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Review Article

Peptide–Polymer Conjugates: A Promising Therapeutic Solution for Drug-Resistant Bacteria

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By 2050, it is estimated that 10 million people will die of drug-resistant bacterial infection caused by antibiotic abuse. Antimicrobial peptide (AMP) is widely used to prevent such circumstances, for the positively charged AMPs can kill drug-resistant bacteria by destroying negatively charged bacterial cell membrane, and has excellent antibacterial efficiency and low drug resistance. However, due to the defects in low *in vivo* stability, easy degradation, and certain cytotoxicity, its practical clinical application is limited. The emergence of peptide–polymer conjugates (PPC) helps AMPs overcome these shortcomings. By combining with functional polymers, the positive charge of AMPs is partially shielded, and its stability and water solubility are improved, so as to prolong the *in vivo* circulation time of AMPs and reduce its cytotoxicity. At the same time, the self-assembly ability of PPC enables it to assemble into different nanostructures to undertake specific antibacterial tasks. At present, PPC is mainly used in wound dressing, bone tissue repair, antibacterial coating of medical devices, nerve repair, tumor treatment, and oral health maintenance. In this study, we summarize the structure, synthesis methods, and the clinical applications of PPC, so as to present the current challenges and discuss the future prospects of antibacterial therapeutic materials.

1. Introduction

With the wide applications and abuse of antibiotics, the antimicrobial resistance (AMR) and drug-resistant bacteria have become a serious problem to global health. By 2050, 10 million people are expected to die from drug-resistant infections [1], which not only put tremendous pressure on the health care system but also lead to prolonged illness and increased pain for patients. What is more, the overuse of antibiotics has contributed to the emergence and further spread of superbugs, which have the multidrug resistance (MDR) [2]. Therefore, how to treat drug-resistant bacteria has become an important research issue.

Bacteria resist the action of antibiotics by four main molecular mechanisms: reducing membrane permeability to reduce antibiotic penetration, expelling antibiotics through the effluent system, destroying antibiotics or modifying them to inactivate them, and modifying target sites to reduce affinity for antibiotic [3, 4]. There are two ways that bacteria can obtain AMR: one is via vertical (endogenous) and the other is via horizontal (exogenous). Vertical evolution refers to the intergenerational accumulation of spontaneous resistance mutations in bacterial genomes, whereas horizontal evolution refers to the transfer of resistance genes from resistant bacteria to susceptible bacteria, which includes three mechanisms: conjugation, transduction, and transformation [4, 5].

Current therapeutic approaches for AMR and drug-resistant bacteria include antibiotics with new targets; antibiotic resistance breakers (ARBs), which can overcome the mechanism of bacterial resistance and re-sensitize the reaction of resistant bacteria to antibiotics, such as β-lactam inhibitors; and a group of viruses called phages, which can cause the host bacteria to lyse and so on [5–7]. However, these therapeutic approaches would still be caught in the dilemma of increasing bacterial resistance, because they all exert strong

antimicrobial selective pressures on the drug-resistant bacteria, which leads to the appearance of new drug-resistant bacterial mutants even more quickly [7, 8]. Meanwhile, ARBs or antibiotic adjuvants, including modified enzyme inhibitors, membrane permeators, and efflux pump inhibitors, have the risk of adverse reactions due to potential drug interactions and face the challenge of how to administer ARBs in a more scientific and efficient manner [5, 9–11]. As for phages, the high degree of specificity, the lack of phage pharmacological model, and the high risk of causing inflammation by altering intestinal flora and increasing epithelial cell permeability make the clinical application of phages difficult [12–20]. Given the limited efficiency of these approaches, a new approach or drug is urgently needed to address the AMR problem.

Researchers hope to introduce antimicrobial peptides (AMPs) to solve the problems of AMR and drug-resistant bacteria. In the mid-1990s, the concept of AMPs took off [21]. AMPs, also known as host defense peptides, are a group of highly bioactive polypeptide substances widely existing in plants, animals, and microorganisms, which are formed by long-term evolution in nature, and it can fight off exogenous pathogens. As a group of small, biologically active proteins, unlike traditional antibiotics that target specific organs within the cell [22, 23], AMPs have a cationic–hydrophobic amphiphilic structure, which is positively charged, and they work by using electrostatic interactions to destroy the negatively charged bacterial membranes and by regulating immune responses and inflammation [24, 25]. At present, several models have been proposed to explain this process, including barrel-stave model, carpet-like model, toroidal-pore model, and disordered toroidal-pore model [26–30]. Compared with traditional antibiotics, ARBs, and bacteriophages, AMPs can better regulate the immune response of the host and have a relatively broad spectrum of anti-biofilm activity with relatively slow development of bacterial resistance [31, 32]. Human AMPs also act as natural disease-fighting agents, more than 100 of which were discovered as broad spectrum of antibacterial activity [31, 33, 34]. However, AMPs also have several disadvantages, such as easy degradation, low stability *in vivo*, low salt sensitivity, high toxicity to mammalian cells due to a lack of selectivity, difficult extraction, and high manufacturing costs, which also limit their clinical applications [35–40]. Given these shortcomings of AMPs, the researchers used two different approaches to overcome them [41]: one is to imitate the key structural characteristics and characteristics of natural AMPs to synthesize cationic polypeptides with excellent antibacterial activity, proteolytic stability, biocompatibility, and biodegradability [42–44]. However, the high cytotoxicity of these synthetic AMPs is yet to be overcome [45].

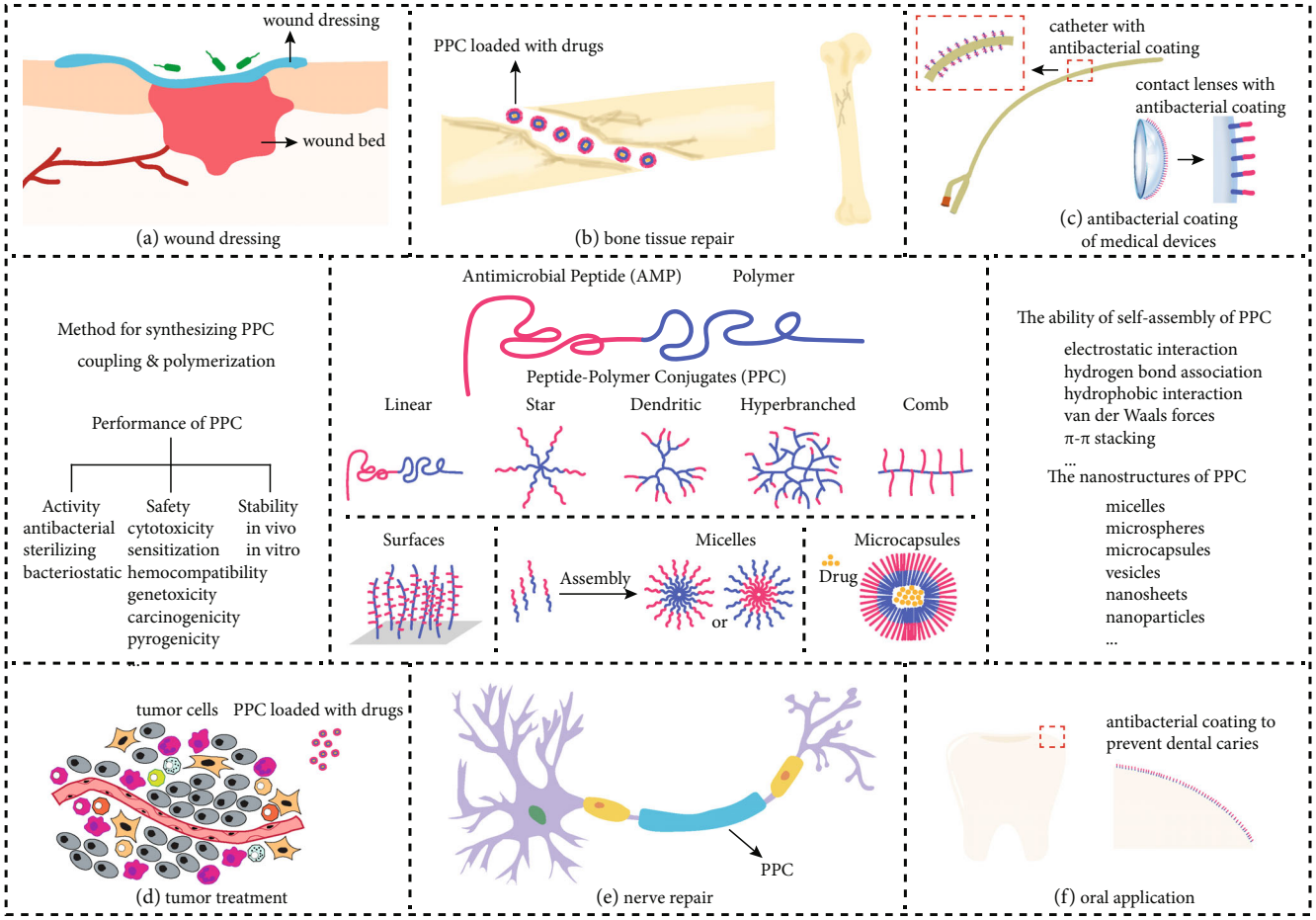
In recent years, there have been many innovative and valuable works aiming at the novel anti-bacteria conjugates to better overcome these shortcomings of AMPs. Therefore, in this study, we focuses on peptide–polymer conjugates (PPC), which are the combinations of AMPs and functional polymers with excellent biocompatibility, while reducing the cytotoxicity and improving the antibacterial selectivity [38, 39, 46–48]. As illustrated in Scheme 1, in the following study, starting from the synthesis and self-assembly of PPC, we sort out the existing assembly products and applications of PPC in bio-medicine and classified the usage of PPC by organs to elucidate the current situation and possible future of PPC.

