Anti-biofouling and Antimicrobial Biomaterials for Tissue Engineering

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Abstract Biofouling from nonspecific protein adsorption and microorganism adhesion is a continuous challenge in numerous biomedical applications such as implants, biosensors, and tissue-engineered scaffolds. The bacteria attached to the biomaterial surface can encapsulate themselves within a protective extracellular polymeric layer, leading to the formation of biofilm that is difficult to combat or eliminate. A promising strategy to prevent device-related infections is the development of new biomaterials that are anti-biofouling and/or antimicrobial. In general, anti-biofouling materials exhibit low adhesion or resistance properties towards a variety of bacteria, while antimicrobial ones can kill microorganisms approaching the surfaces or in the surrounding areas. In this chapter, we briefly introduce the recent strategies in the design and applications of anti-biofouling and antimicrobial materials.

Keywords Biomaterials · Anti-biofouling · Anti-microbial · Biofilm · Infections Polyethylene glycol (PEG) · Zwitterionic · Releasing-based · Contact-based Medical implants · Tissue engineering

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Introduction and Principles of Anti-biofouling and Antimicrobial Biomaterials

Biofilm Formation and Associated Infections

In recent decades, biomaterials have been increasingly used in tissue engineering and many medical devices, involving wound dressings, orthopedic implants, vascular prostheses, urinary catheters, etc. Bacterial adhesion and biofilm formation on biomaterial surfaces have been considered as one of the major challenges that can lead to serious consequences, such as implant infections, the failure of medical devices, and associated health risks. Even under sterile surgical conditions, bacterial contamination of the implantation sites cannot be prevented. Hospitalized subjects are also at a high risk of acquiring device-related bacterial infections in some cases up to ~60% [1]. For example, bacteria attached on the urinary catheter can form a biofilm within 24 h [2]. The infection risk in patients with urinary catheter is ~50% after 10 days, and the subsequent treatment and replacement can cause considerable morbidity.

Biofilm formation by microorganisms is a complex and dynamic process, often involving more than one microbial species. The initial attachment of bacteria is reversible until the bacteria secrete adhesive proteins, extracellular polymeric substances (EPS), and then irreversibly bind to the material surface. The following step is bacterial colonization and proliferation inside the extracellular matrix. Communication occurs via quorum sensing among same [3, 4] or different bacterial species [5, 6] within the biofilm, which enables co-colonization within the same extracellular matrix. After rapid proliferation of bacteria, the biofilm grows to be mature and eventually the extracellular matrix ruptures, leading to the dispersal of planktonic bacteria and possible spread of the infection. Biofilm is an effective strategy to render bacteria highly tolerant to environmental stresses as well as strongly resistant to antibiotics [1]. Previous reports showed that an antibiotic dose up to 1000-fold higher is required to kill bacteria inside the biofilm [7]. Therefore, developing biomaterials with anti-biofouling and/or antimicrobial properties is in urgent demand as alternatives to antibiotics to fight against infections associated with medical devices.

A variety of biomaterials with or without intrinsic antimicrobial activity have been developed to combat bacterial biofilm and associated infections. They can be divided into either anti-biofouling or antimicrobial materials, the first one is able to prevent protein adhesion and bacterial attachment, while the other one can kill microorganisms by the biomaterial itself (e.g., a polymer) or by adding antimicrobial agents.

Anti-biofouling Biomaterials

Anti-biofouling biomaterials are designed to prevent the adhesion of microorganisms, proteins, and other biomolecules by minimizing interaction forces between the material surfaces and biological environments. Most anti-biofouling materials

fall into three types: (1) PEG-based materials, (2) hydrophilic zwitterionic materials, or (3) superhydrophobic low surface energy materials.

PEG-Based Biomaterials

PEG is one of the frequently used polymers to endow biomaterial surfaces with protein-resisting properties owing to both the hydration effect and steric hindrance [8]. Considering that indirect bacterial attachment on surfaces can occur as a result of protein adsorption, a biomaterial that is able to repel protein adsorption can potentially also resist the contamination of bacteria [9]. Since PEG has been widely used against protein adhesion to substrates, many studies have focused on designing materials with PEG to resist bacterial adhesion [10–14]. The polymer chain can be hydrated with water molecules via hydrogen bonds, and the water layer acts as a barrier to impede the attachment of biomolecules and bacteria [1].

Park and coworkers [10] reported the preparation of PEG-based polyurethane substrates with terminal hydroxyl, amino, and sulfonate groups. *E. coli* and *S. epidermidis* were used to test the adhesion of bacteria in tryptic soy broth and human plasma-containing media. Results showed that the bacterial attachment was affected by both the PEG molecular weight and media. PEG of higher molecular weight showed better bacterial-resistant ability compared with the lower molecular weight equivalents.

Norde et al. [15] studied the influence of PEG brush length on the adhesion of different bacteria and yeasts. Two types of bacteria (*S. epidermidis* and *P. aeruginosa*) and two types of yeasts (*C. tropicalis* and *C. albicans*) were used in the tests. It was found that longer PEG brushes resulted in stronger resistance to bacteria and yeasts. In addition, more hydrophobic microorganisms (*P. aeruginosa* and *C. tropicalis*) were more prone to adhere onto the surface than the more hydrophilic ones (*S. epidermidis* and *C. albicans*), indicating that hydrophobic force was more favorable for the adhesion of microorganisms.

It is believed that the benefit of longer polymer chains is related to more efficient coverage of the material surface. Via self-assembled monolayers (SAMs), short PEG chains also showed anti-biofouling abilities. Prime et al. designed SAMs presenting oligo (ethylene glycol) groups to disturb bacterial attachment [16]. Cooper and coworkers researched SAMs with various terminal groups including -CH_3, -OH, -COOH, and -$(OCH_2CH_2)_3$-OH. It was found that -$(OCH_2CH_2)_3$-OH SAMs displayed the lowest adhesion while -CH_3 surface have the highest fouling [17].

