Polymer Journal (2018) 50, 33–44

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REVIEW

Antimicrobial cationic polymers: from structural design to functional control

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Antimicrobial cationic polymers mainly contain two functional components: the cationic groups and the hydrophobic groups. The antimicrobial activity is influenced by the type, amount, location and distribution of these two components. This review summarizes the designs and syntheses of antimicrobial cationic polymers by controlling the above two factors. It involves the structural designs from primary to secondary structures, from covalent to noncovalent syntheses and from bulk to surface. Furthermore, it will discuss how to advance structural designs toward functional controls for optimizing the antimicrobial performances and biocompatibility of antimicrobial cationic polymers. It is anticipated that this review will provide some guidelines for developing molecular engineering of antimicrobial cationic polymers with tailor-made structures and functions.
Polymer Journal (2018) **50,** 33–44; doi:10.1038/pj.2017.72; published online 1 November 2017

INTRODUCTION

Antimicrobial polymer is one of the important research orientations in polymer science for treatments with infectious diseases caused by pathogenic microbes.[1] So far, many different types of antimicrobial polymers have been devised,[2–7] including antimicrobial cationic polymers,[8,9] biocide-released polymers[10,11] and so forth. Among them, antimicrobial cationic polymers have attracted most of the attentions in this field, because compared with antibiotics, antimicrobial cationic polymers may not induce serious microbial drug resistance. Owing to this feature, lots of efforts have been devoted to promote their advancements.

Antimicrobial cationic polymers mainly consist of two functional components: one is the cationic groups and the other is the hydrophobic groups. An overall picture of their antimicrobial mechanism is that antimicrobial cationic polymers can be primarily adsorbed onto the membrane of pathogenic microbes with the aid of their cationic groups; then the hydrophobic groups mainly insert into the membrane and disrupt it, thus leading to the death of pathogenic microbes.[12] Therefore, these cationic and hydrophobic parts are both essential for the antimicrobial performances of antimicrobial cationic polymers.

In general, the primary and secondary structural designs have a crucial role in fabricating antimicrobial cationic polymers. As for the primary structural design, improving their antimicrobial activity to pathogenic microbes and reducing their hemolytic effect are two main aspects that need to be considered. In addition, devising the secondary structures of antimicrobial cationic polymers based on α-helical and induced globally amphiphilic conformations can adjust the spatial distribution of the cationic and hydrophobic groups, thus probably benefiting to increase the antimicrobial activity.

Recently, host–guest systems constructed by antimicrobial cationic polymers and water-soluble macrocycles have been developed,[13] which are highlighted by the following two features. One is to regulate the antimicrobial activity of antimicrobial cationic polymers. The other is to selectively differentiate Gram-positive and Gram-negative bacteria and fungi. This host–guest strategy can be applied to a variety of antimicrobial cationic polymers, thus providing new opportunities for constructing smart antimicrobial materials.

This review aims to summarize different levels in fabricating antimicrobial cationic polymers (Scheme 1). It will include their designs of primary and secondary structures and discuss the relationship between their structures and antimicrobial activity. By marrying supramolecular chemistry to antimicrobial cationic polymers, we will further highlight how to fabricate dynamic, reversible and adaptive antimicrobial materials. It is highly anticipated that this review will be helpful for the structural design and functional control of antimicrobial cationic polymers.

PRIMARY STRUCTURAL DESIGNS OF ANTIMICROBIAL CATIONIC POLYMERS

Antimicrobial cationic polymers should contain two functional components,[12] the cationic groups and the hydrophobic groups. The above two functional components can be connected in enormous ways for constructing various antimicrobial cationic polymers with tunable antimicrobial activity. Herein, we discuss different kinds of cationic and hydrophobic groups and analyze the key factors in monomer designs. In addition, the topological designs of antimicrobial cationic polymers are discussed. It is hoped that the primary structural designs will be helpful for establishing the fundamentals of molecular engineering of antimicrobial cationic polymers.

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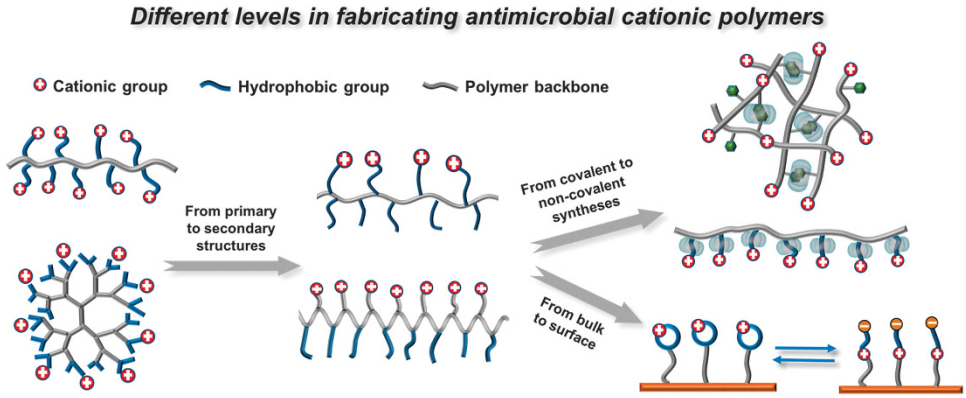
Received 30 June 2017; revised 15 September 2017; accepted 19 September 2017; published online 1 November 2017



Scheme 1 Schematic representations of different levels of structural designs for fabricating antimicrobial cationic polymers from primary to secondary structures, from covalent to noncovalent syntheses and from bulk to surface.

Monomer designs

Primary structural design of antimicrobial cationic polymers starts with the rational devisal of monomers. To enrich the polymer on the surface of microbial membranes and then to penetrate into their lipid bilayer,[7] two necessary components need to be contained in a monomer, the cationic and the hydrophobic groups.

Cationic groups. Cationic groups are the ones that facilitate the adsorption of antimicrobial cationic polymers to the surface of microbial membranes. There are several choices that bear the cationic centers, including ammonium ions,[14–17] sulfonium ions,[18] phosphonium ions[19,20] and so forth. This section mainly focuses on ammonium-based and iminium-based cationic groups because of their simple syntheses and broad usages.