2. Synthesis and Self-Assembly of PPC

As shown in Figure 1, coupling and polymerization, as two methods of synthesizing PPC, have their own characteristics and advantages [49–54]. The coupling is particularly suitable for the linkage of AMPs with low molar mass polymers. However, the purification of reactants of coupling is complicated by the addition of an excess of AMPs to the polymer in order to improve the coupling efficiency [55–58]. In addition, in the coupling reaction, the functional groups of AMPs and functional polymers, which can react with each other, such as carboxyl and amino, are necessary. In addition, the formation of amide bonds, especially peptide bonds, is a common method of conjugation. Moreover, oxidation, photo cross-linking, Michael addition, and Schiff base reaction are also the methods of coupling [53].

The polymerization involves initiators and macromonomers, and has some advantages that coupling does not have. With ring-opening polymerization (ROP) of α-amino acid *N*-carboxyanhydrides (NCAs), single-electron-transfer living radical polymerization, nitroxide-mediated radical polymerization, atom transfer radical polymerization (ATRP), reversible addition-fragmentation chain transfer, ROP of other monomers, and other methods, the polymerization can synthesize PPC with long polypeptide chains and various macromolecular structures [51, 59–62]. Among them, NCA-ROP provides a convenient way to synthesize PPC, which have various macromolecular structures, such as linear polymer, star copolymer, dendritic copolymer, and hyperbranched polymer, and has attracted more and more attention [63]. Compared with coupling, this step-by-step synthesis method of polymerization can provide various PPCs with controllable chain length, low polydispersity, and high amine functionalization, and can realize various topologies of PPC [63, 64]. While maintaining the functions of AMPs and functional polymers, PPC possess new properties that do not exist in AMPs and functional polymers alone [48]. For example, when AMPs is combined with biocompatible polymers, its positive charge can be partially neutralized, so as to help AMPs escape the attack of the immune system, improve its *in vivo* stability, and prolong its *in vivo* circulation time. Meanwhile, the cytotoxicity of AMPs was also reduced [65–67].

Self-assembly has become an advantage and research hotspot of PPC. PPC has obtained self-assembly ability by adjusting non covalent bond forces, such as electrostatic interaction, hydrogen bond association, hydrophobic interaction, van der Waals forces, π–π stacking, and spontaneously connected to form clear and aggregates under equilibrium conditions [68–70]. Specifically, PPC is amphiphilic, which can form ordered nanostructures under the synergistic action of hydrophobic force of hydrophobic part and hydrogen bond of hydrophilic part. During the assembly



Scheme 1: Different macromolecular structures, self-assembly behaviors, and applications of peptide–polymer conjugates (PPC). (a) PPC is used as wound dressing to help inhibit bacteria and promote wound healing. (b) PPC is applied on bone tissue repair to help bone tissue repair by inhibiting bacteria and delivering drugs. (c) PPC is served as antibacterial coatings on medical devices, such as urinary catheters and contact lenses, to avoid infection caused by the use of medical devices. (d) PPC assists cancer treatment. It can destroy tumor cell membrane through safe and efficient delivery of AMPs and electrostatic interaction. (e) PPC for the use of nerve repair to remyelinate demyelinated damaged nerve fibers and avoid infection. (f) For oral health maintenance, PPC is used as the antibacterial coating of teeth helps prevent dental caries.

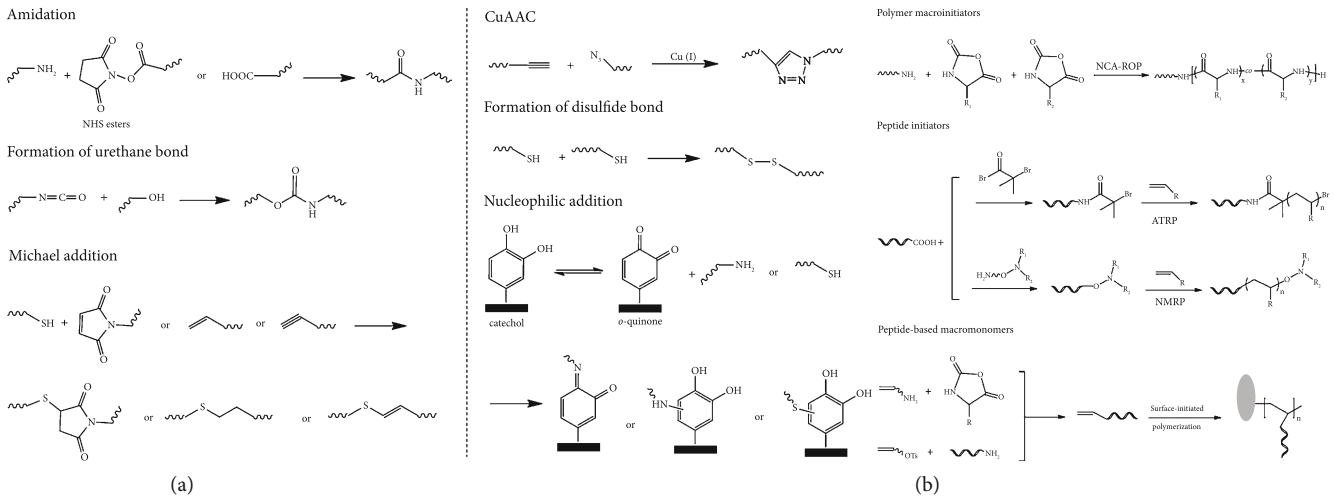


Figure 1: The synthesis process of PPC. (a) Synthesis of PPC by coupling methods. (b) Synthesis of PPC by polymerization methods. Reprinted with permission from ref [53]. Copyright 2018 American Chemical Society.

process, the hydrophobic parts gather with each other due to hydrophobicity, forming the hydrophobic core of the assembly. The hydrophobic force is the main driving force to drive the self-assembly of amphiphilic molecules and maintain the structural stability of the assembly. The hydrogen bond makes the hydrophilic parts close to each other closely stacked on the surface of the assembly with a specific secondary structure, which contacts with water and further drives the completion of the assembly. In PPC, AMPs is often located on the surface of the assembly with hydrophilic peptide chain, whereas polymers are often located in the core of the assembly because of hydrophobicity. Such a structure enables AMPs on the surface of the assembly to effectively contact and kill bacteria, and the hydrophobic core makes it possible to load drugs to treat diseases.