While PEG has often been termed the “gold standard” of the anti-biofouling field, it suffers several nonnegligible weaknesses in biomedical applications. It is prone to undergo oxidative damage and thus unstable in long-term applications. In addition, though PEG is generally considered as a biologically inert material with no immunogenicity or antigenicity, it has actually been demonstrated to provoke immune reaction in some conditions [18]. For example, PEG antibodies have been found in animal studies after immunization with PEG-modified proteins and nanoparticles, leading to the loss of therapeutic efficacy and related adverse effects [19–23].

Poly Zwitterionic-Based Biomaterials

Recently, zwitterionic polymers have been emerging as promising alternatives to PEG, which are electrically neutral with balanced positive and negative charges in one moiety. The charged pairs result in a stronger hydration via ionic effects than that of PEG formed by hydrogen bonds, which in turn can enhance the anti-biofouling ability of zwitterionic biomaterials [24].

Cheng et al. developed poly(sulfobetaine) (pSB) and poly(oligo ethylene glycol) (pOEG)-grafted glass surfaces via atom transfer radical polymerization (ATRP) and tested the adhesion of both *S. epidermidis* (Gram-positive) and *P. aeruginosa* (Gram-negative) strains. It was found that PSB-grafted surfaces showed reduced adhesion by 92% and 96% than bare glass in a short term (3 h). And PSB-grafted surface was more effective in resisting long-term bacterial adhesion and biofilm formation, while SAMs surface failed to achieve a significant effect (Fig. 1). This result was probably owing to the higher surface densities of polymer brushes grafted via ATRP compared with SAM method [25].

Cheng et al. also systematically studied the zwitterionic poly(carboxybetaine) (pCB) grafted from glass surfaces for their resistance to biofilm formation. Results showed that pCB coatings reduced long-term biofilm formation of *P. aeruginosa* up to 240 h by 95% at 25 °C while the unmodified glass was completely covered by bacterial biofilm. At the optimal growth temperature of 37 °C, the glass surface was completely covered in 15 h, while pCB-modified surface could inhibit 93% of *P. aeruginosa* accumulation for 64 h [26].

In addition to surface-modified materials, several hydrogels designed with zwitterionic polymers have attracted increasing attentions [27, 28]. For example, in 2013,

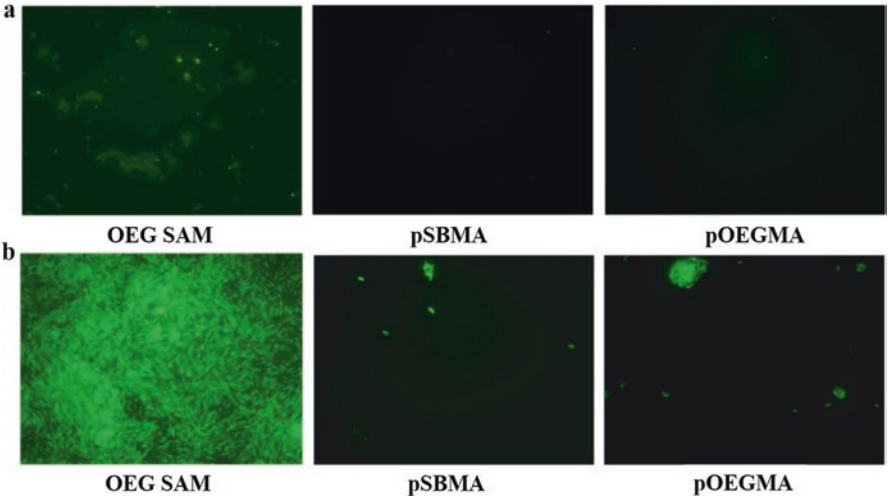

Fig. 1 (**a**) Fluorescence microscopy graphs of *S. epidermidis* attachment on various surfaces at 48 h. (**b**) Fluorescence microscopy graphs of *P. aeruginosa* attachment on various surfaces at 24 h. (Images reprinted with permission of Cheng et al. (2007). Copyright 2007 Elsevier Ltd. [25])

Zhang et al. developed a zwitterionic PCB hydrogel that could efficiently prevent foreign body capsule formation for 3 months and promote angiogenesis in the surrounding tissue when implanted subcutaneously in a mouse model. In the foreign body reaction, nonspecific protein adsorption is thought to be the first step to trigger the formation of a dense collagen layer. The collagen layer will isolate the implants from surrounding tissues, impeding mass transport and electrical communication between implants and the physiological environment [29]. The mechanism of pCB hydrogels is possibly due to the fact that the macrophage cells in anti-biofouling samples tend to differentiate to the pro-healing state.

Huang and coworkers synthesized zwitterionic pSB nanocomposite hydrogels as chronic wound dressings [30]. The prepared hydrogels displayed evident resistance to adsorption of bovine serum albumin (BSA), bacteria of Gram-positive *S. epidermidis*, and Gram-negative *P. aeruginosa* (Fig. 2). Zhang et al. proved that zwitterionic pCB hydrogel with high water content and excellent anti-biofouling properties could promote skin wound healing in a mouse model in comparison with pHEMA hydrogel and

