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REVIEW ARTICLE

Strategies on designing multifunctional surfaces to prevent biofilm formation[#]

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Abstract Bacteria adhesion and biofilm formation have raised severe problems on public health, food industry and many other areas. A variety of reagents and surface coatings have been developed to kill bacteria and/or limit their interaction with surfaces. It has also attracted many efforts to integrate different bactericidal elements together and maximize antibacterial efficiency. Herein, we review mechanisms for both passive and active approaches to resist and kill bacteria respectively, and discuss integrated strategies based on these two approaches. We also offer perspective on future research direction.

Keywords antimicrobial, surface, multifunctional

1 Introduction

Microorganisms universally attach to surfaces and produce extracellular polysaccharides, DNA, and proteins. This eventually results in the formation of a biofilm, a notorious situation that deteriorates public health and impedes a broad range of medical and industrial applications [1]. Bacterial adhesion onto indwelling medical devices and the subsequent biofilm formation are the major causes for nosocomial infections. A biofilm, defined as a matrix-enclosed bacterial population, is a densely packed community of microbial cells growing on surfaces and surrounding themselves with secreted polymers. Once developed, it can hardly be eliminated, because it is less responsive to antibiotics and biocides than the planktonic bacterial form [2]. Nowadays, biofilm has posed a serious problem for public health because of the increased resistance of biofilm-associated organisms to antimicrobial agents and the potential for these organisms to cause infections in patients with indwelling medical devices [3]. For medical implants and devices, bacterial attachment adversely affects their functionality and limits their lifetime. Bacterial infections represent a common and substantial complication in the clinics, even leading to death. In some other areas, for example, in dairy industry, most contaminated milk and milk products are associated with scratched surfaces of improperly cleaned or sanitized equipment [4].

In recent decades, researchers have paid considerable attention to developing antibacterial surfaces to directly kill bacteria upon contact, and/or to reduce the extent of initial bacterial attachment, and thereby to prevent subsequent biofilm formation. It is well known that there are two major types of materials either actively or passively preventing bacterial adhesion and biofilm formation. Respectively, they are actively "bacteria-killing" materials, including cationic polymers, antimicrobial peptides, antibiotics, silver ions, nitric oxide, etc., and passively "bacteria-resistive" materials, such as polyethylene glycol (PEG), zwitterionic polymers, and their derivatives [5–7]. Both types of materials have demonstrated their respective efficiency as a successful anti-bacteria strategy. However, they can hardly achieve 100% efficacy in permanently protecting a surface, and usually delay, rather than fully prevent, biofilm formation. In this paper, we firstly review different antibacterial mechanisms for active approaches and passive approaches, and then discuss strategies to integrate these approaches to further improve the antibacterial efficiency. State of the art examples are illustrated to inspire future research directions of antibacterial surface.

2 Mechanism for active approaches

2.1 Cationic polymers

Cationic polymers have gained increased interests from

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both academic and industrial communities as antimicrobial materials to mitigate, combat or eradicate microbial causes for infections [8]. This class of positively charged materials interacts with negatively charged bacteria cell membrane, and kills the bacteria through various pathways.

Among all the cationic polymers, chitosan is one of most extensively used showing antimicrobial properties for both Gram-positive and Gram-negative bacteria. When the polymer is strongly charged, such as at $pH < 6$, chitosan derivatives, such as chitosan acetate was able to kill *Escherichia coli* (*E. coli*) in an efficient way [9]. The mechanism for such antimicrobial property is due to electrostatic interaction between NH_3^+ groups of chitosan and phosphoryl groups of phospholipid components of cell membranes [10]. PEGylated quaternized chitosan derivatives also showed antimicrobial efficacy against bacteria. By introducing cationic charge through quaternization of the amino group, these derivatives formed porous hydrogels. Their inner quaternary ammonium salts structure acted as "anion sponge" and would interact with regions of the anionic microbial membrane in the internal nano-pores, leading to microbial membrane disruption and subsequent microbial death [11].