Through self-assembly, PPC can form nanostructures with different shapes and functions, such as micelles, vesicles, nanosheets, nanoparticles, and other nanostructures. They have biocompatibility, stability, and good antibacterial activity, showing great potential in antibacterial, anti-biofilm, anti-MDR, wound dressing, implant coating, drug delivery, and even gene delivery [61, 71–78]. The following are several examples of products of the self-assembly of PPC, each with different mechanisms and advantages.

Micelle: the conjugates of tritrpticin AMPs and poly(-acrylic acid)-*b*-polystyrene will self-assemble in water and form micelles, and the active segment of AMPs will locate on the surface of micelles [79]. Compared to the two individual components, the micelles have stronger bactericidal effects on *Escherichia coli* and *Staphylococcus aureus*. The detailed interaction between antibacterial micelles and bacterial membrane is still unclear, and further efforts are needed to study its antibacterial mechanism in the future.

Microsphere: grafting AMPs onto microspheres can maintain the stability of AMPs and improve its exposure area, which is helpful to give full play to its practicability [80]. In the study of Li et al., NF-κB essential modifier binding domain (NBD) polypeptide was combined with other substrates to prepare microspheres to help load and release drugs [81].

Hydrogel: Rezaei and his team loaded piscidin-1 to prepare wound dressings with controllable release, antibacterial activity, biocompatibility, and biodegradability to avoid wound infection and help heal wounds faster [82].

Recent advances in the field of AMPs mainly focus on the artificial design and synthesis of AMPs, the optimization of functional polymers, the synthesis and optimization of PPC, and the self-assembly of PPC. Due to the needs of transformation and the advantages of material properties, the research hotspot has gradually changed to different medical applications of PPC.

3. The Treatments of Drug-Resistant Bacteria in Different Tissues or Organs by PPC

In view of the advantages of PPC, such as better *in vivo* stability, higher biocompatibility, longer *in vivo* circulation time, more stable antibacterial properties, and better drug resistance, PPC has a trend to replace traditional antibiotics and AMPs in many applications. Relevant cases are presented in Table 1.

3.1. Wound Dressing and Healing. Microbial infection is one of the important factors leading to slow wound healing, and appropriate antibacterial wound dressing is an important approach to prevent microbial infection and also a necessary condition to accelerate wound healing [97]. The dressings should support the sustained drug release of loaded antimicrobials to achieve long-term antimicrobial activity and maintain a healthy concentration of healing tissues [98].

AMPs and its simulators have a broad-spectrum antibacterial effect on bacteria and even fungi, which is very suitable for application in wound infections caused by drug-resistant bacteria [99, 100]. Meanwhile, AMPs can also induce cell migration and proliferation at the wound site, promote vascular repair, regulate immune response, and help wound healing [101–103]. However, due to its sensitivity, easy degradation, and certain cytotoxicity, its biomedical application has been affected to a certain extent [104]. Conjugated AMPs with polymers emerged in order to solve this problem, which can improve the stability of AMPs while reducing their cytotoxicity [66, 105, 106]. In current clinical application, various natural polymer materials [e.g., gelatine, alginate (ALG), silk, collagen (COL), chitosan, and hyaluronic acid (HA)] and synthetic polymer materials [e.g., polyurethane (PU), poly(lactide-co-glycolide), poly(vinyl alcohol), and poly-ε-caprolactone] are regarded as potential tissue-engineering materials [107–110]. These materials may not have any antibacterial activity on their own, but when combined with AMPs, they can not only exert their own properties to aid wound repair but also have antibacterial abilities. For example, bacterial cellulose can enhance the wound healing through regulation of angiogenesis and formation of connective tissue [111, 112]. But its lack of antimicrobial activity requires it to be functionalized with antimicrobial agents [113], such as AMPs, so the peptide can conjugate with hydrogel made of bacterial cellulose to inhibit bacteria and promote wound healing. The actual case is that, a bifunctional peptide, combining an AMP and a cellulose binding peptide (CBP), is designed to be fixed on membranes of bacterial cellulose with tight control over peptide concentrations. Based on this, Weishaupt et al. have developed a cellulose membrane, which was modified by AMP tet009 against *S. aureus* and *Pseudomonas aeruginosa*, and it has good antibacterial ability and can effectively treat and prevent wound infection [83].

Different types of injuries require corresponding repair methods, and their requirements for wound dressing are also different. Therefore, the requirements for the composition of PPC are also different. For example, in the face of scalded wounds, it is very crucial to keep the wound moist. Therefore, choosing a dressing that can keep the wound in a moist, breathable, and antibacterial microenvironment is particularly necessary to prevent wound infection, promote cell proliferation, and accelerate wound healing [114]. In addition, as one of the main components of extracellular matrix, HA not only has a significant impact on cell migration and proliferation but also has good water absorption ability,

Table 1: Inhibition effect of PPC on different bacteria in different application scenarios.

Application scenarios	PPC	Bacterial species	PMID	Date and references
Wound dressing	AMP–CBP (cellulose binding peptide) immobilized on cellulose membranes or electrospun fibers.	*Staphylococcus aureus* and *Pseudomonas aeruginosa*	32159927	2020 [83]
	The Tet213-conjugated ALG/HA/COL wound dressing.	*Escherichia coli* and *S. aureus*	3142174	2019 [84]
	The engineered MeTro/GelMA-Tet213 hydrogels.	Methicillin resistant *S. aureus*, and *E. coli*	28579065	2017 [71]
Bone tissue repair	Three layers of vertically oriented TiO_2 nanotubes, a thin layer of calcium phosphate coating, and a phospholipid (POPC) film were impregnated with a potent broad-spectrum AMP (HHC-36).	*S. aureus* and *P. aeruginosa*	23680363	2013 [85]
	Polyelectrolyte multilayer film containing AMP (ponericin G1).	*S. aureus*	20004967	2010 [86]
Antibacterial coating for medical devices	Antibacterial vesicles based on peptide-mimetic alternating copolymers.	*E. coli* and *S. aureus*	29020450	2017 [87]
	Antimicrobial peptide melimine coating for titanium.	*S. aureus* and *P. aeruginosa*	26871890	2016 [88]
	Melimine-coated contact lenses.	*S. aureus* and *P. aeruginosa*	24759327	2014 [89]
	Anti-adhesive antimicrobial peptide coating of catheters.	*P. aeruginosa*, *S. aureus*, and *Staphylococcus saprophytic*	27914268	2017 [90]
	Hydrogel coatings containing AMP (HHC-36).	*S. aureus*, *Staphylococcus epidermidis*, *P. aeruginosa*, and *E. coli*	28140564	2017 [91]
Tumor treatment	Melittin-lipid nanoparticles.	—	32111828	2020 [92]
Nerve repair	Hydrogels grafted with poly(L-lysine).	—	22251248	2012 [93]
Oral application	The peptide of Ser(p)–Ser(p)–polyphemusin I (DPS-PI).	*Streptococcus mutans*	30929087	2019 [94]
	A peptide-based 2-tier protective system for dental resin composite restorations.	Biofilm of oral microflora	30753942	2019 [95]
	Dental adhesives copolymerized with AMP–polymer conjugates.	*S. mutans*	33834166	2020 [96]