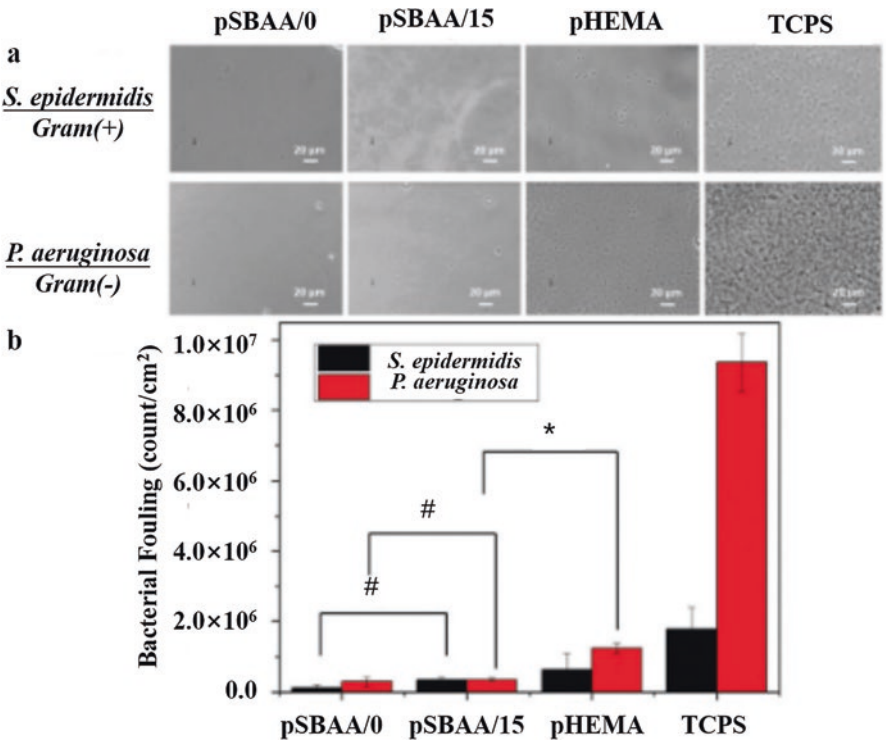

Fig. 2 (**a**) Bacterial fouling tests on pSBAA/0, pSBAA/15, pHEMA, and TCPS. *P. aeruginosa* and *S. epidermidis* were used in the tests and imaged using phase-contrast microscope. pSBAA/0 is hydrogels without adding any nanoclay and pSBAA/15 is hydrogels with 15% nanoclay. (**b**) The quantitative results for bacterial adsorption on all hydrogels. (Images reprinted with permission of Huang et al. (2016). Copyright 2016 The Royal Society of Chemistry [30])

the commercial product Duoderm [31]. A wound dressing is expected to be anti-biofouling also because traditional dressings can typically damage newly generated tissues upon removal and provide an opportunity for microorganism colonization.

Zwitterionic polymers have also successfully imparted anti-biofouling properties to various nanoparticles, such as gold nanoparticles [32–34], magnetic iron nanoparticles [35, 36], quantum dots [37, 38], and silica nanoparticles [39]. Jia covered silica nanoparticles with functional zwitterionic pCB layer via ATRP method and tested the stability of particles in protein-containing solutions. Results showed that the pCB layer is effective in protecting nanoparticles from nonspecific protein fouling [39].

Antimicrobial Biomaterials

In the past decade, the number of FDA-approved antimicrobial biomaterials has been continuously increasing, indicating the demand for alternatives to traditional antibiotics which often undergo drug resistance and difficulty to penetrate the biofilm [1]. Antimicrobial materials are designed to kill bacteria and prevent biofilm formation, while anti-biofouling materials are passive and vulnerable to microorganism invasion once their barriers are damaged. The antimicrobial biomaterials can be divided into those where the matrices integrated with antimicrobial agents that are released, or those where the materials themselves are active ingredients.

Releasing-Based Antimicrobial Biomaterials

An effective approach for imparting biomaterials with antimicrobial activity is to combine them with different releasing biocides/antibacterial agents, such as antibiotics, silver, quaternary ammonium compounds (QACs), and nitric oxide. These agents can be integrated with the biomaterials by suitable approaches, including physical adsorption, conjugation, or complexation.

Biomaterials Loaded with Antibiotics

The indwelling medical devices, for example, orthopedic implants and catheters, can be coated with an antibiotic-releasing layer to combat device-related infections. The greatest benefit by direct loading of antibiotics is that high systemic doses can be effectively avoided, preventing over-dosing problem and potential toxic side effects to other tissues in the body [40].

Antibiotics including vancomycin, cefamandole, gentamicin, cephalothin, carbenicillin, and amoxicillin have been widely used in controlled releasing devices [41]. Antibiotic-containing polymethyl methacrylate (PMMA) beads, which are fabricated by mixing the desired antibiotics with PMMA and forming into beads,

have been clinically used as a kind of bone cement for about 30 years [42]. The primary advantage of PMMA beads is the clinical familiarity as well as the efficacy to eliminate acute infections in bone. However, since PMMA is non-biodegradable and hydrophobic, the incorporated antibiotics could not be totally released from the beads, thereby leading to a loss of 25–50% [40]. In addition, the non-biodegradable PMMA beads need to be removed by a second surgery if the antibiotic release has finished. Considering these issues, biodegradable materials have been developed as possible alternatives to bone cements, with the increasing popularity of cement-less prostheses in hip arthroplasty [43].

The use of antibiotic-containing biodegradable materials has the benefit of slow release of the antibiotic to the material–tissue interface, with the release of antibiotic following the kinetics of material degradation. For instance, poly(lactic acid) (PLA) and poly(lactic-co-glycolic acid) (PLGA) are effective biodegradable implant coatings that have been used to locally deliver antibiotics. Different from PMMA, these polymers can be used in several different forms, such as coatings, electrospun fibers, and microspheres [44]. Muller et al. combined fusidic acid and rifampicin on PLA to kill *S. aureus* both in vitro and in a rabbit infection model [45].

Clinical implant materials should be customizable to allow local antibiotic delivery to specific infection sites avoiding damaging bone cells. David et al. analyzed the inhibitory impact of PLA implants coated with single or double antibiotics (gentamicin, ciprofloxacin, colistin, daptomycin, or cefoxitin) on bacteria isolated from osteomyelitis. Results showed that all antibiotics, no matter alone or in combination, had a burst release and a dose-dependent antibacterial activity [46].

Recently, mesoporous materials such as hydroxyapatite (HA) has been loaded with different antibiotics (tobramycin, vancomycin, cephalothin, carbenicillin, and amoxicillin sodium salts). These antibiotic-containing HA materials have also been applied as practical methods for the decontamination of dental implants. All these studies have demonstrated that antibiotic-containing HA materials could fight against bacterial adhesion and impede biofilm formation as well as maintain a continuous agent release ability.