Ammonium groups. Cationic primary, secondary, tertiary and quaternary ammonium groups are commonly regarded as one of the common cationic groups in antimicrobial cationic polymers. The antimicrobial cationic polymers bearing quaternary ammonium groups have intrinsic positive charges without pH-dependence, while the primary, secondary and tertiary ammonium groups of the polymers can be only obtained by protonation of their corresponding amines. It is noteworthy that the polymers bearing primary, secondary or tertiary ammonium groups usually exhibit relatively high antimicrobial potency and low hemolytic activity, compared with that containing quaternary ammonium groups. Inspired by the natural host defense peptides, Kuroda *et al.*[21] investigated the bactericidal and hemolytic activity of polymers with primary, tertiary amine groups and quaternary ammonium groups, respectively. It is shown that copolymers bearing primary and tertiary amine groups can be modulated to have potent bactericidal activity while minimizing the hemolysis. In this system, this kind of copolymers with primary amine groups presented greatest antimicrobial activity (*Escherichia coli*) and selectivity over red blood cells (RBCs). By manipulating the component of antimicrobial cationic polymers, maximum value of hemolytic activity/minimum inhibitory concentrations (HC_{50}/MIC) was obtained (>125) with 16 μg ml^{-1} MIC value. Therefore, the low hemolysis and high bactericidal activity can be achieved in one system, which are important in medical applications.

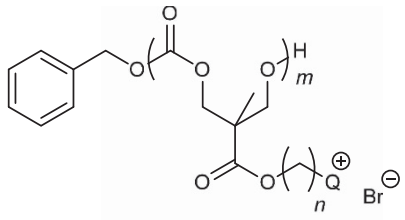
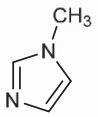
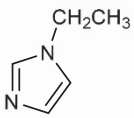
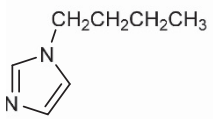
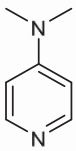
Iminium groups. Apart from the ammonium groups, the iminium structures are another common form of the cationic groups, like pyridinium,[22–25] imidazolium[26,27] and guanidinium salts.[28,29] The difference between ammonium and iminium groups is that the positive charges of the latter ones are delocalized evenly through the π bonds or aromatic conjugated systems, which may influence their adsorptive ability to membrane. For example, Yang and coworkers investigated the antimicrobial activity of polymers bearing different iminium groups (pyridinium and imidazolium groups) and quaternary ammonium group (Table 1).[30] It is revealed that iminium-containing cationic polymers have relatively low MICs against various bacteria and fungus, compared with the analogs of quaternary ammonium groups. The MICs were obtained after 18 h incubation under 37 °C. Therefore, the delocalization of the positively charges on the iminium groups could be regarded as a beneficial factor for enhancing the antimicrobial performances.

Hydrophobic groups. After adsorbed to the surface of microbial membranes, the hydrophobic groups of antimicrobial cationic polymers can insert into the lipid bilayer of microbial membranes and disrupt it. This can cause the cytoplasm leakage, thus leading to the cell death of microbes.[31] In general, the hydrophobic groups are usually used to penetrate into the membrane and their length and types need to be considered in the monomer design.

Chain length of hydrophobic groups. For most of the effective antimicrobial cationic polymers, the hydrophobic groups are mainly hydrophobic alkyl chains, and their chain lengths often affect the antimicrobial activity of the polymers. For instance, Hedrick and coworkers designed a series of polycarbonates with different lengths of alkyl chains between the quaternary ammonium moiety and the polymer backbone, then studied their antimicrobial activity.[32] As shown in Table 2, their MICs against various pathogenic microbes decrease as the spacer chain length grows from 3 to 8. Because within a certain range, lengthening the chain can result in a more hydrophobic structure that can more strongly interact with the lipid bilayer of microbial membranes, thus increasing the antimicrobial activity. Some antimicrobial cationic polymers even present high value of HC_{50}/MIC over 250 with good selectivity against *Staphylococcus aureus*. Such effect can be also confirmed by many other research groups based on various systems.[15,33] It should be pointed out that excessively increasing the chain length can bring about two disadvantages. One is that superabundant hydrophobic structures may lead to intense aggregation between the polymers, thus weakening their biocidal activity. The other one is that such structures could result in increased hemolytic activity. Therefore, an appropriate chain length of the hydrophobic group should be optimized.

Types of hydrophobic groups. A majority of antimicrobial cationic polymers use linear alkyl groups as their hydrophobic groups.

Table 1 MIC values of antimicrobial cationic polymers bearing different kinds of iminium groups against various microbes

 *Q = different substituents*	*MIC (mg l^{-1})*			
	S. aureus (*Gram +*)	*E. coli* (*Gram −*)	*P. aeruginosa* (*Gram −*)	*C. albicans* (*fungus*)
	< 4	31	250	125
	< 4	16	250	125
	< 4	8	31	125
	< 4	31	125	125
	< 4	31	31	250
	125	125	1000	250

Abbreviation: MIC, minimum inhibitory concentration.
Adapted with permission from ref. 30. Copyright 2014 American Chemical Society.

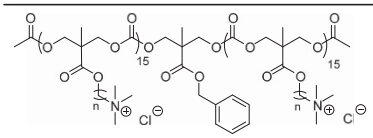
Besides that, cyclic or fused cyclic structures can be also utilized. To investigate how the cyclic hydrophobic groups influence the antimicrobial activity, Gellman and co-workers synthesized two kinds of nylon-3 random copolymers with cyclohexane groups or analogs acyclic groups (Figure 1a).[34] The polymers with cyclohexane groups show higher antimicrobial activity and weaker hemolytic effect than the ones carrying similar acyclic groups. In addition, Decho and co-workers connected derivatives of resin acids to the poly(ε-caprolactone) as hydrophobic groups (Figure 1b).[35] This kind of polymers, containing resin ring structures, exhibit considerable antimicrobial activities against a broad spectrum of bacteria (MICs: Gram-positive bacteria 0.7–10.1 μM; Gram-negative bacteria 3–40 μM) with high selectivity (HC_{50} even higher than 860 μM). From the experiments, they suggested that the great antimicrobial activity was related to the structure of resin acids and hydrophobicity. Therefore, cyclic hydrophobic groups are potential

candidates for fabricating antimicrobial cationic polymers with high efficacy.

Topological designs

The topology of polymers determines the way that its monomer structures are placed along the chain. Different spatial distributions of these functional groups will generate different forms of hydrophobic and hydrophilic regions deploying in the polymer, which could exert influences to the bioactivity of an antimicrobial agent. For this concern, plenty of methods have been developed for regulating the topological structure of a polymeric antimicrobial. Owing to well-established polymerization methods, a variety of antimicrobial cationic polymers with different topological structures can be easily prepared.