Polyethylenimine (PEI) is a weakly basic, aliphatic, nontoxic synthetic polymer. Primary, secondary, and tertiary amino groups in the structure of PEI could be further converted to quaternary ammonium groups, which rupture bacterial membrane through electrostatic interactions [12–14]. In addition, it is well known that certain polycationic agents such as polymyxin and its derivatives polylysines and protamine can increase the permeability of the Gram-negative bacterial to solutes that are normally unable to penetrate [15]. Similar to these cationic permealizers, PEI also has a strong permeabilizing effect on Gram-negative bacteria [16]. A series of antibiotics, such as novobiocin, tobramycin, and kanamycin, mixed with PEI solution, were reported to show improved antibacterial effects compared with pure antibiotics [17]. Therefore, PEI and its derivatives showed effective antibacteria properties both by themselves and by working together with other antimicrobial agents.

2.2 Antimicrobial peptides

Antimicrobial peptides (AMPs) are natural polymers that could be found among all classes of lives. They are part of the innate immune system, and are also called host defense peptides. As novel therapeutic agents, these peptides are potent, broad-spectrum antibiotics showing effectiveness against Gram-negative and Gram-positive bacteria, enveloped viruses, fungi and even transformed or cancerous cells [18]. Although the exact working mechanism of AMPs remains controversial, there is a consensus that these peptides selectively disrupt cell membranes and the amphipathic structural arrangement of the peptides plays an important role. The head group charge of phospholipids on cell membranes and peptide charge distribution appears to drive the peptide-membrane interactions [19–21]. Considering that they are of low-toxicity and broad spectrum, AMPs could be further integrated with bacteria-resisting surface for novel indwelling applications. Antimicrobial coating on planar surfaces has been achieved based on covalent immobilization of naturally abundant, unmodified AMPs suitable for large scale applications [22]. *E. coli* was used to characterize the antimicrobial property of this AMP surface. When this AMP surface was cultured with human histiocytic lymphoma, no significant cytotoxicity was observed, indicating certain extent of biocompatibility of this AMP surface.

2.3 Antibiotic

Antibiotics are a type of antimicrobial agents specifically used to inhibit and/or kill bacteria. They have been widely involved in medical treatment for bacterial infections. For example, in dentistry, antibiotics have been integrated with bone cements for orthopedic and orthodontic implants [23,24]. The local delivery of antibiotics can prevent adhesion and growth of significant numbers of bacteria after cement hardening *in situ*. Based on the working mechanism, antibiotics are generally classified into four groups [25,26]. Two of them target the bacterial cell wall (penicillin and cephalosporin) or the cell membrane (polymyxin), or interfere with essential bacterial enzymes (rifamycin, lipiarmycin, quinolones, and sulfonamides). The other two directly inhibit protein synthesis (macrolides, lincosamide and tetracycline), or indirectly inhibit through interfering DNA/RNA synthesis.

Certain antibiotics have difficulty to penetrate the biofilm and reach the individual bacterium [27], and their use is typically combined with other materials that can assist the penetration of antibiotics to kill bacteria [28]. Drug penetration is usually based on strategies to disrupt the multicellular structure of the biofilm, e.g., to dissolve the matrix of biofilm by using enzymes [29], and to prevent the synthesis of biofilm matrix by using chemical reactions [30]. Once antibiotics reach the individual bacterium, they may suffer from resistance. For those antibiotics that can hardly enter the bacterium to perform killing functions, they may need the assistance of penetrating agents, as mentioned in section 2.1.

2.4 Silver and its derivatives

Silver has been used for centuries to kill bacteria, however, the mechanism has not been elucidated until recent decades. The antimicrobial effect of silver derivatives including silver ion or silver nanoparticles (Ag NPs) has been generally related to their interaction with thiol (sulfhydryl) groups of enzymes and proteins [31,32], and phosphorus groups of DNA [33,34]. On most occasions,

there is abundance of thiolated proteins on bacteria cell membrane; silver can interact with their thiol groups and in turn affect bacterial cell viability.

Nowadays, silver ions and nanoparticles have attracted researchers' attention on integrating them with bacteria surfaces [35,36]. Silver ions can interact with phosphorus moieties in DNA, inhibiting bacteria growth by preventing DNA replication [37]. They have been used as a significant component for disinfecting filters and coating materials. Nano-sized silver particles were reported to exhibit antimicrobial properties through the same mechanism as silver [38], and have been used as a carrier for antibiotic delivery [39,40].

2.5 Copper and its derivatives

Similar to silver, copper has microbial killing property, and has been used to inhibit bacteria and virus since ancient time [41]. It is suggested that copper could mediate redox cycling by generating reactive oxygen species to become toxic [42,43]. The antimicrobial mechanism of copper has been reviewed elsewhere and is related to oxidative property of copper in the cell [44,45].