which can absorb tissue exudate and maintain wound wetness [115–117]. For wounds caused by hemorrhagic trauma, appropriate materials are needed to help repair the blood vessels of the wound and prevent inflammation. In addition, COL can meet these requirements because it can promote wound healing by promoting cell migration and proliferation [118, 119], can accelerate wound healing by its ability to promote angiogenesis [120], and can effectively address wound inflammation due its ability to promote chemotaxis, promote the recruitment of macrophages to the wound site, and attenuate the polarization of pro-inflammatory macrophages [121]. At present, with the increasing complexity of wound conditions and the increase of bacterial drug resistance, the development of composite dressing materials with multiple functions has become a general trend. In addition, these composite materials can retain the advantages of various polymer materials. Stimulating fibroblast aggregation to help wound healing is an essential function of many wound dressings. In the study of Lin et al., a natural composite composed of ALG, HA, and COL was used as wound dressing substrate because it has good biocompatibility and can stimulate the aggregation of fibroblasts to help wound healing [84]. In addition, Lin et al. conjugated the AMP Tet123 onto on the substrate, and the results showed that the multifunctional wound dressing (ALG/HA/COL-Tet213) had good biocompatibility and antimicrobial activity that can release AMPs in a sustainable manner to inhibit or kill bacteria in infected wounds and can accelerate wound tissue repair and accelerate wound healing (Figure 2).

Many nanomaterials have been developed as wound dressings to promote wound healing in different situation, such as hydrogels [122], sponges [123], electrospun mats [124], and nanofibers [125]. Wound dressings should exhibit certain biological properties (i.e., support keratinocyte adhesion, proliferation, and differentiation) and have appropriate mechanical and degradation properties [126]. In view of these requirements, hydrogel has become the focus of research, because as a hydrated three-dimensional network composed of polymers, it has good biocompatibility, degradation properties, expansion properties, and suitable mechanical properties [127–129]. The PPC can be used as raw materials to assemble hydrogels as wound dressings, which not only plays the antibacterial role of AMPs but also helps absorb tissue exudate [130]. Meanwhile, hydrogels can also be loaded with drugs to help accelerate wound healing [131]. In order to overcome the disadvantage of low adhesion of hydrogel, a composite meth-acryloyl-substituted recombinant human tropoelastin (MeTro)/gelatin methacryloyl

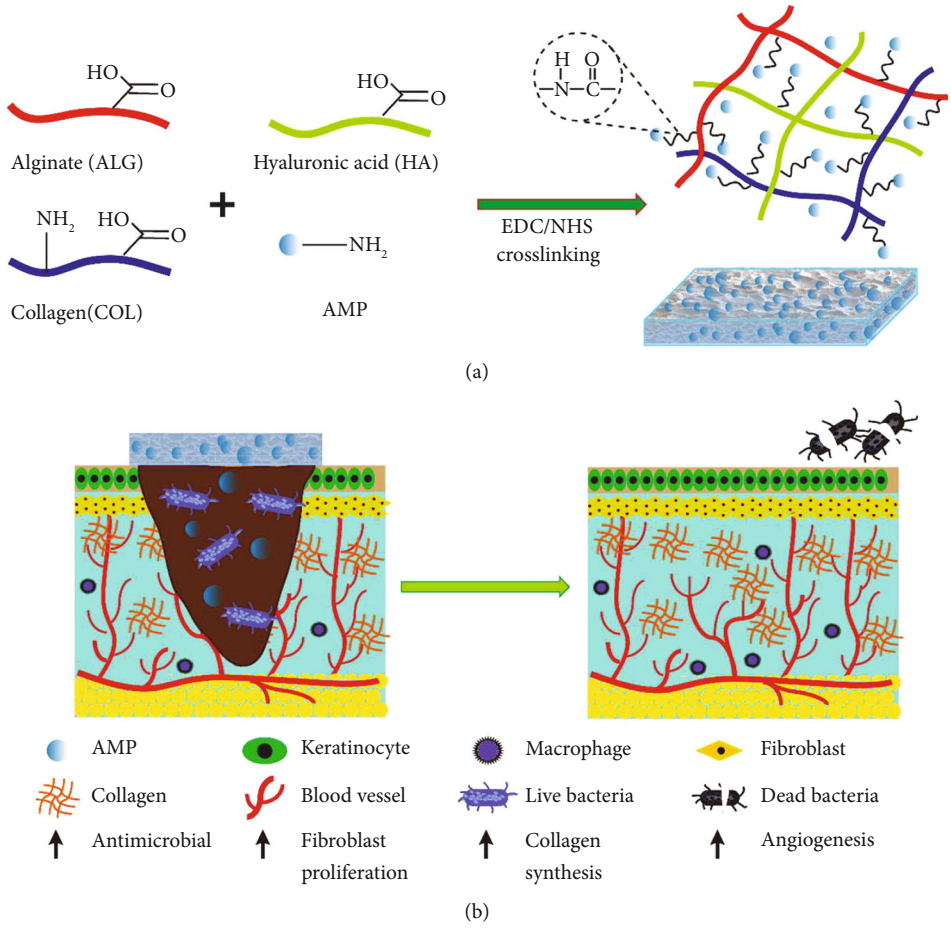


Figure 2: Schematic of the preparation of the ALG/HA/COL-AMP wound dressings. (a) The Tet213-conjugated ALG/HA/COL wound dressings were prepared using the chemical reaction between the carboxyl groups and the amino groups on ALG, COL, HA, and Tet213. (b) The slow release of Tet213 due to the cleavage of the amide bond combined into the wound-dressing substrates helps kill bacteria, avoid the unrestrained release of Tet213 at the tissue sites, and excessive dressing changes. Reprinted with permission from ref [84]. Copyright 2019 Elsevier.

(GelMA) hydrogel mediated by visible light has been created, which has strong adhesion and can better prevent wound infection and promote wound healing [71].

3.2. Bone Tissue Repair. Nanocomposite biomaterials, as a relatively new material, contain biopolymers and biodegradable matrix structures that help bone tissue regenerate and degrade *in situ*. In orthopedic surgery, biomaterials are often used to permanently replace lost tissue or to support the process of bone tissue regeneration at the defect site, thereby compensating for lost function and optimizing appearance [132]. Implants with permanent functions need to be stable and biocompatible in the body, whereas implants that help regenerate bone tissue need to be able to degrade in situ and be replaced by new bone tissue [133]. Nanocomposite biomaterials have corresponding characteristics and can effectively help bone regeneration.

Whether natural and synthetic polymers, and whether they degraded or not, the high risks of microbial growth on the implanted devices are a common and serious problem in orthopedic surgery [134, 135]. The formation of bacterial biofilms at the interface between implants and tissues may cause persistent infection, so antibacterial treatment of implants is required [136]. Given the resistance caused by traditional antibiotics, AMPs are a new weapon in orthopedic implants against resistant bacteria [137]. Combining these materials with AMPs, the resulting implants not only have good biocompatibility and biodegradability but also have good antibacterial and vascular repair effects, which can help bone tissue repair faster and better [138].