Table 2 MIC values of antimicrobial cationic polycarbonates bearing different chain lengths of alkyl groups against various microbes

 *n = number of methylene groups*	*MIC (mg l^{-1})*		
	n = 3	*n = 6*	*n = 8*
S. aureus (Gram +)	500	31	4
E. coli (Gram –)	16	4	4
S. epidermidis (Gram +)	1000	125	16
P. aeruginosa (Gram –)	> 1000	1000	125
C. albicans (Fungus)	500	250	125

Abbreviation: MIC, minimum inhibitory concentration.
Adapted with permission from ref. 32 Copyright 2013 American Chemical Society.

Main-chain cationic polymers. Main-chain cationic polymers refer to linear polymers bearing cationic centers along the macromolecular chains, which can be usually synthesized by the intermolecular condensation or the self-condensation of monomers.[36] In a main-chain cationic polymer, the multiple cationic centers are densely deployed in the polymeric backbone, which can enhance the adsorption of the polymer to the surface of microbial membranes. Moreover, the molecular weights of the main-chain cationic polymers prepared in these ways are not very high due to the limitation of the synthetic methods, For example, Zhang and co-workers synthesized an imidazolium-containing antimicrobial polymer and evaluated its bactericidal activity and biocompatibility (Figure 2).[37] This main-chain cationic polymer can greatly inhibit the growth of most pathogenic bacteria. Interestingly, this kind of polymer with relative low degree of polymerization shows almost non-hemolytic effect towards RBCs. For example, its HC_{50}/MIC value against methicillin-resistant *S. aureus* is higher than 3000, which was obtained after 24 h incubation under 37 °C. Because of their relatively low molecular weights, the main-chain cationic polymers can fill the gap between small molecular antimicrobials and long-chain antimicrobial cationic polymers.

In addition, Cakmak *et al.*[38] utilized benzyl amine and epichlorhydrin to synthesize a series of polyelectrolytes with various molecular weights and evaluated their antimicrobial activity against bacteria, yeast and fungi. It is suggested that longer polymer chains and higher density of positive charges could impose more considerable inhibition on the growth of the bacteria and yeast with MICs 2.5 and 0.625 μg ml^{-1}, respectively. On the basis of different synthetic methods, the number of positive charges, spacer length and molecular weight could be readily tuned to be more practical in real application.

Following the application of ring-opening polymerization, a new kind of antimicrobial polycarbonate hydrogels with broad spectrum was constructed.[39] This kind of antimicrobial polycarbonate hydrogels can be rapidly biodegraded in 4 to 6 days, and present excellent ability to kill Gram-negative bacteria, Gram-positive bacteria and even fungi

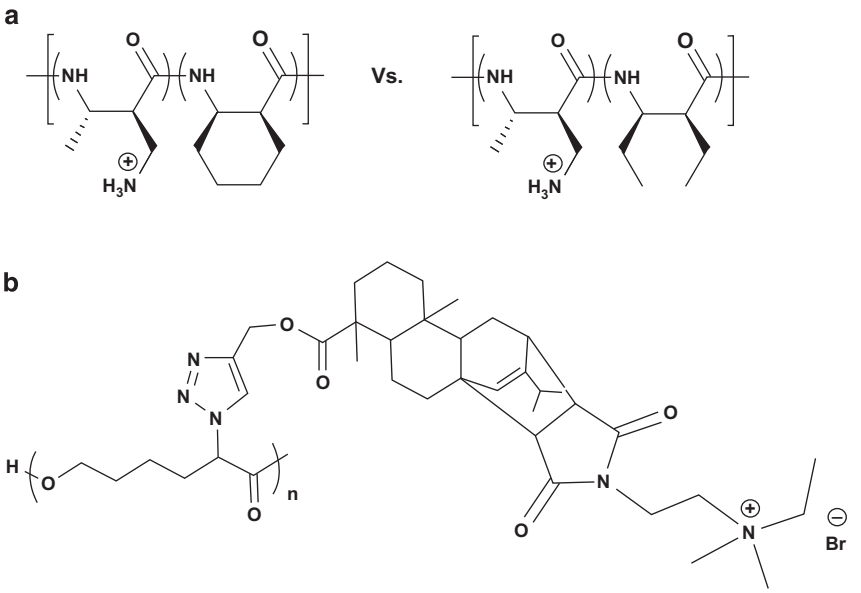


Figure 1 (**a**) Nylon-3 random copolymers with cyclohexane groups and analogous acyclic groups. Adapted with permission from ref. 34 Copyright 2013 American Chemical Society. (**b**) An antimicrobial polymer with resin derivatives as hydrophobic groups. Adapted with permission from ref. 35 Copyright 2012 The Royal Society of Chemistry.

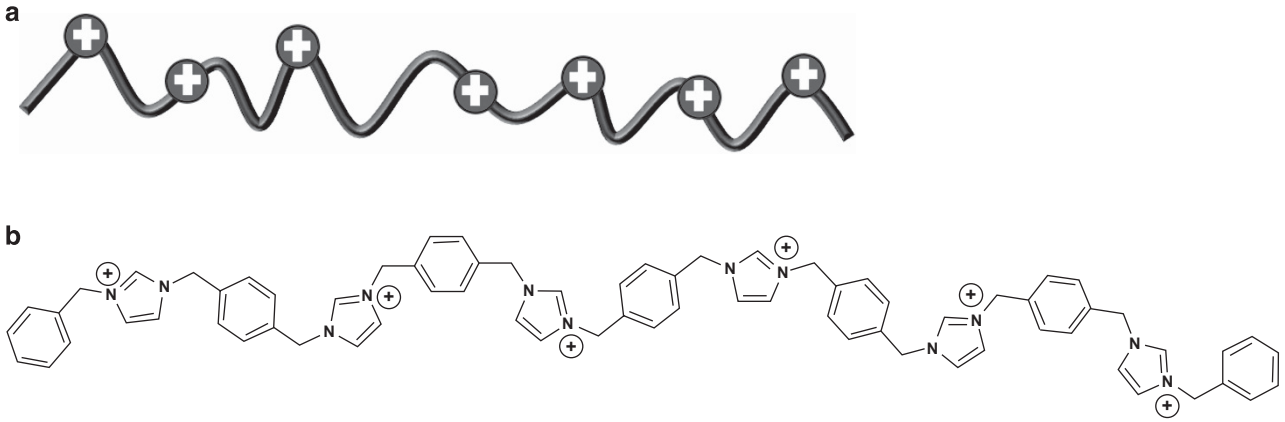


Figure 2 (**a**) Schematic representation of the main-chain antimicrobial cationic polymer. (**b**) Main-chain polyelectrolytes fabricated by benzyl amine and epichlorhydrin for antimicrobials. Adapted with permission from ref. 38 Copyright 2012 Elsevier Ltd. A full colour version of this figure is available at the *Polymer Journal* journal online.