Copper nanoparticles (Cu NPs) also have significant promise as bactericidal agent [46] and have been used in various fields, such as medical instrument and devices, water treatment and food processing [47,48]. Compared with Ag NPs, Cu NPs showed even better antibacterial effect under certain particle size, such as against *Escherichia coli* and *Bacillus subtilis* [49]. The mechanism of antibacterial action of Cu NPs could be probably through the direct effect of Cu ions liberated from the NPs to form certain reactive complex between Cu NPs and cellular medium organics [50].

2.6 Nitric oxide

More than 50 years ago, nitric oxide (NO) has been used to prevent spoilage of meats [51]. Nowadays, NO with constant concentration in situ was proved to be a novel approach to inhibit implant-associated infections. It has been reported that many bacteria are able to reduce NO to nitrogen [52], e.g., *P. aeruginosa* is able to convert NO ultimately to nitrogen through the NO reductase pathway [53]. When intracellular concentration of NO is too high, NO gas appears to be lethal to the bacteria [54]. Such deleterious effect is typically caused by the reaction between NO and superoxide (O_2^-). O_2^- is a weak oxidant, but interacts with NO to form powerful oxidant species such as peroxynitrite ($ONOO^-$) and dinitrogen trioxide, which lead to the damage of DNA and proteins [55,56]. By taking advantage of antibacterial function of NO, local release of NO has been incorporated with material design [57] and surface coatings [58,59]. For example, NO releasing material has been designed as a coating for PVC tubes by integrating polyurethane with NO donor, diazeniumdiolated dibutylhexanediamine (DBHD-N_2O_2). Such coating can effectively kill bacteria attached on the surface of PVC tubes. In addition, release of NO on local surface has been reported by using catalysts for NO generation for anticoagulation and antithrombosis purposes [59–61]. These examples indicate that NO as a novel antimicrobial and anticoagulation strategy may find broad future applications.

3 Mechanism for passive approaches

3.1 Polyethylene glycol (PEG) and its derivatives

Polyethylene glycol (PEG) (structure shown in Fig. 1(a)) and its corresponding oligomers are the most commonly used nonfouling materials. It has been reported that self-assembled monolayers (SAMs) of PEG can uniformly resist bacterial attachment and reduce microbe adhesion by 99.7% [62]. As the number of ethylene glycol moieties increases, the negative interfacial tension between the PEG SAMs and water increases, leading to enhanced bacterial resistance [63]. The effect of resisting bacteria on PEG or PEG-terminated surface has been attributed to the interaction of water with surface at molecular-level (i.e., surface hydration). Thermodynamically, the removal of water from PEG chains is unfavorable, and this gives rise to a steric repulsion that, according to Andrade and de Gennes [64], contributes to the nonfouling property of PEG surfaces. Experimental data have shown that the nonfouling property was promoted with increasing length and density of the PEG chains on the surface [7]. There is significant research on the fabrication of substrates coated or covalently grafted with PEG based linear polymers [65,66], comb-like polymers (with ethylene glycol units as side chains such as PEGMA [67,68]), hyper-branched polymers [69], and hydrogels [70,71], aiming at resisting bacterial attachment for various applications ranging from those in the marine industry to biomedical devices.

3.2 Zwitterionic polymers and derivatives

Unlike non-ionic PEG, zwitterionic polymers have an equivalent number of homogenously distributed anionic and cationic groups on their polymer chains [72]. Common zwitterionic polymers include polybetaines carrying a positive and a negative charges on the same monomer unit such as 2-methacryloyloxylethyl phosphorylcholine (MPC) [73,74], sulfobetaine methacrylate (SBMA) [75,76], and carboxybetaine methacrylate (CBMA) [6,77] (Fig. 1(b)). Zwitterionic-like polymers involve polyampholytes made from 1 : 1 positive and negative charged monomers that can be chosen from acid or amine-containing methylates or acrylates [78], or from charged