In order to achieve better antibacterial effect and repair effect, AMPs on implants need not only to reach a certain concentration locally but also need to control the release rate to maintain a relatively long time concentration [139]. Recently, the strategies adopted can be roughly divided into two kinds. One is chemical factor, that is, selecting suitable polymer materials and AMPs to ensure relatively strong electrostatic interaction between them. In addition, the other is morphological factor, that is, expanding the contact area to be able to bind more AMPs [140].

Currently, a third strategy is gaining increasing attention, which is to assemble polymer membranes containing

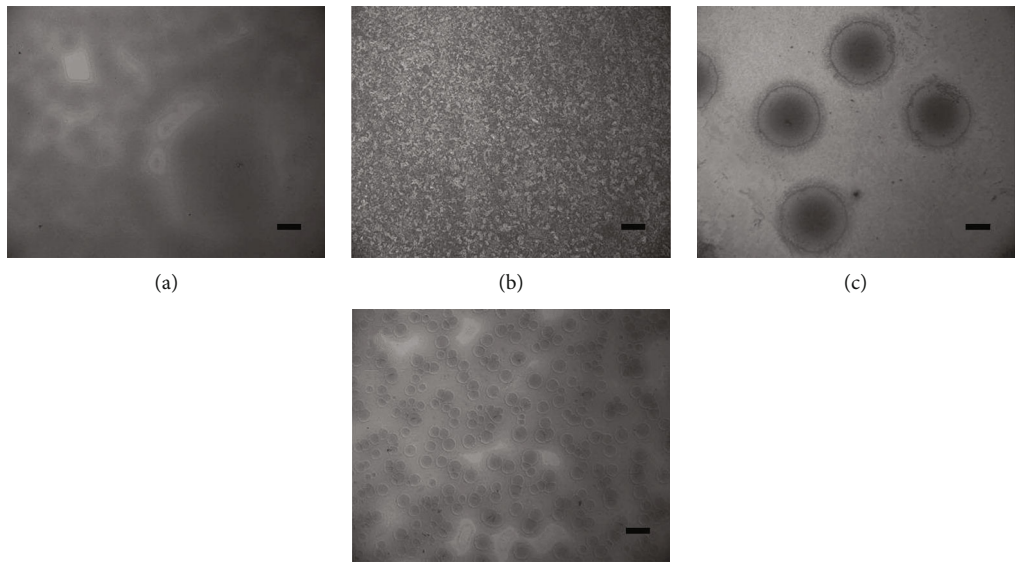


Figure 3: Polyelectrolyte multilayer film prevents biofilm formation. (a) Blank silicon substrate. Uncoated substrate is almost completely covered by *Staphylococcus aureus*. (b) (Poly 2/alginic acid/ponericin G1/alginic acid)$_{75}$ film. The substrate is completely void of bacteria, showing 100% inhibition of *S. aureus* attachment on substrates coated with alginic acid films. (c) (Poly 2/chondroitin sulfate/ponericin G1/chondroitin sulfate)$_{75}$ film. (d) (Poly 2/dextran sulfate/ponericin G1/dextran sulfate)$_{75}$ film. (Scale bars: 200 μm). (Four films and controls were examined; the experiment was repeated three times.) Reprinted with permission from ref [86]. Copyright 2010 Elsevier.

AMPs layer-by-layer on a solid support [85, 86]. Compared to other methods of local drug delivery, such as hydrogels, this way could lead to implants with the ability to release AMPs in a controlled and continuous manner, making them more effective against resistant bacteria [141]. *S. aureus*, is one of the most common pathogens that cause infection in orthopedic surgery, and it will cause serious harm to patients [142]. Using a non-cytotoxic multilayered coating that programmed the release of AMP HHC-36 from the titanium surface, Kazemzadeh-Narbat et al. were able to effectively eradicate *S. aureus* and found no cytotoxicity of the implant [85]. In another study of Shukla et al., an AMP ponericin G1 that is effective against *S. aureus* was incorporated into a hydrolytically degradable polyelectrolyte multilayer film to exert its own function (Figure 3) [86].

In addition, to using the implants' antibacterial coating to fight bacterial infections, AMPs can also play a role in bone tissue repair through their ability to self-assemble. Bone repair is a complex process involving the interaction between cells and cytokines, among which growth factors play a very important role in cell proliferation, differentiation, and the formation of extracellular matrix [143]. However, growth factors tend to degrade *in vivo* without carrier protection. Therefore, using antibacterial carrier to carry growth factors can not only exert antibacterial effect but also promote bone repair. Zhou et al. synthesized peptidemimetic alternating copolymers, which not only have good antibacterial activity and low cytotoxicity but also can self-assemble into vesicles with antibacterial activity and load growth factors (Figure 4). Therefore, the polymer vesicles can perform both antibacterial and repair tasks during bone repair [87]. Compared with the previous step-by-step work, this is undoubtedly fast and efficient. It is worth noting that how to ensure that AMPs in combination with polymers still maintain antibacterial activity should be one future focus of the research.

3.3. Antibacterial Coating for Medical Devices. Various medical devices, such as urinary catheter, endotracheal tube, gastric tube, artificial heart valve, and contact lens, have been widely used in clinic and become an indispensable part of modern health undertakings [144]. However, with the wide use of various medical devices, the cases of biomaterial-related infections are also increasing. On the one hand, this is due to the decline of immunity of people using medical devices because of their basic diseases; on the other hand, it is due to the increase of bacterial drug resistance caused by antibiotic abuse all over the world. At the same time, the existence of medical devices as foreign bodies in non-human tissues will also lead to the reduction of the body's local immune defense ability [145]. According to previous studies, the pathogens of medical device related infections usually come from the commercial skin floor or the hospital environment brought in during the use and implantation of medical devices. These pathogens will adhere to the surface of medical devices and form biofilms, and then invade human tissues in contact with medical devices, resulting in infection or body damage [146]. Due to the existence of antibiotic resistance, even if high concentration antibiotics are used, it is often difficult to effectively solve the related infection. Therefore, once the medical device related infection occurs, most of the time, it ends with the removal of medical devices and reoperation [147].

At present, the preventive measures for biomaterial-related infection often start with the medical devices themselves, hoping to make them have antibacterial ability when

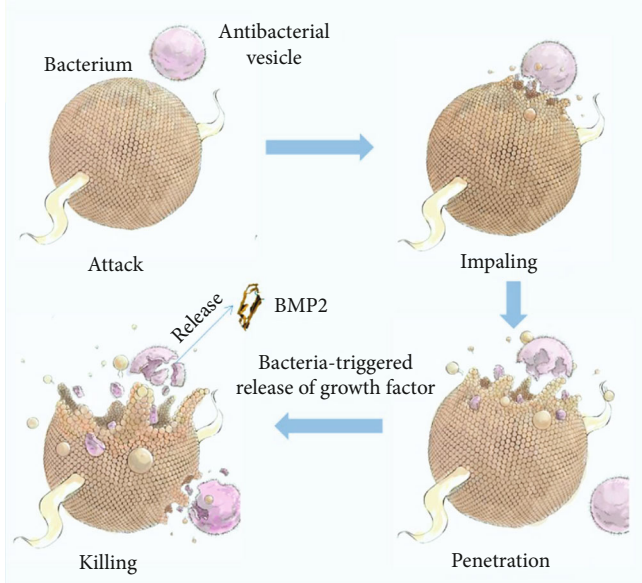


Figure 4: Engineering dual missions in one peptide-mimetic alternating copolymer (PMAC) vesicle for bone repairing: antibacterial and delivery of growth factor. The positively charged PMAC vesicles can attack negatively charged bacteria, impale and penetrate bacteria membrane, and finally kill bacteria. In the meanwhile, the encapsulated growth factors can be released from vesicles for facilitating bone regeneration. The growth factors can be also released in the healthy bone defects due to the degradation of vesicles. Reprinted with permission from ref [87]. Copyright 2017 American Chemical Society.