Biomaterials Loaded with Silver Nanoparticles (NPs)

Silver-loaded biomaterials have been used in medical implants due to the released silver ions being broad-spectrum against both Gram-positive and Gram-negative bacteria. Although the mechanism of their antimicrobial action is not yet completely understood, it is generally inferred that released silver ions are the primary molecular toxicant [47]. Silver ions released from silver-loaded materials destruct the bacterial membrane and damage the function of the enzymes and/or DNA of bacteria [48, 49]. Silver ions can react with the negatively charged groups in the cellular proteins and DNA, such as the carboxyl, phosphate, thiol, and amino groups [50]. It can also inactivate enzymes of the tricarboxylic acid (TCA) cycle, generating harmful hydroxyl radical. The needed concentration of silver for a required antibacterial effect ranges from 10 nM to 10 μM [51].

Silver NPs are facile to be incorporated into various materials for further applications, such as hydrogels, nanofibers, and films. Hydrogels formed by synthetic polymers such as poly(N-vinyl pyrrolidone) (PVP), poly(vinyl alcohol) (PVA), poly(acrylamide-co-acrylic acid), and natural polymers such as gelatin, chitosan, and alginate have been prepared to encapsulate silver NPs. Thomas and coworkers developed a technique called the breathing-in/breathing-out (BI-BO) method to load silver NPs. By exposing to solutions of different concentrations, hydrogels could sequentially swell and shrink, thus encapsulating silver NPs from the solution into the network. The antibacterial activity of hydrogel materials was influenced by the cycle numbers, and it was reported to be optimal after three cycles to kill *E. coli* [52].

Silver NP-loaded hydrogels can also be prepared by the formation of hydrogel and the encapsulation of NPs simultaneously [53]. Gonzalez et al. [54] prepared in situ silver NP-embedded matrix using $AgNO_3$ as the silver source and hydrogel polymer as the container and stabilizer. Hydroxyl ethyl methacrylate monomer (HEMA), cross-linking agents, and photoinitiator were added into the hydrogel synthesis system, while UV irradiation was used to reduce the silver ions and also form the HEMA hydrogel. Via the in situ synthesis and encapsulation methods, the aggregation and precipitation issues of silver NPs can be reduced. Zhang et al. reported a one-step in situ photo-polymerization reaction to simultaneously formed silver NPs and the PCB hydrogel. Results showed that silver NPs could be homo-dispersed in the hydrogel matrix without precipitation. In vitro tests proved that the resulting matrix could effectively kill both Gram-positive (*S. aureus*) and Gram-negative bacteria (*E. coli*) while resisting their adhesion [31].

Besides the antibacterial effects and material fabrication approach, silver-associated cytotoxicity must be considered. Eukaryotic cells have been shown to withstand 10 ppm exposure of silver [49]. High-level exposure of silver NPs could lead to nonnegligible toxicity to a variety of organs such as lung and liver.

Biomaterials Loaded with Quaternary Ammonium Compounds (QACs)

Unlike the release-based antibacterial silver ions, QAC-containing materials possess a long-term antibacterial mechanism [55]. Materials containing QAC have been proven to damage both Gram-positive and Gram-negative bacteria by disrupting the cellular membranes [56]. The positively charged ammonium groups interact with the negatively charged acidic phospholipid groups of the bacterial cellular membrane, disturbing the stability and integrity of the lipid bilayers. Further, the potassium ions release from the inner cytoplasm which in turn damage the original osmoregulation and other physiological functions of bacteria [57]. It was found that the antibacterial activity of QACs was relevant to the alkyl chain length. QACs possessing an alkyl chain of 12–14 carbons achieved an optimal activity against Gram-positive bacteria and yeast, whereas alkyl chain length of 14–16 carbons effectively resisted Gram-negative bacteria. QACs with alkyl chain lengths less than four or more than 18 were found to be virtually ineffective.

Biomaterials Loaded with Nitric Oxide (NO)

NO is a well-known factor to inhibit the platelet activation and adhesion. It has been used in many polymer-based materials, for example, silicone rubber, PVC, PVP, and PU, for medical applications in various blood-contacting devices to prevent thrombosis [58]. In recent years, NO has been found to resist biofilm formation, thus NO-loaded biomaterials have attracted increasing attentions to develop dual-functional (antithrombotic and antibacterial) biomaterials.

In 2005, an NO-stored sol-gel derived film was developed to coat silicone elastomer and subcutaneously implanted in a rat model to evaluate the anti-infection effect. After treated with NO-releasing coatings, the *S. aureus*-infected wounds showed an 82% reduction, indicating a promising application of NO-releasing biomaterials to treat *S. aureus* infections [59].

Anton et al. assessed possible benefits of a low-concentration NO-releasing carbon-based coating on monofilament polypropylene meshes in vitro and in vivo. NO-releasing coatings showed significant bactericidal effect on biofilms of *S. aureus*, *E. coli*, and *P. aeruginosa* in vitro. However, no obvious beneficial effects of this NO-releasing coating on subcutaneously in vivo implanted surgical meshes could be found [60].

Danie reported the synthesis of NO-modified xerogels using tertiary thiol-bearing silane to trigger the release of NO by photoactivation at physiological temperature. After exposing the NO-modified xerogels to visible irradiation, the bacterial adhesion (*P. aeruginosa*) was significantly reduced by 88% compared to TEOS xerogel controls [61].

Contact-Active Antibacterial Biomaterials

Another approach for the fabrication of antibacterial biomaterials is based on the non-releasing mechanism, where the polymers themselves are intrinsically antimicrobial and thus kill the bacteria in contact with the material surface. The polymers are often cationic and able to capture negatively charged bacterial cell envelop, interacting and further damaging the cell membrane to eventually kill the bacteria. Figure 3 showed the main classes of cationic natural and synthetic polymers possessing positive charge in the backbone or in the side chain [1].

Chitosan is an extensively studied, natural-derived cationic polymer, which is the N-deacetylated derivative of chitin. Chitosan-based materials, such as coatings and films, have been applied as wound dressings and scaffolds in tissue engineering [62]. Previous studies have demonstrated the ability of chitosan to inhibit the growth of a wide variety of bacteria, including *E. coli, P. fluorescens, S. aureus*, and *K. pneumoniae* [63]. It is reported to completely inactivate *E. coli* after a 2-day incubation with concentrations of 0.5–1% at pH 5.5. Meanwhile, only 0.1% concentration of chitosan was required to inhibit *E. coli* growth. Due to the different acetylation degree of chitosan, the antibacterial effect varied and displayed a higher sterilizing efficiency with 7.5% acetylation when compared with that of 15%.