natural amino acids (glutamic acid, aspartic acid, and lysine) [79,80]. It has been suggested that a nano-scale homogenous mixture of balanced charge groups from polyzwitterionic materials is the key to control nonfouling properties. The nano-scale mixing of oppositely charged moieties render zwitterionic polymers the overall charge neutrality; this prevents charged species (e.g., proteins, cells, bacteria or other microorganisms) from binding to zwitterionic polymers. In addition, zwitterionic polymers provide even stronger hydration (the key to nonfouling property) through ionic solvation [81] than PEG, and outperform PEG in certain nonfouling applications [82]. Bacterial resistance property of grafted CBMA and SBMA polymers on glass surfaces has been systematically studied [5,6]. Results showed that compared with grafted PEG coating, CBMA and SBMA coatings maintained even longer-term inhibition of biofilm formation due to decreased bacterial adhesion. For example, when CBMA polymer was grafted from glass substrates, the resulting surface effectively resisted long-term biofilm formation of *Pseudomonas aeruginosa* PAO1 up to 240 h by 95% at 25°C and 64 h by 93% at 37 °C, and suppressed *Pseudomonas putida* strain 239 biofilm accumulation up to 192 h by 95% at 30 °C, with respect to the uncoated glass reference [5]. Based on the distinctive nonfouling property, zwitterionic materials have also been utilized in many areas beyond antibacterial applications [73,79,83–88].

3.3 Novel polymers identified from combinatorial chemistry

Recently, a series of polymers showing broad-spectrum resistance to bacterial attachment were discovered through combinatorial methodology [89,90]. Using high throughput assay to assess bacterial attachment on hundreds of unique acrylate and methacrylate polymers in parallel, new class of bacterial-resistant materials were discovered and proved to be effective comparing with commercially available silver hydrogel materials. Figure 1(c) shows one of the novel monomers that were identified to construct highly efficient bacterial resistance surface [89,90]. These novel materials have been speculated that their nonfouling property is related to the contact angle or roughness of the surface, which further correlates with bacterial attachment. Further time-of-flight secondary ion mass spectrometry (TOF-SIMS) spectra study confirmed that the bacteria-surface interaction is dependent on surface chemistry, and cannot be explained solely by surface hydrophobicity or roughness. Obviously bacterial response to surfaces is sophisticated, it is suggested that elimination of hydrogen binding between the material surface and bacteria (e.g., lipopolysaccharides, lipoteichoic acids or exopolysaccharides present on the bacterial cell surface [89]), and the appearance of certain chemical groups (e.g., ester group and the weakly amphiphilic structure) may play an important role for the bacterial resistance. Overall,

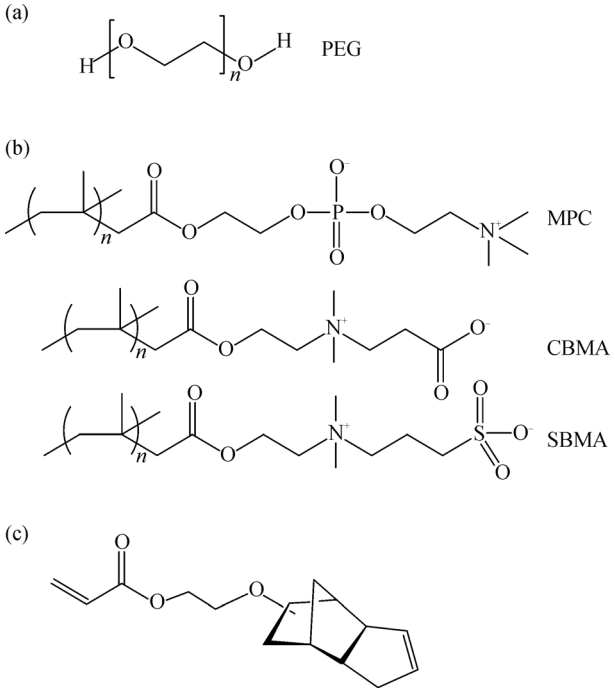

Fig. 1 (a) Chemical structure of PEG; (b) Chemical structure of typical zwitterionic polymers: MPC, CBMA and SBMA; (c) Chemical structure of novel monomer identified from combinatorial high throughput assay

these polymers represent novel bacteria-resistant materials that are beyond the prediction based on current understanding of bacteria-surface interactions.

4 Applying active and passive approaches simultaneously

To inhibit bacterial occupancy on a surface (e.g., an implantable biomaterial surface), materials with either resisting or killing capability have been developed and practiced individually as a surface coating. However, the sole resisting capability is not enough because even the best nonfouling surface still has a tiny amount of bacteria attached (e.g., due to gravity, surface defect, etc.), which would grow to a biofilm in the long run through cell division and adhering to other planktonic bacteria [91]. Neither is the sole killing capability, because it can either be used up or be saturated upon bacteria adhesion onto the surface, and resistance to certain bactericidal materials (e.g., antibiotics) can also be developed [92]. Therefore, there is a strong need for combining both capabilities.