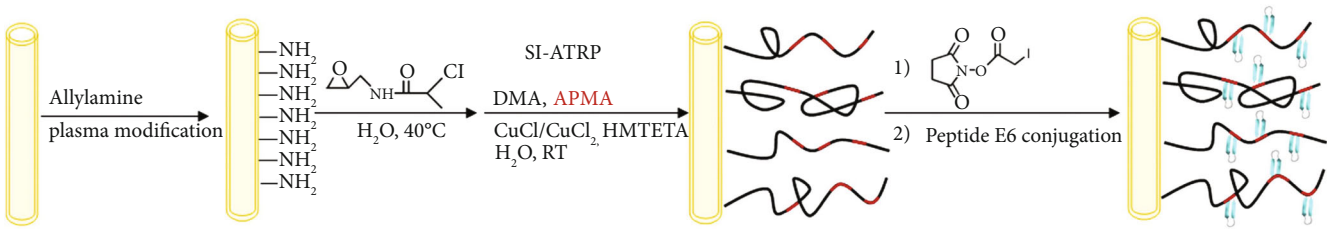


Figure 5: Functionalization of polyurethane (PU) catheter with AMP-brush coating. The catheter was initially treated with allylamine to generate a surface layer containing amine group. This was followed by a reaction with epoxy containing atom transfer radical polymerization (ATRP) initiator to generate polymerization initiating sites. Poly (*N*,*N*′-dimethylacrylamide (PDMA)-*co*-*N*-(3-aminopropyl) methacrylamide hydrochloride (APMA) brushes were grown from these initiator modified PU catheter by surface initiated ATRP (SI-ATRP). The sulfhydryl group of C-terminal cysteine peptides E6 (sequence RRWRIVVIRVRRC) was used tether it to the PDMA-*co*-APMA brush functionalized with iodoacetic acid *N*-hydroxysuccinimide ester. Reprinted with permission from ref [90]. Copyright 2017 Elsevier.

manufacturing related medical devices, so as to better avoid the generation of biofilm and infection. The current common method is to directly bind AMPs to the surface of medical materials and directly kill pathogenic bacteria or store AMPs in antibacterial coatings, such as microporous calcium phosphate coatings, nanotubes, polymer coatings, and hydrogels, through the release of AMPs to achieve antibacterial effect [148, 149].

For the direct covalent binding and fixation of AMPs on the surface of biomaterials, there are relevant studies on contact lenses. As a broad-spectrum AMP, melimine has good antibacterial activity. Melimine can be covalently combined to the surface of contact lenses by coupling with 1-ethyl-3-[3-dimethylaminopropyl] carbodiimide hydrochloride, so as to have antibacterial effect and reduce the occurrence of eye infection caused by wearing contact lenses [88, 89]. In addition to contact lenses, urinary catheters are also common medical devices and biomaterials in daily life. In order to solve the problem of urinary tract infection caused by the current use of urinary catheters, Yu et al. prepared AMP (C-terminal cysteine peptides E6) coating on PU (a common biomedical plastic used for catheter manufacturing) by using anti-viscosity hydrophilic polymer coating, so as to reduce the occurrence of urinary tract infection (Figure 5). Compared with catheters without AMPs coating, catheters with AMPs coating can reduce bacterial adhesion on the surface by more than 4 logarithms (from 1.2×10^6 to 5×10^1 CFU/ml), so as to effectively prevent infection. At the same time, the number of planktonic bacteria in urine was also inhibited by nearly 3 logarithms (from 1.1×10^7 to 1.47×10^4 CFU/ml) [90]. These advances can prolong the service life of urinary catheters and improve the experience of patients.

However, there are also some disadvantages of directly covalently binding AMPs to the surface of biomaterials. First, the activity of AMPs covalently fixed on the surface of the device is affected, and its antibacterial activity decreases

compared with free AMPs [150, 151]. Second, once the surface of medical devices is covered with proteins, dead cells, platelets, and dead bacteria, there is a physical barrier between AMPs and the bacteria to be killed, which will be difficult to play its antibacterial effect [146]. In addition, because AMPs is fixed on the surface of medical devices or biomaterials, its scope of action is limited, and it is difficult to effectively kill bacteria far away from the surface of medical devices or bacteria that have invaded surrounding tissues.

Researchers try to store AMP in antibacterial coating and fix it on the surface of medical devices to overcome the above shortcomings. When the medical devices are implanted or contact with the human body, AMPs can be released from the antibacterial coating and maintain a certain concentration in the surrounding tissues in the form of free AMPs, so as to kill the possible pathogenic bacteria. It is worth noting that in order to avoid bacteria escaping into the surrounding tissues and increase the difficulty of antibacterial, the release of AMPs needs to be rapid, stable, and lasting [152]. At present, AMPs have been applied to microporous calcium phosphate coatings [153], nanotubes [154], hydrogels [155], and polymer coatings [156]. For example, research has used hydrogel coating to store AMP HHC36 and control its release, so that titanium materials have the function of resisting *S. aureus*, *Staphylococcus epidermidis*, and other bacteria, thereby avoiding the damage caused by biofilm formation [91]. Of course, this method inevitably has some disadvantages. Although the release of AMPs can effectively kill the bacteria that may exist in the tissues around the medical device and effectively avoid the formation of biofilm, this effect is limited, because AMPs are difficult to produce an effect on internalized bacteria, so it is difficult to avoid the occurrence of infection characterized by intracellular bacteria. However, some scholars have tried to use cell-penetrating peptides combined with AMPs to treat intracellular bacterial infections [157, 158].

Infection related to medical devices has always been a major problem in modern medical and health undertakings. AMPs play an antibacterial role by forming PPC on the surface of biomaterials and effectively reduce the occurrence of infection. However, there are still many problems in the application of PPC in medical devices, which need to be studied and solved by researchers.

3.4. Other Applications of PPC in the Body. In addition to the three types mentioned above, PPC are used in the body in many other forms. In addition, the existence of PPC broadens the application of scenarios of AMPs, and these applications are not limited to only antibacterial applications like dental applications but also include tumor therapy, nerve repair and regeneration, and other applications.

PPC shows good anticancer potential. Under normal circumstances, neutral phospholipids, that is, phosphatidylcholines and sphingomyelins [159], are located in the outer leaflet of plasma membranes, whereas in cancer cells, the phospholipid phosphatidylserines (PS) are transferred to the outer leaflet rather than staying in the inner leaflet, making the outer plasma membranes negatively charged. For this reason, some AMPs selectively target cancer cells by binding to negatively charged PS located in the outer leaflet of plasma membranes of cancer cells [160]. Thereby, AMPs bind and destroy the cancer cell membranes mainly through electrostatic interaction [161, 162], so it is not easy to develop drug resistance. However, AMPs are easy to be degraded by protease in the process of *in vivo* treatment, and they are also easy to miss and cause side effects, so some improvements are needed [36–41], such as combining with polymers to synthesize PPC. At present, the main methods are: the PEGylation of AMP [163], using bacteriophage as the carrier of AMPs [164], encapsulating AMPs with liposome [73, 165], or using polymer nanoparticles to deliver AMPs to treat tumors [166]. For example, melittin has good anticancer activity, but due to its non-specific cytotoxicity and hemolytic activity, it is difficult to strike a balance between efficacy and safety. To this end, researchers have used self-assembling melittin–lipid nanoparticles (Figure 6) [92], perfluorocarbon nanoparticles delivery system [167], redox sensitive polymer-based nanocomplex [168], and other nanoencapsulation methods [37] to make melittin druggable and to exert its anticancer effect safely *in vivo*.