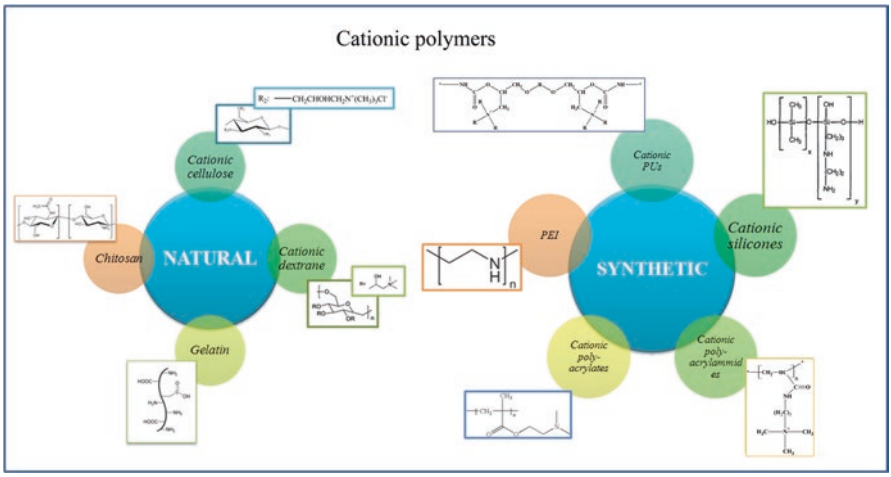

Fig. 3 The main classes of cationic natural and synthetic polymers. (Images reprinted with permission of Francolini et al. (2017). Copyright 2017 John Wiley & Sons Ltd. [1])

Chitosan has also been modified with other molecules or groups such as quaternary ammonium to augment its antimicrobial ability. The antibacterial activity of diethylaminoethyl chitosan and triethylaminoethyl chitin was evaluated against a number of bacterial species in vitro. The triethylaminoethyl chitin had a greater activity against *S. aureus* than against *E. coli*. And 500 ppm of triethylaminoethyl chitin was needed to completely eliminate *S. aureus* within 2 h.

Anton et al. immobilized chitosan via poly-acrylic acid (PAA) brushes and then grafted them on a polyethylene surface. *E. coli* and *S. aureus* were both used to test the samples by inhibition zone methods. After the treatment of chitosan, the polyethylene displayed clear inhibition zones of 35 mm^2 for *E. coli* and 275 mm^2 for *S. aureus* [64]. Chitosan and its derivatives have also been incorporated with other anionic polymers, including hyaluronic acid, alginate, carrageenan, heparin, and pectin.

Polyethyleneimine (PEI), a kind of synthetic hyperbranched polymer, is positively charged to serve as an antimicrobial agent against bacteria and fungi [65]. Compared with the unmodified PEI, low molecular weight counterparts with acid-labile imine linkers [66], disulfide bonds [67], or folate-PEG were designed with the aim to enhance biodegradability and biocompatibility.

Glass and metal surface have been coated with hydrophobic *N*,*N*-dodecyl methyl-PEI. The *E. coli* and *S. aureus* strains were 100% removed from the glass or polyethylene surface owing to the disruption of cell membrane and the leakage of cellular proteins [68, 69]. *N*,*N*-dodecyl methyl-PEI has also been used for the coating of orthopedic fracture-fixation hardware, which was made of titanium (Ti) and stainless steel. The treated surface was revealed to effectively prevent the biofilm formation of *S. aureus* both in vitro and in vivo [70].

Milovic used N-hexyl, methyl-PEI to covalently coat onto an amino-glass slide to combat *E. coli* and *S. aureus*, revealing a 10^9-fold reduction of live bacteria in the

surface-exposed solutions and a 100% elimination of the surface-attached bacteria. In addition, the immobilized N-hexyl, methyl-PEI was proven to be harmless to monkey kidney cells while lethal to bacterial cells [71].

In 2015, Merve et al. coated brush-like polyethyleneimine (PEI) on polyurethane (PU) ureteral stents with the aim to develop permanent antibacterial surface since the biofilm formation on stents severely limited their long-term usage. PEI chains with different molecular weights (Mn: 1800 or 60,000 Da) were alkylated with bromohexane to break the bacterial membranes with increasing polycationic character. Both kinds of PEI brushes exhibited antibacterial activity by reducing the adhesion of *K. pneumonia, E. coli*, and *P. mirabilis* species to 10^2-fold, while no cytotoxicity was observed on L929 cells [72].

Besides PEI, cationic PU-based materials were also developed for contact-killing materials. Antibacterial QA compound-containing PU was coated to aluminum and PVC substrates, showing excellent biocompatibility and bacterial growth reduction to 83–100% against both *E. coli* and *S. aureus*. PU catheters were coated by a multistep process involving a vapor phase plasma-induced polymerization with acrylic acid and dimethyloctadecyl [3-(trimethoxysilyl) propyl] ammonium chloride. The coating was stable in aqueous media and uniformly dispersed on PU catheters, as well as displaying antimicrobial activity against *E. coli* strains in vitro [73].

Applications in Tissue Engineering

Wound Dressings

An ideal wound dressing is expected to provide a moist environment, protect the wound from microorganism invasion and infections, remove wound exudate, as well as promote wound healing. Materials such as hydrogel and hydrocolloid are suitable for the fabrication of wound dressings due to their hydrophilic properties. However, the moist environments are also prone to breed microbial infections, which will delay the wound healing process and induce other infection-associated complications. Therefore, wound dressings with antibacterial activity is of great necessity in clinical applications.

Fan designed a series of acrylic acid and N,N-methylene bisacrylamide hydrogels loaded with Ag/graphene composites of different mass ratios. The hydrogel with the optimal Ag to graphene mass ratio of 5:1 (Ag5G1) exhibited strong anti-infection abilities and excellent wound-healing performance (98% wound closure) within 2 weeks. The effect can be attributed to the antibacterial performance of Ag nanoparticles and the porous structure of graphene [74].