To increase antimicrobial efficacy, both active and passive strategies have been employed together; however, a direct combination may not significantly improve the biofilm prevention in the long run. For example, a non-leachable bacteria-killing material such as an antimicrobial peptide along with a resistive zwitterionic polymer can be permanently co-immobilized on a surface [93]. But active and passive elements dilute each other and their respective effectiveness can be compromised: the total bactericidal capability is less than a surface purely of antimicrobial peptide moieties; the total bacteria-resisting properties are also greatly reduced, because antimicrobial peptides actively attract and stick to bacteria [94]. It should be noted that most non-leachable bacteria-killing materials have cationic natures and rely on bacterial binding to function properly [92,94]. They are highly desirable for long-term biofilm prevention, but inherently incompatible with bacteria-resistant materials when both of them function simultaneously.

When leachable antimicrobials are combined with non-fouling surfaces, the above-mentioned incompatibility between active and passive approach can be resolved. For example, salicylate, a naturally occurring compound produced by many plants to protect against the invasion of bacteria and fungi, has been integrated in surface design as a leachable antimicrobial. Salicylate and its derivatives have been broadly used as non-steroidal anti-inflammatory drugs (NSAIDs) because these compounds are able to inhibit the inflammatory response of the body [95]. Salicylate and other NSAIDs are also shown to prevent bacterial adhesion onto medical devices although the mechanism has not been identified. It has been reported that salicylate interferes biofilm formation at a low concentration and inhibits the growth of bacteria at a high concentration. Based on leachable salicylate and nonfouling/biocompatible zwitterionic surface, both active and passive antimicrobial elements have been integrated [96]. Specifically, salicylate was incorporated into a cationic carboxybetaine ester hydrogel, poly(*N*,*N*-dimethyl-*N*-(ethylcarbonylmethyl)-*N*-[2-(methacryloyloxy)-ethyl] ammonium salicylate) (pCBMA-1 C2 SA), as its anionic counter ion. This new hydrogel gradually released antimicrobial salicylate to inhibit the growth of planktonic bacteria and created a nonfouling surface upon the hydrolysis of carboxybetaine esters into zwitterionic groups to prevent protein adsorption and bacterial accumulation. Results showed that the growth of both Gram-negative *E. coli* and Gram-positive *S. epidermidis* was inhibited by 99.9%. This strategy to control the release of small and hydrophilic compounds from hydrogels is applicable to the delivery of other negatively charged drugs. It should be noted that this approach was not able to kill bacteria after the last bit of salicylate was released (i.e., about 50% salicylate released within 2 days, and nearly 100% salicylate released within 17 days). It thus becomes a challenging issue on how to control the release of antimicrobials to achieve an appropriate period of time of bacteria inhibition for specific applications.

Most antimicrobial functions are achieved by organic structures, such as drugs, quaternary ammonium and peptides. Alternatively, inorganic antimicrobial agents can be introduced into the zwitterionic polymer system to fulfill bacteria killing functions, such as Ag NPs that can be easily synthesized with decreased toxicity for human bodies [97]. To integrate Ag NPs into the surface, pre-synthesized zwitterionic polymer brushes were saturated with $AgNO_3$ solution and then treated via UV irradiation to reduce silver ions to colloidal silver particles. The newly formed organic-inorganic hybrid surface contained both grafted zwitterionic polymer brushes and embedded Ag NPs, killing more than 99.8% of *E. coli* in 1 h, and releasing 98.7% of dead bacterial cells from the surface [38]. It should be noted that the embedded Ag NPs are leachable, but they can be easily regenerated by re-saturating the surface in Ag ion solution followed by irradiation. This is an advantage of this hybrid surface comparing with surfaces integrated with other types of leachable agents. To increase the loading of Ag^+ or Ag NPs, they could be optionally integrated into the base polymer (in addition to the surface coatings), allowing for a larger sink for leaching of these antimicrobials.