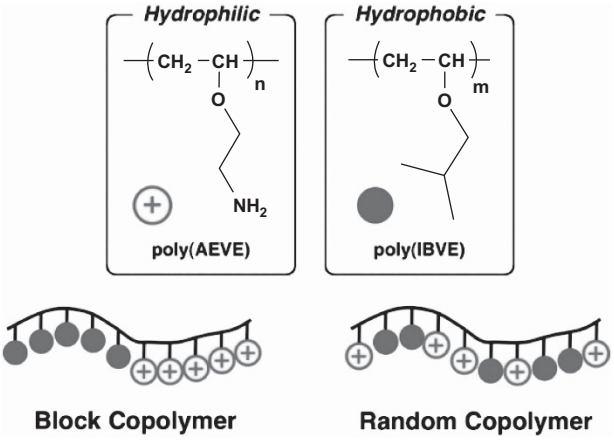


Figure 3 Amphiphilic poly(vinyl ether)s with block and random copolymers. Adapted with permission from ref. 45. Copyright 2011 American Chemical Society. A full colour version of this figure is available at the *Polymer Journal* journal online.

with 99.999% kill efficiency after 18 h incubation at 37 °C. The microbial inhibition prerequisite of antimicrobial hydrogel is directly contacting on the surface, and the hydrogels present non-hemolytic to RBCs after 1 h incubation. Therefore, the development of the antimicrobial hydrogels can be well utilized in implantable and wound-healing biomaterials.

Side-chain cationic polymers. Different from the main-chain cationic polymers, there are a series of side-chain cationic polymers, which can be used as antimicrobials. Side-chain cationic polymers can be fabricated by many methods of living polymerization.[40,41] Therefore, their molecular weight and molecular weight distribution can be fine-tuned. In addition to the homopolymers, the random, alternating and block copolymers can be prepared in a designed manner.[42,43] Thus, the spatial distributions of cationic centers and hydrophobic groups are able to be rationally adjusted.

Yoon and co-workers prepared block copolymers of polystyrene-*b*-poly(4-vinyl pyridine) and random copolymers of poly(styrene-*r*-4-vinyl pyridine), both bearing 4-vinyl pyridinium units as the cationic groups.[44] Compared with their random analogs, the block copolymers allow for better accumulation of the cationic groups. As a result, the block polymers display better antibacterial activity against *Pseudomonas aeruginosa* and *S. aureus* than the random polymers. In this system, they suggested that the higher 4-vinyl pyridine unit concentration on the surface of the block copolymers lead to the better antibacterial activity. Kuroda and co-workers also examined the antibacterial and hemolytic activities between amphiphilic block and random copolymers of poly(vinyl ether) (Figure 3).[45] Interestingly, their bactericidal activities against *E. coli* are similar in this work, but the block copolymers display a superior biocompatibility to human RBCs.

Dendritic and hyperbranched cationic polymers. Dendrimers are well-defined macromolecules with narrow polydispersity and definite chemical structures. The high charge density on surfaces is one of the most advantageous characteristics for dendrimers as effective microcidal agents. Cooper and co-workers investigated the structure–activity relationships of poly(propylene imine) dendrimers as polymeric antimicrobials.[46] It is noteworthy that the generation of dendrimers, spacer length of the hydrophobic groups and type of counteranions are of great importance in the inhibitory process. Their influences are suggested to be complicated when several factors are considered simultaneously. For example, higher generation of dendrimers means greater amount of ammonium groups, enabling stronger attachment to microbial membranes. But in the meantime, the permeability of these biocides through microbial membranes would be weakened to some extent due to the larger polymeric size. The overall advantages of dendrimers to general polymeric disinfectant include strong adsorption and binding to the microbial membranes and high capability to disrupt the normal physiological activities of cells.

Compared with dendrimers, the hyperbranched polymers are relatively easier to be synthesized in one pot. Mata and co-workers compared hyperbranched polymers and dendrimers' biocidal potency.[47] Interestingly, the ammonium-terminated hyperbranched polymers showed similar antibacterial effect to the analogous dendrimers. It should be noted that it may not be appropriate to study the structure–activity relationship by hyperbranched polymers, because their topological structures cannot be controlled in a precise way. But for practical concerns, the one-pot preparation of hyperbranched polymers may benefit to mass production. The MICs of this kind of antimicrobial cationic polymers were in range of 4–16 $\mu g\,ml^{-1}$, which indicate considerable antimicrobial activity against *E. coli* and