Chitosan itself has antibacterial properties owing to the cationic amino groups, thus chitosan-based wound dressings for anti-infection treatment have been developed recently. Nimal et al. prepared an injectable hydrogel composed of chitosan and tigecycline. Tigecycline can be released in a sustained manner to significantly inhibit bacterial growth, as well as to prevent skin infections [75]. Tetracycline hydrochloride

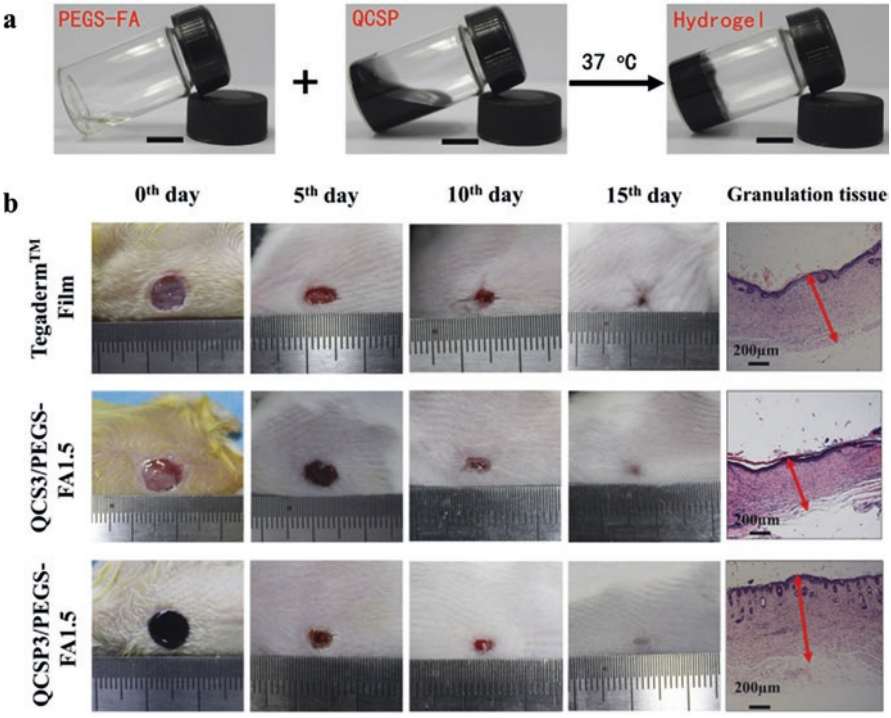

Fig. 4 (**a**) Photographs of PEGS-FA solution, QCSP solution, and hydrogel QCSP3/PEGS-FA1.5. (**b**) Photographs of wounds at 0th, 5th, 10th, and 15th day and granulation tissue at 15th day for commercial film dressing (Tegaderm™), hydrogel QCS3/PEGS-FA1.5, and hydrogel QCSP3/PEGS-FA1.5. (Images reprinted with permission of Zhao et al. (2017). Copyright 2017 Elsevier Ltd. [77])

was also incorporated into chitosan-PEG-PVP hydrogel as an antiseptic and scar preventive dressing. The prepared wound dressing promoted healing process with minimum scar formation and protected the open wound from bacterial invasions [76].

Zhao et al. developed a series of injectable conductive self-healed hydrogels based on quaternized chitosan-g-polyaniline (QCSP) and benzaldehyde group functionalized poly(ethylene glycol)-co-poly(glycerol sebacate) (PEGS-FA) as antibacterial and antioxidant wound dressing for cutaneous wound healing (Fig. 4). The antibacterial injectable hydrogel dressing prolonged the lifespan of dressing upon self-healing ability and promoted the in vivo wound healing process attributed to its multifunctional properties [77].

Nano metals such as silver, ZnO, and TiO_2 NPs have advantages of combating drug-resistant bacteria in infected wounds. A number of silver-containing wound dressings have been developed and approved by the FDA, including Tegaderm™, Duoderm®, Acticoat™, Fucidin®, 3M™, SilvaSorb®, PolyMem® Silver, etc. [78]. Moustafa et al. proposed an approach for the use of chitosan silver-based dressing for the control of diabetic foot infection with multidrug-resistant bacteria.

Chitosan hydrogel dressing loaded with the silver NPs showed promising antibacterial activities, as well as responsive healing properties for the wounds in both normal and diabetic rats [79].

In 2017, zwitterionic polycarboxybetaine (PCB) hydrogel and silver nanoparticles (AgNPs) were developed via a one-step method for the efficient treatment of infected wounds [31]. The PCB-AgNP hydrogel exhibited effective antibacterial ability against both Gram-positive bacteria (*S. aureus*) and Gram-negative bacteria (*E. coli*) in vitro and was able to efficiently treat *S. aureus* infections and accelerated cutaneous wound healing (Fig. 5a). Zwitterionic poly(sulfobetaine acrylamide) (pSBAA)-based hydrogel has also been impregnated with AgNPs and implemented to treat infected chronic wounds [30]. The AgNPs were grown within hydrogel networks by in situ free radical reduction and exhibited germicidal properties against Gram-positive *S. epidermidis* and Gram-negative *P. aeruginosa*. Results showed that pSBAA/Ag hydrogel was non-sticky to the new tissue and could accelerate the epithelialization in the infected diabetic wounds (Fig. 5b).