PPC is also used to help nerve repair and regeneration. Due to the stability and particularity of nerve cells, functional nerve repair and regeneration are a difficult problem. Trauma is a common cause of nerve injury, and the loss of connection between neurons and distal axons often makes nerve repair difficult. How to promote the regeneration of axons from proximal to distal and restore the damaged synapses has become the focus of nerve injury repair. In this process, it is not only necessary to avoid infection and inflammation but also to promote the remyelination of demyelinated myelinated nerve fibers or the repair of unmyelinated nerve fibers. Therefore, a good interaction between appropriate materials and regenerative cells is needed. This material should have many functions, such as antibacterial, inhibiting inflammation, forming tubular structure, and guiding nerve repair. Depending on the actual situation, it can also have the ability to recruit peripheral neural stem cells to differentiate into various cells to help nerve repair [169, 170]. How to develop a novel biomaterial with good bioactivity and biodegradation ability to promote the adhesion, proliferation, differentiation, and functionalization of nerve cells has become an important research direction. Positive charges are known to be involved in these cellular activities, and some positively charged AMPs provide cell-binding sites and positive charges to promote cell function through electrostatic interactions with anion sites of cytoplasmic membrane [171, 172]. Unlike other applications, AMPs applied for this scenario require long-term stability and constant density. With this in mind, the researchers developed several versatile poly(L-lysine) (PLL)-grafted hydrogels, which can promote attachment, proliferation, encapsulation, differentiation, and function regeneration of mouse neural progenitor cells (Figure 7) [93, 173]. Zhang et al. invented a 3D-printed self-adhesive bandage with drug release for peripheral nerve repair, which can tightly wrap the injured nerve, release the drug to the internal area, and promote nerve repair by improving the proliferation and

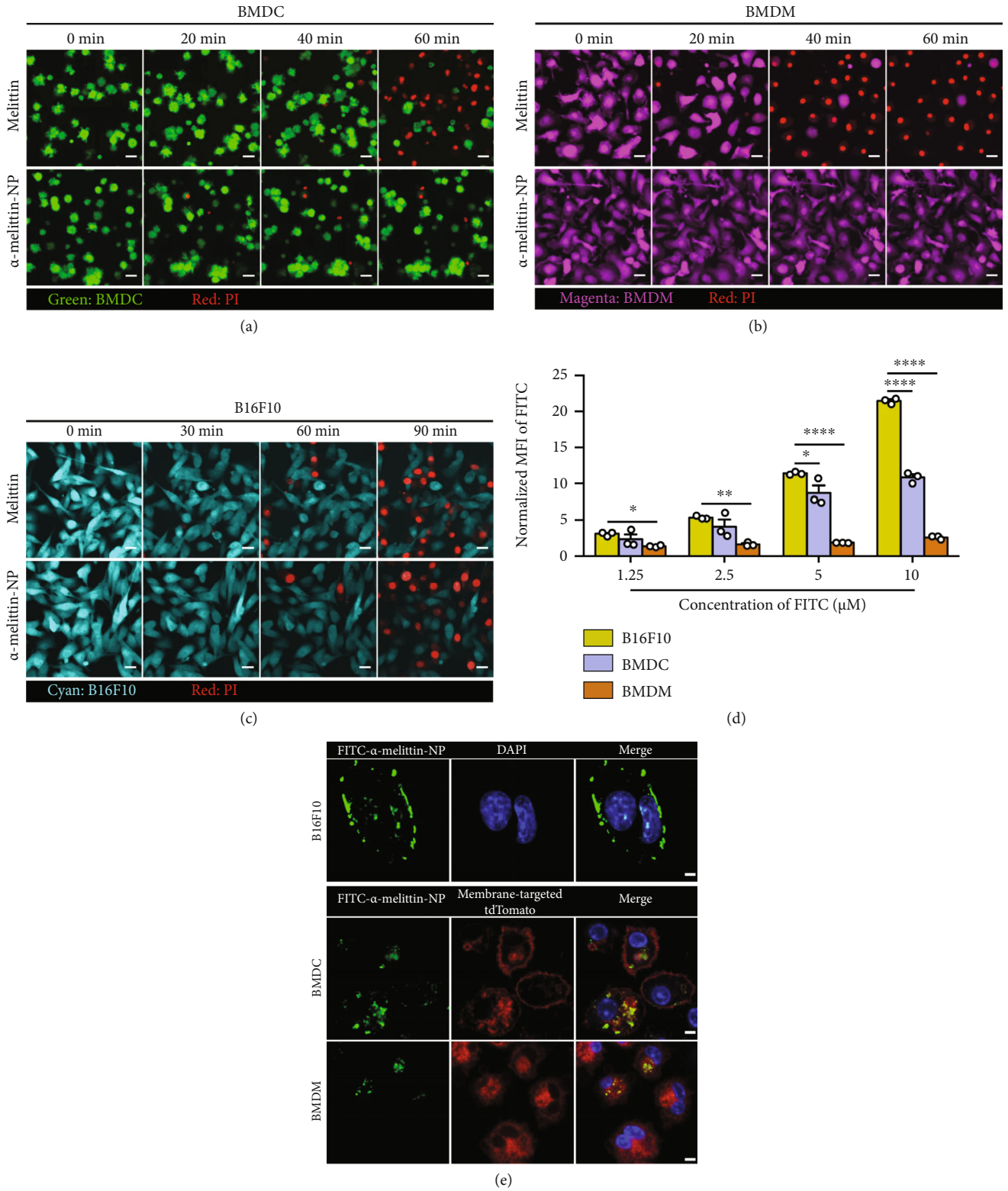


Figure 6: Cell viability of antigen presenting cells and B16F10 melanoma cells after exposure to melittin and α-melittin-NPs (nanoparticles). Real-time and dynamic imaging of (a) bone marrow-derived dendritic cells (BMDC), (b) bone marrow-derived macrophages (BMDMs), and (c) B16F10 cells after incubations with free melittin (5 μM) and α-melittin-NP (10 μM). Green: BMDC, magenta: BMDM, cyan: B16F10. Red indicates PI. All scale bars represent 10 μm. (d) Evaluation of cellular-binding ability by analyzing the MFI of FITC-α-melittin-NPs in B16F10 cells, BMDCs, and BMDMs (n =3 per group). Incubation time: 3 hours. MFI: mean fluorescent intensity. (e) Representative immunofluorescence imaging of cellular binding of FITC-α-melittin-NPs (10 μM) to B16F10 cells, BMDCs, and BMDMs. Incubation time: 3 hours. Blue: DAPI, green: FITC-α-melittin-NPs, red: membrane-targeted tdTomato. (Scale bar: 5 μm.) Reprinted with permission from ref [92]. Copyright 2020 Springer Nature.

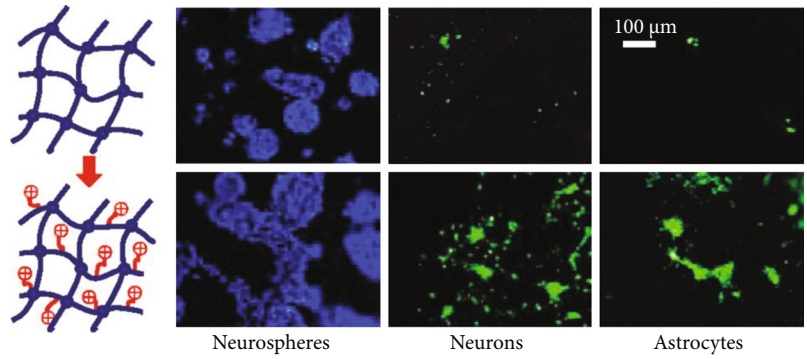


Figure 7: Polyethylene glycol diacrylate hydrogels modified by poly(L-lysine) promotes nerve cell function. Reprinted with permission from ref. [93]. Copyright 2012 American Chemical Society.