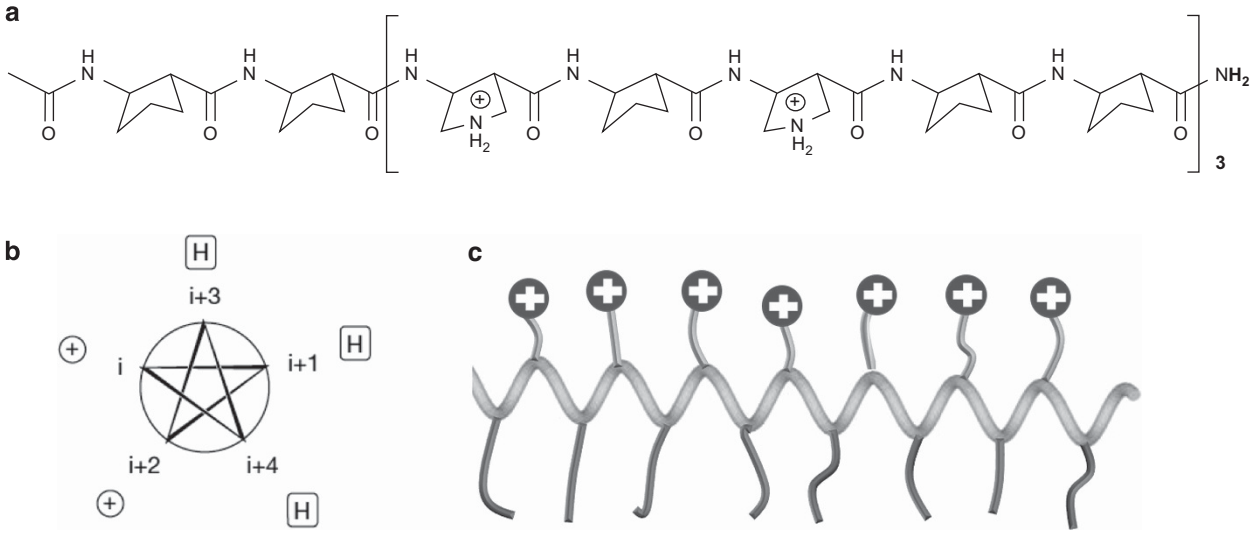


Figure 4 (**a**) Molecular structure of the α-helical β-peptides for antimicrobials. (**b**) Axial projection of α-helical β-peptides with cationic residues (+) and hydrophobic residues (H). (**c**) Schematic representation of α-helical conformation of antimicrobial cationic polymers. Adapted with permission from ref. 62. Copyright 2000 Nature Publishing Groups. A full colour version of this figure is available at the *Polymer Journal* journal online.

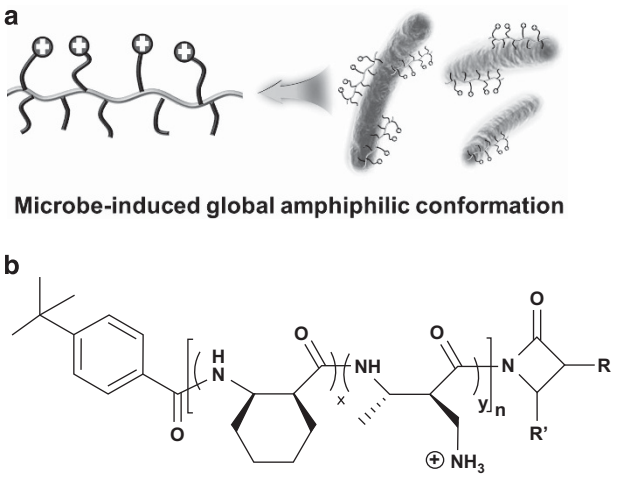


Figure 5 (**a**) Schematic representation of microbe-induced globally amphiphilic conformation. (**b**) Molecular structure of the microbe-induced globally amphiphilic antimicrobial cationic polymers. Adapted with permission from ref. 64. Copyright 2007 American Chemical Society. A full colour version of this figure is available at the *Polymer Journal* journal online.

S. aureus. Therefore, their applications as a kind of promising antimicrobial materials are highly anticipated.

SECONDARY STRUCTURAL DESIGNS OF ANTIMICROBIAL CATIONIC POLYMERS

In addition to the primary structures of antimicrobial cationic polymers, their secondary structures can influence the interactions with microbial membranes as well, thus regulating their antimicrobial activity. The secondary structures of antimicrobial cationic polymers can be mainly formed through two ways: one is α-helical conformation; and the other is microbe-induced globally amphiphilic conformation.[48] By controlling the secondary structures, the hydrophobic groups and the cationic groups can be rationally allocated and directly enriched toward improving the antimicrobial activity.[49] It should be pointed that primary and secondary structural designs are roughly classified for the simplicity of discussion. In fact, primary structure is the basis of secondary structure, suggesting that the influence of primary structure and secondary structure on antimicrobial property cannot be fully separated.

α-Helical conformation

Plenty of antimicrobial peptides (AMPs) with considerable antimicrobial activity have been discovered in nature.[50–54] Most of them also contain two kinds of amino-acid residues: the hydrophilic and the hydrophobic ones.[55] It was revealed that the α-helical conformation of AMPs can benefit to their antimicrobial performances. Owing to the α-helical conformation, the hydrophilic and the hydrophobic groups of AMPs are allocated to the opposite sides of the helix and divided into two different regions, a hydrophilic region and a hydrophobic region. In the presence of pathogenic microbes, the hydrophilic region of AMPs with highly enriched positive charges is strongly adsorbed onto the surface of microbial membranes. And then, the hydrophobic region tends to insert into the membranes and disrupt them, thus leading to the death of microbes.[56,57] Although significant advancements of AMPs have been achieved, they are normally too expensive to be widely used in practical applications.

Inspired by α-helical conformation of AMPs, many research works have focused on improving the α-helical β-peptides and peptoids for antimicrobials.[58–61] As shown in Figure 4, Gellman and co-workers reported an artificial α-helical β-peptides displaying antimicrobial activity against *E. coli*, *Bacillus subtilis*, *Enterococcus faecium* and *S. aureus*, which is similar to the natural peptide (magainin).[62] The MICs to these four kinds of bacteria were 6.3, 1.6, 12.5 and 3.2 $\mu g\,ml^{-1}$, respectively, by incubating the bacteria for 6 h at 37 °C. One of the advantages of the above α-helical β-peptides is that it exhibits almost non-hemolytic effect compared with magainin. Antimicrobial behaviors of α-helical β-peptides have been well explored, though it is not easy to achieve their mass production for further applications.

Induced globally amphiphilic conformation

Along with the further exploration of AMPs, it is found that some of them without α-helical conformation can still exhibit the