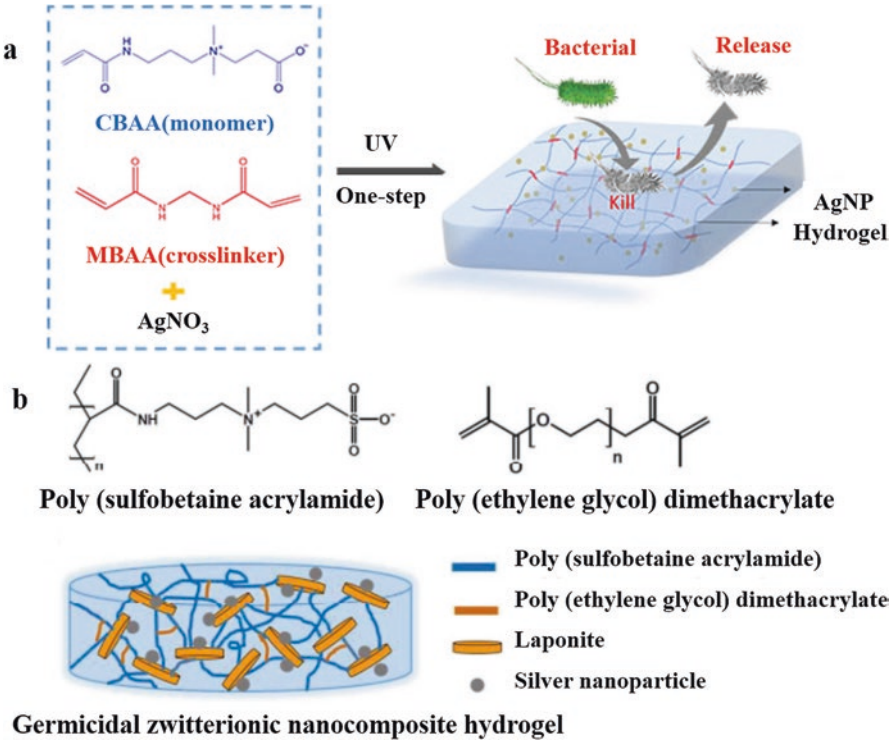

Fig. 5 (**a**) A schematic of the one-step synthetic route of the zwitterionic PCB-AgNP hydrogel. (Images reprinted with permission of Zhu et al. (2017). Copyright 2017 The Royal Society of Chemistry [31].) (**b**) Schematic illustration for structure of antimicrobial zwitterionic pSBAA/Ag composite hydrogel. (Images reprinted with permission of Huang et al. (2017). Copyright 2017 The Royal Society of Chemistry [30])

Orthopedic Implants

Orthopedic implant-related infection constitutes a major concern associated with high morbidity and health costs. There are a lot of new strategies to develop alternative antibacterial biomaterials to conventional antibiotics, such as zwitterionic modification, providing nanostructure-coated metal implants.

Recently, a surface-initiated atom transfer radical polymerization (SI-ATRP) strategy has been reported for surface zwitterionization of metal implants, such as commercial pure Ti (Fig. 6) [80] and biomedical grade 316L-type stainless steel (SUS 316L) [81]. Chang et al. presented a Ti surface with biocompatibility and antifouling properties grafting zwitterionic polySBMA using different anchoring agents of dopamine and silane. The resulting titanium surfaces grafted from dopamine- and silane-anchored polySBMA exhibited superlow fouling ability against the adhesion of proteins, human fibroblast cells (HT1080), *E. coli*, and *S. epidermidis*. Bacterial adhesion tests indicated that pristine metal surface was fully covered by *E. coli* and *S. epidermidis* after 24 h, whereas the SIATRP-treated Ti surfaces reduced 95% of bacterial adhesion relative to uncoated surfaces [80].

Bioceramics are excellent candidates to manufacture bone-like scaffolds which can load biologically active molecules to maintain, repair, or improve bone functions. Zwitterionization of bioceramics enables them to inhibit bacterial adhesion and prevent bone implant infections. SBA-15-type mesoporous material grafting zwitterionic -$NH3^{+}$/-COO^{-} has been synthesized by the co-condensation of

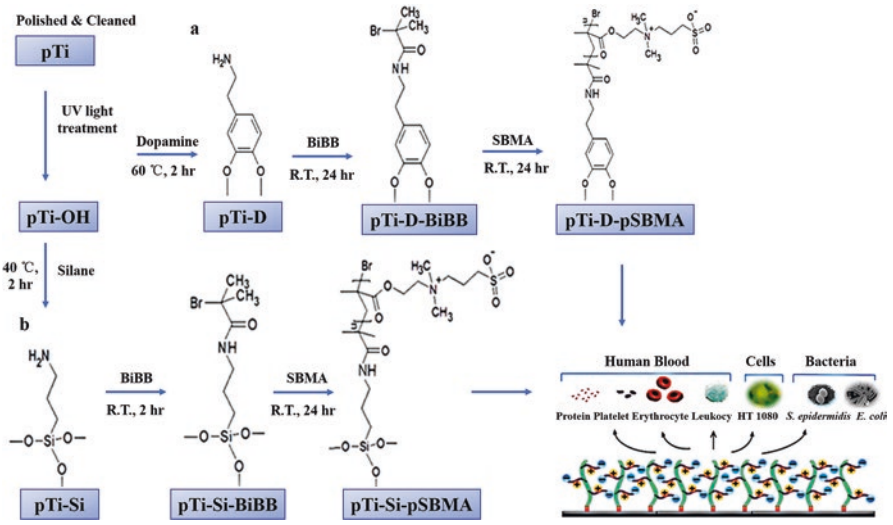

Fig. 6 Schematic illustration of the preparation process of zwitterionic pSBMA-grafted titanium disks via ATRP method with both (**a**) dopamine and (**b**) silane as respective anchoring agents. (Images reprinted with permission of Yu et al. (2014). Copyright 2014 American Chemical Society [80])

3-aminopropyltriethoxysilane (APTES) and carboxyethyl silanetriol sodium salt (CES). The water molecules above the zwitterionic surface would create a strong repulsive force to repel proteins from the surface, rendering the SBA-15 ultralow-fouling materials [82]. Furthermore, the ability of this material to inhibit bacterial adhesion was evaluated by simulating severe infection conditions. The in vitro adhesion assays showed that *E. coli* adhesion to zwitterionic SBA-15 was reduced by ~93% compared with the unmodified materials. After co-culturing with human Saos-2 osteoblasts to evaluate the biocompatibility at the physiological pH of 7.4, all materials exhibited good biocompatibility, with Saos-2 osteoblasts adhering, proliferating, and maintaining their initial morphology and function [83, 84].

