multilayer films, releasing the vancomycin. The hydrophilic antiadhesive coating and HAase-responsive vancomycin release enable the synergistic antiadhesive and antibacterial property for longer time. Catechols are benzene derivatives containing two neighboring hydroxyl groups. They are found abundantly in nature and are now being used as biomimetic functional materials with excellent bioactivity. Catechol present on vancomycin-loaded titanium substrate may exert special effect on osteoblast growth, resulting in bone formation. The osteoblast number is increased on the catechol-modified multilayers because of the promotion of early adhesion of osteoblasts. Integrin $\alpha_v\beta_3$ is up regulated, which is consistent with the promoted initial attachment of osteoblasts. Viability of osteoblasts also increases, promoting the formation of new bone in the infection microenvironment.

5. Conclusions and future perspectives

Bacterial infections on implants pose serious concern in the biomedical field. After the implantation, the host defense mechanism is compromised by the implanted biomaterials, providing the base for bacterial growth and propagation and resulting in series of adverse events and maybe ultimately the failure of implants. These infections, therefore, lead to the morbidity and high surgery cost. Antibiotics have been used for centuries, and antibiotic-loaded biomaterials have been developed to release the antibiotics in a sustained manner. However, the efficacy of this strategy is still challenging due to the passive release of antibiotics and antibiotic resistance, which hinder the successful bacteria killing process. Some alternative strategies such as stimulus-responsive biomaterials have been developed recently to combat the infections. However, owing to the complex systems in bacteria and the hostile environment in body, these biomaterials are not very successful to kill bacteria at the site of infection.

The recently developed adaptive biomaterials can kill the bacteria when they attack the implant surface. At the site of infection, different types of molecules secreted by the bacteria can be used as triggers for the release of antibacterial agents once they interact with biomaterials. These biomaterials can then release the antimicrobial agents that will inhibit the bacterial adherence and biofilm formation. Different biomaterials and antimicrobial agents such as RNA, antibiotics, antimicrobial peptides, and nanoparticles can be used to sense the existence of bacteria at the implant site, leading to the release of antimicrobial agents to inhibit the bacterial growth and successful implantation in the body.

Although some excellent proof-of-concept studies have been successfully demonstrated, practical applications of the adaptive antibacterial biomaterials and implants still face some critical challenges. For instance, accumulation of dead bacteria allows the adhesion of other bacteria and causes a problem in antibacterial response. Some biomaterials with antiadhesive properties do not allow the bacteria to adhere to the implant surface, but they slow down the tissue integration and thus increase the risk of long term infection too. The biggest challenge is to avoid passive release efficiently so that the antimicrobial agents can be retained in the biomaterial systems at long enough term upon implantation *in vivo*. Nonetheless, with the development of novel materials and techniques, these shortcomings would be avoided step by step, and thereby the development and applications of the adaptive antibacterial biomaterials will be surely promoted.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mtbio.2019.100017.

Conflict of 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 article.

Data availability

This is a review article, and thus, no raw/processed data can be shared.

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