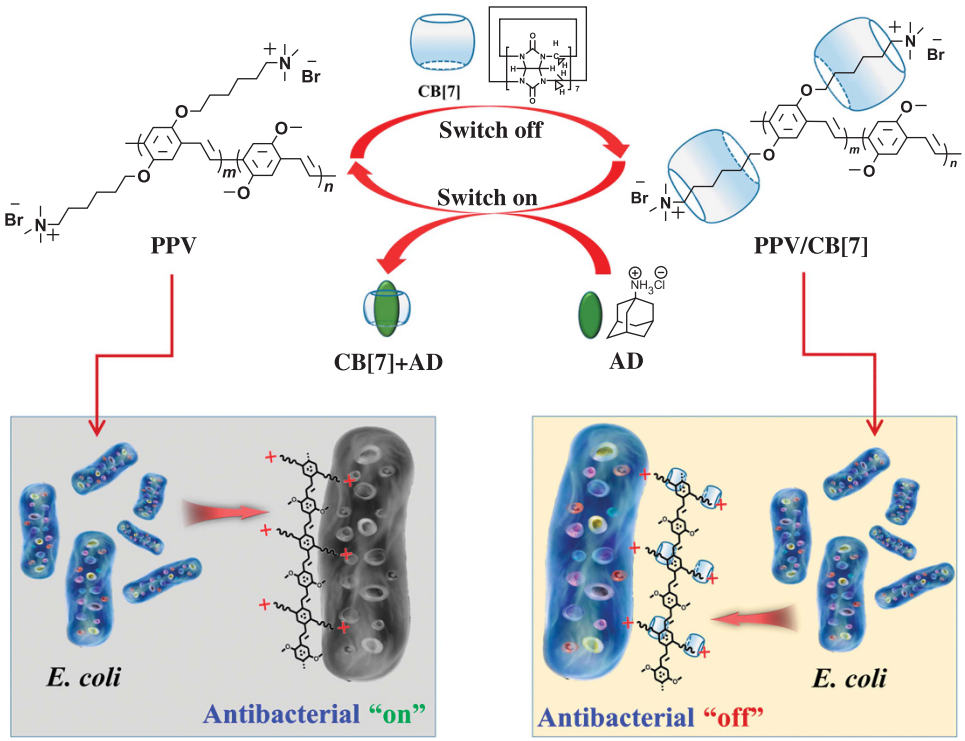


Figure 6 Supramolecular switch based on the host–guest system of CB[7] and PPV. Adapted with permission from ref. 81. Copyright 2015 John Wiley & Sons, Inc.

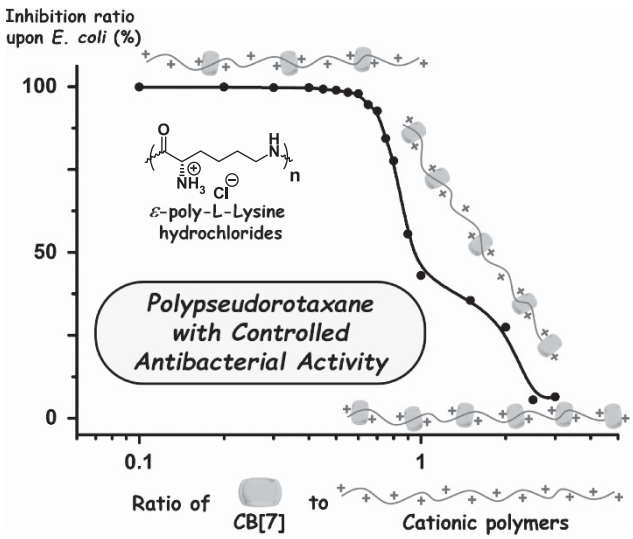


Figure 7 Fabrication of polypseudorotaxanes with tunable antibacterial activity. Adapted with permission from ref. 83. Copyright 2016 American Chemical Society. A full colour version of this figure is available at the *Polymer Journal* journal online.

antimicrobial activity. Another kind of the secondary structure of AMPs should be responsible for their antimicrobial performances, which is named as the biomembrane-induced globally amphiphilic conformation. At first, DeGrado and co-workers successfully fabricated a kind of globally amphiphilic poly(methacrylate) derivatives as antimicrobials by randomly copolymerizing hydrophilic monomers and hydrophobic monomers.[63] After that, as proposed by Stahl and co-workers, the antimicrobial cationic polymers contained cationic and lipophilic subunits and adopted irregular conformations, which could be induced by biomembrane surface into globally amphiphilic conformations. The globally amphiphilic conformation could perform the key roles for considerable antimicrobial activity, as shown in Figure 5.[64] It is found that higher ratio of cationic groups can benefit to reduce the hemolytic effect, while higher ratio of hydrophobic groups is of great importance for antimicrobials. They utilized minimum hemolytic concentration to display biocompatibility of antimicrobial cationic polymers. By balancing the ratio of cationic groups and hydrophobic groups in the random copolymers, they can achieve relatively low hemolysis and high antimicrobial activity with the aid of the globally amphiphilic conformation. The bacteria were incubated at 37 °C for 6 h for MIC measurements. It is found that the minimum hemolytic concentration/MIC ratio is 32 against pathogenic bacteria (*E. coli*, *B. subtilis*, *S. aureus* and *E. faecium*).

For further decreasing the hemolysis of globally amphiphilic antimicrobial cationic polymers, Kuroda and co-workers investigated block and random amphiphilic copolymers as mentioned before.[45] They found that block and random amphiphilic copolymers with similar monomer compositions represent the same level of antibacterial activity; however, the block ones exhibit lower hemolysis compared with the random ones. Because the hydrophobic interaction is more important for hemolysis of RBCs than the electrostatic interaction, and block amphiphilic copolymers can self-assemble into single-molecule cationic nanoparticles with a hydrophobic core, making their hydrophobic groups difficult to insert into the cell membranes of RBCs. This can reduce the hemolytic effect of block amphiphilic copolymers to RBCs. On the contrary, the hydrophobic groups of the random amphiphilic copolymers cannot be protected in this way, thus leading to their higher hemolysis. Therefore, the regular conformation of globally amphiphilic antimicrobial cationic polymers is beneficial for

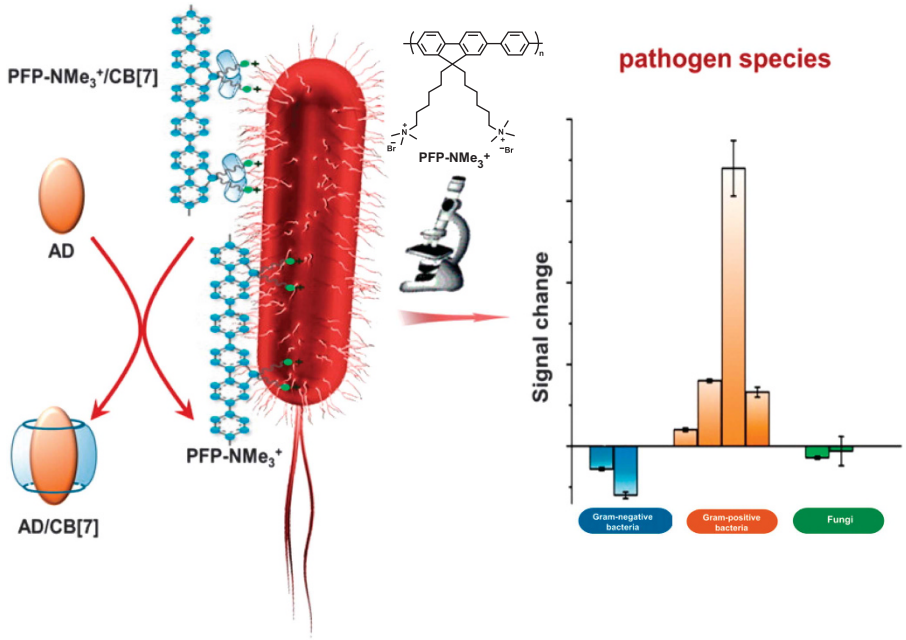


Figure 8 Supramolecular selective differentiations for microbes. Adapted with permission from ref. 86. Copyright 2016 American Chemical Society.