Novel combination of both active and passive approaches has also been explored through a so-called layer-by-layer (LBL) deposition technique [98]. LBL is a simple, low-cost and mild technique for fabrication of multilayers of polymers highly tunable in both morphology and functionality. This technique has been used to regulate bacterial adhesion, to create cationic coatings that kill bacteria on contact, and to include a variety of biomolecules such as proteins, enzymes, drugs and

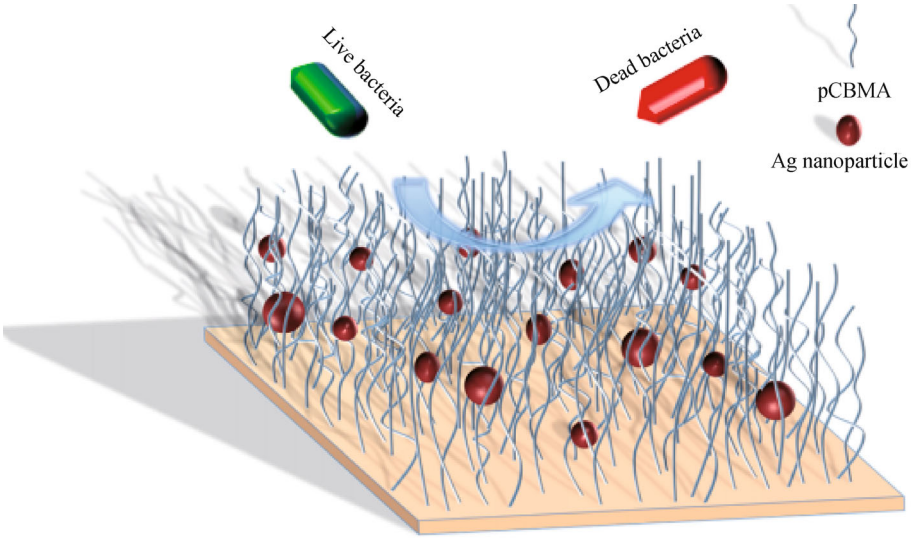

Fig. 2 A convenient strategy to achieving antimicrobial and anti-adhesive purposes using a silver-zwitterion nanocomposite [38]. Copyright © 2013, American Chemical Society

nanoparticles without losing their biological functions within the surface coatings. Typically positively charged polymer and negatively charged polymer can be alternatingly deposited in the LBL film. The charge mixing nature renders zwitterionic-like feature of the surface, providing bacterial resistance capability [99]. Bacterial killing elements can be chosen from leachable antibacterial agents that can be loaded into multilayers (later released upon the upper layer has been removed [99–101]), or chosen from cationic antibacterial polymers, such as chitosan [98,102] (e.g., to construct LBL film with cationic antibacterial chitosan and anionic anti-adhesive heparin).

Overall a direct mixing of both killing and resisting materials on a surface can realize the active and passive functions simultaneously. But it is highly possible that both of the functions are compromised, because when a bacterium approaches the surface, the resisting material does not intend to interact with it, whereas the killing material relies on bacterial binding. When the bactericidal material is leachable, then durability of the active killing function is in question.

5 Applying active and passive approach sequentially

To maximize the viability of combined approach, it is believed that the surface should only commit one function at a time (either killing or resisting), and then perform the other function. In this way, the two functions would not interfere with each other. Based on this idea, a "kill-and-release" strategy has been reported, using a surface that irreversibly converts from one molecular structure to another [103]. Initially, a surface made of antimicrobials is able to kill attached bacteria. Upon certain reaction with external stimuli, the surface changes from antimicrobial status to nonfouling status, and then releases the attached bacteria and resists further bacterial binding. In this "kill-and-release" strategy, antimicrobial and nonfouling functions are achieved sequentially. Furthermore, a nonfouling surface can perform both resisting and releasing functions after most attached bacteria are killed, so this strategy could effectively prevent the formation of biofilm.

One example based on "kill-and-release" strategy is a designed bactericidal polymer capable of turning into zwitterionic polymer through hydrolysis of ester bond (Fig. 3) [103]. Specifically the bactericidal polymer is a cationic precursor for carboxylbetaine (CBMA) polymer, which has been demonstrated to kill more than 99.9% *E. coli* in one hour. After hydrolyzing ester groups on the side chains of this precursor polymer, anionic carboxyl groups were regenerated and zwitterionic CBMA polymer was formed, which was able to effectively release the pre-adsorbed killed bacteria. Moreover, the resulting nonfouling zwitterionic surface can prevent further attachment of proteins and microorganisms and inhibit the formation of biofilm on the surface even 8 days after hydrolysis of ester group. The converting process from bactericidal to nonfouling surface can be finely tuned by adjusting the hydrolysis rate of these polymers.