Liu et al. reported that grafting pSBMA onto titanium alloy or dental implants led to promoted mineralization of the implant surface and increased osteointegration [85]. Ti6Al4V substrates were grafted with zwitterionic pSBMA brushes via SI-ATRP method, generating a stable super-hydrophilic and low-fouling surface without compromising mechanic property of the Ti6Al4V. The prepared surface was capable of attracting both cationic and anionic precursor ions during calcium phosphate apatite mineralization. The surface mineral coverage was enhanced from 32 to 71%, which significantly increased the attachment of the apatite crystals on the material surface.

Catheters

Catheters often need to be replaced at frequent intervals to prevent potential infections; however, this practice imposes considerable costs to the healthcare system. Imparting catheters with improved antibacterial ability can significantly reduce the frequency of implant-related infections [86]. An Ag alloy-coated latex-hydrogel catheter plus (Inc: Murray Hill, New Jersey, USA) was compared in vitro with a nitrofurazone-coated silicone catheter (Rochester Medical Group). Bacterial cells were detached from catheters by sonication and counted, and results showed that nitrofurazone-coated catheters performed better than Ag alloy-coated catheters [87]. Three kinds of catheters involving nitrofurazone-impregnated, Ag alloy-coated, and the standard polytetrafluoroethylene (PTFE) catheters were also compared within 6 weeks, the rate of symptomatic UTIs was 10.6% ($n = 2153$), 12.5% ($n = 2097$) and 12.6% ($n = 2144$), respectively [88].

In 2011, antibacterial coatings on catheters were obtained by an innovative and patented silver deposition technique based on the photo-reduction of the silver solution to form antibacterial silver NPs on the surface of the catheter (Fig. 7). The distribution, the size of clusters on the catheters surface, and the antibacterial capability of the devices against bacterial proliferation were evaluated. Inhibition zone tests performed against *E. coli* revealed a strong antibacterial activity of silver-treated catheters, as well as the main of antibacterial activity after soaking in high water flow for 30 days [89].

A strategy by combining the antibacterial effects of norfloxacin and silver NPs was used to resist bacterial adhesion and encrustation. The polymer films loaded with two

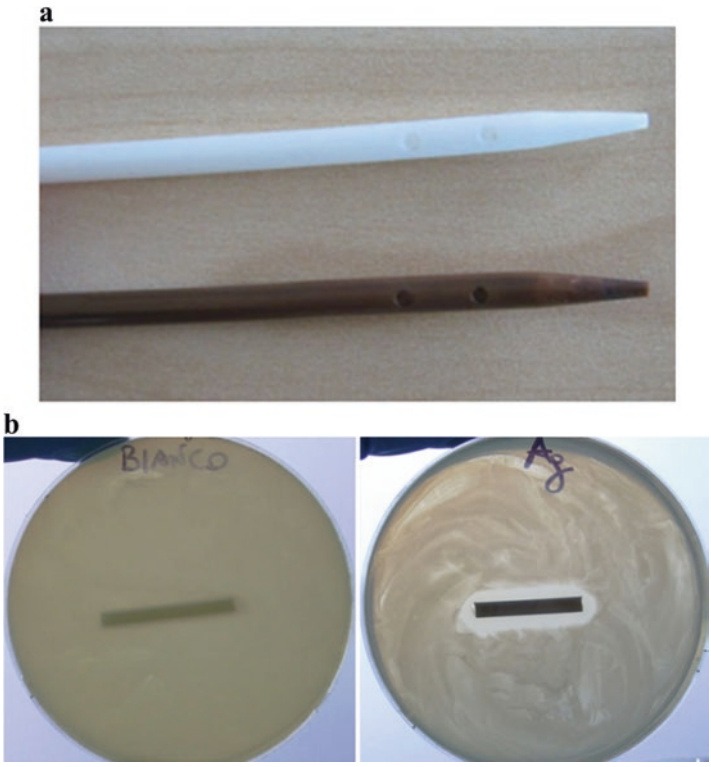

Fig. 7 (**a**) Visual comparison of untreated catheter and silver-treated catheter. (**b**) Test of *E. coli* growth on untreated samples (left) and silver-treated samples (right). (Images reprinted with permission of Pollini et al. (2011). Copyright 2011 Springer Science + Business Media, LLC [89])

antibacterial agents were applied on polyurethane (PUR) and silicon sheets and compared with commercially pure PUR and silicon. The coatings could resist the encrustation for at least 2 weeks in an in vitro encrustation model using artificial urine [90].

Conclusion

We have summarized the main approaches for designing biomaterials against bacterial infections, with special emphasis on advances developed in the past decades. Based on the different modes of action over bacteria, these biomaterials can be classified as anti-biofouling and antimicrobial to suit specific demands.

Anti-biofouling materials are expected to prevent the formation of biofilm on the surface by resisting bacterial attachment or adhesion. These materials usually impede bacteria/coating surface interactions by either exclusion steric repulsion, electrostatic repulsion or low surface energy. Major advances in recent years have

been summarized in this chapter, including the functionalization of biomaterials with PEG, the development of alternatives to PEG such as zwitterionic polymers.

Antimicrobial materials exhibit a bactericidal activity that can kill bacteria by releasing antimicrobial agents or by contact-active mechanisms. Releasing-based agents including antibiotics, silver, quaternary ammonium salts, and nitric oxide have been widely explored to eliminate microbial contaminations. The widespread use of common antimicrobial agents, however, has accelerated the emergence of antibiotic resistance and raised concerns regarding potential toxicity of high-dose silver-containing compounds. Some new approaches involving the development of antimicrobial coatings based on AMPs, enzymes, and switchable cationic polymers have gained great promise recently.

Most of the biomaterials mentioned above have been tried in medical applications, such as wound dressings, orthopedic implants, vascular prostheses and urinary catheters. However, standardized methods to better support translation to the clinical level are still desirable. Meanwhile, the development of controllable antimicrobial biomaterials with actively responsible, switchable, or multifunctional properties is of great demand, to combat bacterial infections in tissue engineering.

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