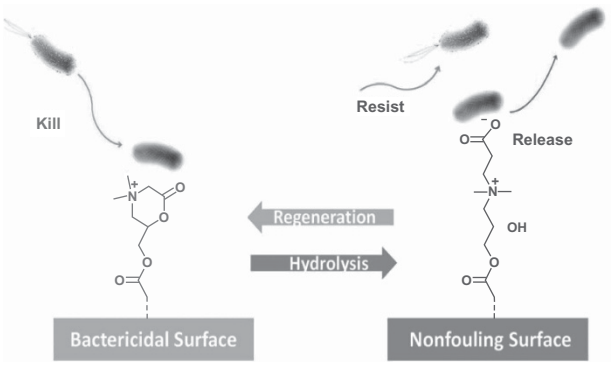


Figure 9 Antimicrobial surface with reversible control over antimicrobial activity and antifouling property. Adapted with permission from ref. 93. Copyright 2011 John Wiley & Sons, Inc. A full colour version of this figure is available at the *Polymer Journal* journal online.

improving their biocompatibility, which needs to be considered in their secondary structural design.

Till now, many kinds of polymeric backbones of globally amphiphilic antimicrobial cationic polymers have been developed.[65–68] By varying the specific structures of cationic groups and hydrophobic groups, the antimicrobial activity against particular microbes can be selectively enhanced as well.[69–77] It should be noted that the physical chemistry behind the globally amphiphilic antimicrobial cationic polymers needs to be studied furthermore for providing the guidelines for fabrication of antimicrobial materials with tailor-made structures and functions.

HOST–GUEST SYSTEMS FOR ANTIMICROBIALS

A host–guest system refers to a host–guest complex involving a guest molecule that can be incorporated into the cavity of a macrocyclic host.[78] The host–guest complexation is driven by noncovalent interactions. In contrast with covalent bonds, the dynamic nature of noncovalent interactions can impart the host–guest systems with the abilities to be reversible, degradable and adaptive. By combining the host–guest systems with antimicrobial cationic polymers, these advantages can be inherited into new antimicrobial materials with switchable antimicrobial activity.

Regulation of antimicrobial activity

As mentioned before, the cationic groups and hydrophobic groups of antimicrobial cationic polymers are two key motifs for antimicrobials. From another perspective, they can be also regarded as the guest motifs for host–guest complexations. By using a water-soluble macrocyclic host, such as cucurbit[n]urils (CB[n]s)[79] and cyclodextrin,[80] the hydrophobic group can be encapsulated into the cavity of the host. Besides, the cationic group can further enhance the host–guest complexation by introducing electrostatic interactions. In this way, the antimicrobial activity of antimicrobial cationic polymers is able to be regulated. There are three possibilities for this regulation: antimicrobial switch; antimicrobial enhancement; and antimicrobial reduction.

As for the antimicrobial switch, Wang and co-workers reported the first example of a host–guest system based on cationic poly(phenylene vinylene) derivative (PPV) and CB[7] for switching the antimicrobial activity reversibly (Figure 6).[81] PPV with quaternary ammonium side chains alone represented good antibacterial activity against *E. coli*. The cationic PPV could close to the surface of bacteria by electrostatic interaction, and hydrophobic side chains caused the membranolysis. When the PPV is complexed with CB[7], the hydrophobic groups lose the capability for inserting into the membrane of bacteria. The antibacterial activity of PPV can be recovered by removing CB[7] through the competitive replacement. In addition, a similar idea can be extended to poly(fluorene-co-phenylene) derivative (PFP) for switching on and switching off its antibacterial activity.[82]

For continuously controlling the antimicrobial activity, our group developed a general strategy for fabrication of polypseudorotaxane with tunable antibacterial activity,[83] as shown in Figure 7. As a proof of the concept, ε-poly-L-lysine was chosen as the model polymer,[84] and CB[7] was selected as the macrocyclic host. ε-poly-L-lysine is a natural polymer approved as a nutritional food preservative. On the

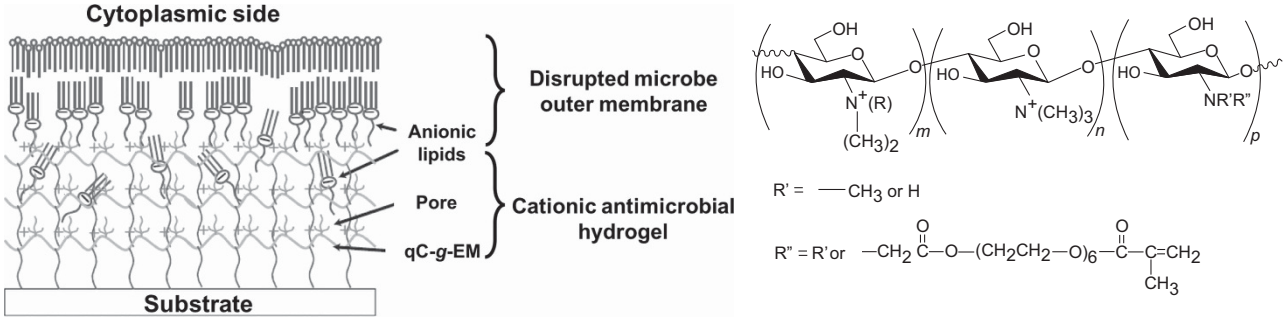


Figure 10 Antimicrobial surface based on porous polymeric hydrogels. Adapted with permission from ref. 94. Copyright 2011 Nature Publishing Groups. A full colour version of this figure is available at the *Polymer Journal* journal online.

basis of host–guest complexation, it can be easily incorporated into CB[7] to form a polypseudorotaxane. By simply tuning the molar ratio of CB[7] to ε-poly-L-lysine, the antibacterial activity of this polypseudorotaxane against *E. coli* can be fine-regulated in a wide range of the inhibition ratio from 0 to 100%.