By reversing the sequence of kill-and-release, a "resist-and-kill" strategy has also been developed [104]. Specifically, a heparin/chitosan LBL film was prepared as a base coating, and a degradable poly (vinylpyrrolidone)/poly (acrylic acid) (PVP/PAA) multilayer film was deposited as a top coating [104]. Results showed that during the first 24 h, the top PVP/PAA was continuously removed, preventing bacteria from attaching on the surface. After the removal of PVP/PAA film, the underlying heparin/chitosan LBL film was exposed and provided contact-killing antibacterial properties.

Both "kill-and-release" and "resist-and-kill" strategies

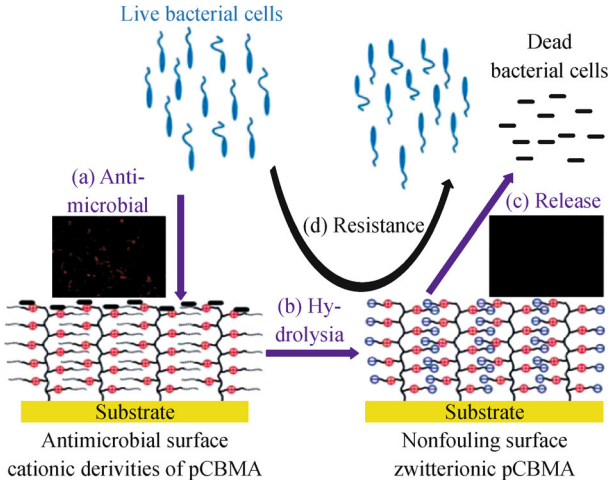

Fig. 3 A surface switches from an antimicrobial status to a nonfouling one upon hydrolysis [93]. Copyright © 2008 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim

can be promisingly utilized as an improved approach to prevent biofilm formation. The amount of bacteria for a bacterial resistant surface to exclude is typically much larger than that for a bactericidal surface to handle, but the bacterial resistant surface cannot kill the planktonic bacteria. These factors should be considered when choosing the right strategy in dealing with a specific antimicrobial need. Nevertheless for those multi-function surfaces, once one function has been consumed, it cannot be easily regenerated. This inspires researchers seeking new ways to develop novel surface that can freely and repeatedly switch between active and passive approaches to further improve antibacterial efficiency.

6 Repeatedly switching between active and passive approaches

Recent years, many efforts have been made to design novel surfaces being able to repeatedly switch between bacterial killing (active) and resisting/releasing (passive) functions. Significant progress involves the development of novel smart polymer (CB-OH/CB-Ring) that can alternate between two equilibrium forms driven by acidic or basic conditions [105]. A surface made of this smart polymer can repeatedly kill bacteria (using a cationic structure), release killed bacteria, and resist further bacterial attachment (using a nonfouling zwitterionic structure) (Fig. 4) [106]. In an "active" mode, CB-Ring surface kills over 99.9% of *E. coli* K12 attached on it under dry conditions. Once the material is placed in wet condition, it converts from CB-ring to CB-OH, the "passive" mode, releasing 90% of the previously attached and killed bacteria, and resisting further bacteria attachment. To regenerate CB-Ring from CB-OH and re-achieve the "active" mode, acidic conditions such as acetic acid can be applied. Based on similar molecular switching mechanism, new polymers have been developed with comparable smart antimicrobial and nonfouling features [107,108]. In addition, a thermo-responsive, nano-patterned surface has been fabricated showing switchable attach & kill, and release functionalities [109].

In addition to zwitterionic polybetaines, polyampholytes made from 1 : 1 positively and negatively charged monomers also showed excellent nonfouling property [81]. Many smart surfaces were designed based on polyelectrolyte materials due to their highly controllable property to various environmental stimuli [110–113]. Based on the concept that a nonfouling zwitterionic nature