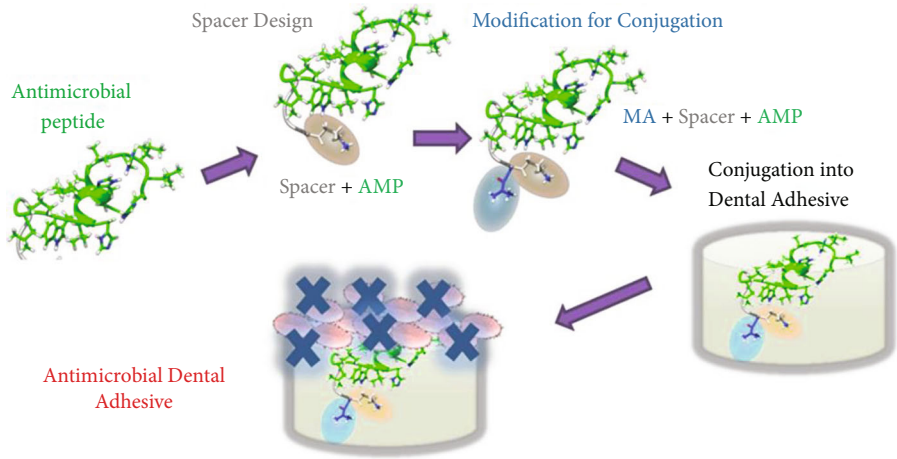


Figure 8: Methacrylate (MA)–AMP monomers are copolymerized into dental adhesives as AMP–polymer conjugates to form antimicrobial dental adhesive. Reprinted with permission from ref. [96]. Copyright 2020 American Chemical Society.

migration of Schwann cells. The scheme is suitable for combining with AMPs to form PPC and improve the antibacterial properties of the material [174].

Due to its rapid dilution and biodegradation, the application of AMPs in oral cavity is limited, whereas PPC has overcome the disadvantages of AMPs in dental application to some extent. For example, as a common dental disease, dental caries is often caused by bacterial infection and dental plaque formation [94]. Although AMPs can overcome resistance to traditional antibiotics to a certain extent and play an antibacterial effect, the actual effect is not ideal because it is difficult to maintain a certain threshold concentration in the oral cavity [42]. Therefore, PPC have been designed to construct antibacterial coatings on teeth [95]. For example, Zhang et al. have combined hydroxyapatite-binding diphosphoserine (DPS) domain with an AMP (polyphemusin) to create a new antibacterial coating for teeth to prevent and treat cavities [94]. In addition, this antibacterial coating has good stability in oral cavity, so it has a long-lasting antibacterial effect. As dental composite restoration materials are often re-destroyed by bacteria planted at the interface of the restoration, resulting in restoration failure, in addition to being used as a coating to prevent dental caries, PPC can also be involved in dental restoration. Xie et al. combined AMP (AMPM5) with monomers in dental adhesive formulation to form an adhesive system with good mechanical properties and antibacterial activity (Figure 8) [96]. In addition, this adhesive can treat secondary dental caries and enhance the durability of dental composite restorations.

3.5. Limitations of PPC. Even though PPC has been applied in many fields, there are still many problems and directions for progress in its research. First, there is currently no unified method to test the antibacterial properties of PPC, so it is difficult to directly compare their results in the face of different studies. How to reach a consensus on the test of antibacterial properties of PPC and formulate a set of unified test methods that can be compared horizontally is worthy of careful study. Second, at present, most of the studies on PPC are *in vitro*, there are relatively few *in vivo* studies, and there is a lack of data in human experiments. Due to the complexity of human internal environment, the actual efficacy of PPC still needs more data support. Therefore, more animal models and even clinical trials are needed to evaluate the feasibility of PPC *in vivo*. In addition, the current research on biocompatibility of PPC has great limitations. According to the guidance documents of FDA [175], the test indicators of biocompatibility include cytotoxicity, sensitization, hemocompatibility,

pyrogenicity, implantation, genotoxicity, carcinogenicity, reproductive and developmental toxicity, and degradation assessments. However, the current research mainly focuses on cytotoxicity and hemocompatibility, and is unable to more comprehensively evaluate the biocompatibility of PPC, and there is a lack of research on the possible long-term effects of PPC, such as genotoxicity, carcinogenicity, reproductive, and developmental toxicity. Apart from these, with the emergence of superbacteria caused by antibiotic abuse all over the world, how to better use PPC in combination with antibiotics to limit the occurrence of super drug-resistant bacteria and biofilm should be a research hotspot we need to consider. Extending from drug-resistant bacteria, we can also consider applying PPC to antifungal undertakings. Through the joint use of PPC and antifungal drugs, we can use their synergy to achieve the purpose of antifungal or use PPC with anticancer drugs to achieve the synergy of anticancer and antibacterial. Finally, at present, the research of intelligent antibacterial agents is a hotspot. We should consider how to use more appropriate ways or components to design PPC to realize its intelligent antibacterial effect at the treatment site, such as specific release when the tissue microenvironment reaches certain conditions, slow release, and gradual degradation with the progress of the disease. From what has been discussed above, these research directions put forward higher requirements for the design of functional polymers of PPC. For AMPs itself, its high synthesis cost limits the commercialization of AMPs. Research, develop, and design a new and convenient synthesis method to reduce the production cost of AMPs, which is conducive to the wider application of AMPs and PPC.

4. Conclusions

The existing countermeasures, including new antibiotics, antibiotic resistance blockers (ARB), and phage therapy, cannot effectively solve the problem of drug-resistant bacteria. Compared with them, AMPs destroy bacterial membrane through electrostatic interaction, can better regulate host immune response, and have relatively wide anti-biofilm activity, and the development of bacterial drug resistance is relatively lagging. In order to overcome the disadvantages of poor stability and high cytotoxicity of AMPs *in vivo*, researchers combined AMPs with functional polymers. Through coupling or polymerization, AMPs and functional polymers can form –PPC. In addition, PPC can obtain self-assembly ability through electrostatic interaction, van der Waals forces, and other ways to form a variety of different nanostructures, such as micelles, vesicles, and microspheres, so as to play different specific functions. In addition, the function of PPC is influenced by a variety of factors, such as the specific sequence of AMPs, or the properties of the functional polymers. In this study, we focus on the practical application of PPC from six aspects: wound dressing, bone tissue repair, medical device coating, tumor treatment, nerve repair, and oral application. For different specific applications, PPC can better adapt to different situations in practical applications by changing its composition and nanostructure. In view of the limitations and problems existing in the practical application of PPC, we believe that it is necessary to formulate a unified evaluation standard for antibacterial performance, carry out more comprehensive *in vivo* and clinical research, completely evaluate the biocompatibility index of PPC, consider the prospect of the combined use of PPC and other drugs, and realize the intelligent antibacterial effect of PPC. At the same time, AMPs should also be further studied and developed.

Data Availability

Data supporting this research article are available from the corresponding author or the first author on reasonable request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Xuqiu Shen: conceptualization, writing—original draft, writing—review & editing, and project administration; Yiyin Zhang: writing—original draft, writing—review & editing, and project administration; Qijiang Mao: writing—review & editing and project administration; Zhengze Huang: writing—review & editing; Tingting Yan: writing—review & editing; Tianyu Lin: writing—review & editing; Wenchao chen: writing—review & editing; Yifan Wang: supervision; Xiujun Cai: supervision; Yuelong Liang: supervision & conceptualization.

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