Host–guest strategy can also help to improve the performance of antimicrobial cationic polymers. For example, Wang and co-workers utilized CB[8] to crosslink the phenylalanyl-poly(ethylenimine) (PhePEI) to obtain a hyperbranched antimicrobial cationic polymer.[85] Compared with PhePEI itself, crosslinked PhePEI/CB[8] hyperbranched polymers exhibit higher antibacterial activity. Thus, CB[8] is regarded as the supramolecular activator for antibacterial regulation. By manipulating the molar ratio of PhePEI to CB[8], the antibacterial activity could also be easily regulated as well.

Selective differentiation for microbes

Differentiation of various microbes has an important role in clinical antimicrobial treatments, because some of the microbes are pathogenic and some of them are harmless or even beneficial for human body. It should be noted that killing all the microbes without differentiation may destroy the perfect balance among different microbes in human body. For this concern, the host–guest systems of antimicrobial cationic polymers can also help to this point. For example, Wang and co-workers reported that with the help of CB[7], the above mentioned system of PFP-CB[7] can display different responses in interaction with various microbes, as shown in Figure 8.[86] Wang and co-workers first used the PFP-CB[7] acting on the surface of bacteria, then amantadine (AD) was utilized to release the encapsulated hydrophobic side chains of the PFP. During this *in situ* disassembly process, the change ratio of fluorescence intensity to different microbial samples represented quite different. The optical signal changes to both Gram-negative bacteria (*P. aeruginosa* and *E. coli*) and fungi (*Saccharomyces cerevisiae* and *Candida albicans*) decrease greatly, while the change of fluorescence intensity to Gram-positive bacteria (*B. subtilis*, *S. aureus* and *E. faecalis*) increases after adding AD. Thus, it can be used as a supramolecular fluorescent probe to selectively discriminate different kinds of microbes with fast responsiveness. The reason behind this phenomenon can be ascribed that the cell membrane of Gram-negative bacteria, peptidoglycan of Gram-positive bacteria and mannatide of fungi endow them with unique interfacial properties, thus resulting in different interaction ability with PFP-CB[7] before and after disassembly by AD. Previous reports had demonstrated that the interactions to Gram-negative bacteria and fungi are mainly driven by electrostatic interactions, and Gram-positive bacteria could be driven by hydrophobic interactions. Thus, the disassembled PFP-CB[7] by adding AD displays better inserting abilities to Gram-positive bacteria. This phenomenon indicates that the various surface properties of different microbes could lead to different interactions between pathogens and antimicrobial cationic polymers. Similar strategy could be extended to many other kinds of antimicrobial cationic polymers and water-soluble macrocyclic hosts.

ANTIMICROBIAL SURFACES

Compared with small-molecule bactericides, antimicrobial cationic polymers can be easily processed for fabricating antimicrobial surfaces.[87–89] Such antimicrobial surfaces have great potentials for combating infections in the areas such as medical devices, clinical treatments and so forth.[90–92] For successful fabrication of antimicrobial surfaces, there are two convenient methods for introducing antimicrobial cationic polymers: one is the covalent modification and the other is the noncovalent self-assembly. In recent years, lots of research works have employed reversible chemistry into the surfaces in molecular level or modified their mesoscopic structures for improving their antimicrobial performances.

Utilization of reversible chemistry in antimicrobial surfaces

Previously, dead microbes, staying on the antimicrobial surfaces, render them losing their antimicrobial activity, thus making them fail to recycle. To address this problem, the reversible chemistry is introduced in antimicrobial surfaces. The key to tackle this problem is to transform the antimicrobial surfaces into the antifouling ones, thus leading to free leaving of dead microbes. Then, the antimicrobial activity can be recovered by transforming the antifouling surfaces into the antimicrobial ones once again. For example, Jiang and co-workers designed an antimicrobial surface based on cyclic lactones, as shown in Figure 9.[93] At first, this surface is high positively charged, which attracts and kills microbes. After that, the hydrolysis of cyclic lactones on the surface can transform it into a zwitterionic one with typical antifouling property, thus releasing dead microbes from the surfaces. Then, the cyclic lactones can be regenerated by reversible bond-forming reactions on the surfaces, thus recovering their antimicrobial activity.

In addition to reversible covalent bonds, the host–guest interaction can be also used in this case. For example, Chen and co-workers developed a supramolecular versatile strategy for reversible control over the antimicrobial surface.[80] In detail, an adamantine-containing polymer is attached to the surface initially, and then the β-cyclodextrins modified with quaternary ammonium salts (CD-QAS) bind with the adamantine groups on the surface by host–guest interactions, thus endowing it with antimicrobial activity. As a result, bacteria can be attracted and killed on this surface. For cycle uses, the surface is

treated with SDS and dead bacteria can be eliminated from the surface along with CD-QAS, thus regenerating this surface.

Construction of the mesoscopic structures in antimicrobial surfaces
Efforts in antimicrobial surfaces have not only focused on controlling their structures in molecular level but also devoted to constructing their mesoscopic structures for improving their antimicrobial performances. For instance, Chan-Park and co-workers devised an antimicrobial surface based porous polymeric hydrogels, as shown in Figure 10.[94] It is found that the porous structures of the hydrogels with abundant positive charges can adsorb anionic phospholipids from microbial membranes and disrupt them, thus killing microbes. This surface is regarded as an 'anion sponge' that exhibits broad antimicrobial activity against *E. coli*, *Fusarium solani*, *S. aureus* and *P. aeruginosa*. Similar strategies may be extended to many kinds of porous hydrogels or other porous materials. It is believed that such 'anion sponge' design may open up a new avenue for fabricating antimicrobial surfaces.

CONCLUSION

In conclusion, we have summarized the designs of antimicrobial cationic polymers from primary to secondary structures, from covalent to noncovalent synthesis, and from bulk to surface. In general, the cationic and hydrophobic groups of these polymers should be rationally devised and regularly allocated for optimizing their antimicrobial performances and biocompatibility.

Although many systems of antimicrobial cationic polymers have been developed, there still remain some important issues that need to be studied. First, the antimicrobial mechanism should be investigated furthermore and many new potential mechanisms need to be explored. Second, the gap between the antimicrobial performances of these polymers in aqueous solution and on the different kinds of surfaces is necessary to be bridged. Third, these polymers with low microbial drug resistance may be useful for clinical treatments of microbial infections. Finally, the precision synthesis of antimicrobial cationic polymers is required for establishing the fundamentals of structure–activity relationships, while simple and economic mass production is highly desirable for practical applications.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

The research was supported by National Natural Science Foundation of China (21434004). We thank to Dr Jiang-Fei Xu and Dr Haotian Bai for helpful discussion.

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