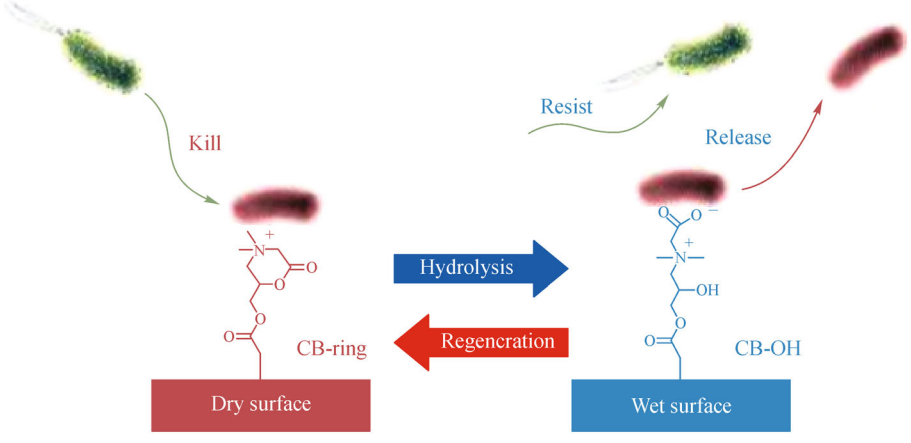

Fig. 4 A smart polymer coating repeatedly switches between the bacterial attacking function (ester precursor) and bacterial defending function (zwitterionic form) [106]. Copyright © 2012 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim

can be obtained from two separate monomers or components, it has been realized to freely switch between bacteria killing and resisting functions using a surface grafted with cationic poly ((trimethylamine) ethyl methacrylate chloride) (pTMAEMA) brushes and anionic counter ions of different sizes and valences [114]. Cationic pTMAEMA brush was able to efficiently kill bacteria with regular counter ions such as chloride anions. After washing the brush with electrolyte solutions containing large and high valence anions, i.e., hexametaphosphate, which bind the cationic pTMAEMA more strongly, the cationic nature of the surface was neutralized and the killed bacteria on surface were released. To regenerate the cationic pTMAEMA brush, the surface can be simply placed in sodium chloride solution for 2 h.

A common feature for these switchable surfaces is that they repeatedly kill bacteria (using a cationic structure), release killed bacteria and resist further bacterial attachment (using a zwitterionic or neutralized zwitterionic-like structure). These surfaces integrate both active and passive elements, and demonstrate the ability to repeatedly kill and resist/release bacteria, each at a time, rather than at the same time when respective capability is compromised. Nevertheless, these smart materials/surface require an external trigger (i.e., acidic or basic condition, ions, or temperature change) to switch between the molecular structures/functions. Such a trigger may not be available in many scenarios.

7 Summary and perspective

Over the last century, researchers have developed a series of methods to resist and kill bacteria on surfaces to effectively prevent the formation of biofilm. Significant interests have been focused on surfaces integrating traditional antimicrobial agents with newly synthesized bacteria-resistant or bacteria-release materials. Compared with conventional antibacterial surface with a single functionality, these surfaces, despite of various designs, have made considerable progress to create nonfouling and antimicrobial functionalities potentially being used in marine, industrial and medical applications. Nevertheless many challenges remain in this field and could be future research directions.

7.1 Long-term usage

Different strategies have been used to integrate bacterial killing and resisting/releasing functions on surfaces and to regenerate or recycle these functions for repeated usage. However, few studies has explored the life time for each of the functions to be efficiently maintained. In another word, the capability of the surface to perform bacterial killing and/or bacterial resisting/releasing decreases over time, as more tough bacteria that are hard to remove occupy the surface. Depending on the antimicrobial requirement in specific scenarios, the long-term functioning can be a highly desirable feature, e.g., for implantable medical devices. Research on how to eliminate bacteria adsorption on the surface in an extremely efficient way is crucial to long-term applicability of antimicrobial surfaces.

7.2 Switchable without external assistance

For those smart switchable antibacterial surfaces discussed in section 6, they all require an external assistance to realize the switching between bacterial killing and bacterial resisting/releasing functions. The external stimuli include pH, ions, and temperature, as discussed in this review. Other external stimuli such as UV, infrared radiation, and magnetic field are likely to be realized in the future; some of these stimuli can only be done at lab conditions, and some of them cannot be available for antimicrobial applications inside human bodies. Future research can focus on novel surface design by automatically performing different antimicrobial functions without external assistance, to broaden the applicability of smart antimicrobial surfaces.

7.3 Other challenges

It can be a complicated issue to develop antimicrobial surface to be a practical product. Bacteria debris, surface defects, contaminations, etc., can strongly downgrade the antimicrobial efficacy of the surface. To address these factors, it is crucial to optimize the design and fabrication process. Moreover, the fabrication of surfaces should be facile, low-cost and reproducible; these are also important criteria for future surface design.

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