Materials Today Bio 19 (2023) 100586

Contents lists available at ScienceDirect

Materials Today Bio

journal homepage: www.journals.elsevier.com/materials-today-bio

Antibacterial coatings on orthopedic implants

Xionggang Chen [a], Jianhong Zhou [a,*], Yu Qian [a,**], LingZhou Zhao [b,***]

[a] Institute of Physics & Optoelectronics Technology, Baoji Advanced Titanium Alloys and Functional Coatings Cooperative Innovation Center, Baoji University of Arts and Sciences, Baoji, 721016, PR China
[b] Department of Stomatology, Air Force Medical Center, The Fourth Military Medical University, Beijing, 100142, PR China

ARTICLE INFO

Keywords:
Orthopedic implants
Antibacterial properties
Coatings
Infections

ABSTRACT

With the aging of population and the rapid improvement of public health and medical level in recent years, people have had an increasing demand for orthopedic implants. However, premature implant failure and postoperative complications frequently occur due to implant-related infections, which not only increase the social and economic burden, but also greatly affect the patient's quality of life, finally restraining the clinical use of orthopedic implants. Antibacterial coatings, as an effective strategy to solve the above problems, have been extensively studied and motivated the development of novel strategies to optimize the implant. In this paper, a variety of antibacterial coatings recently developed for orthopedic implants were briefly reviewed, with the focus on the synergistic multi-mechanism antibacterial coatings, multi-functional antibacterial coatings, and smart antibacterial coatings that are more potential for clinical use, thereby providing theoretical references for further fabrication of novel and high-performance coatings satisfying the complex clinical needs.

1. Introduction

With the aging of global population and increases in the prevalence of diabetes and other health problems, there have been more and more patients suffering bone defects caused by osteoporosis, sports injury, and accidents, seriously threatening human health and quality of life [1,2]. Accordingly, the demand for orthopedic implants has been increasing. It has been recently reported that there are more than 7.5 million implantations per year in the U.S. (e.g., joint, hip, fracture fixation devices, spinal). In 2018, the orthopedic implant market was valued at $46.5 billion [3]. And the global orthopedic implants market is predicted to reach $79.5 billion by 2030, almost two times the market value in 2019 [4]. Implant-related infections (IRIs) have been the most common and complex problem in clinical orthopedics [5], which are also the most common cause of implant failure. A rise in demand for orthopedic implants also increases the risk of IAIs. Infection rates range from 2 to 5% for primary implantation, and this can double following revision surgery [6,7]. Biofilm formation is the essential feature of IRIs, which is involved throughout the occurrence, development, prevention, and treatment of IRIs [8,9]. Once formed, biofilm is difficult to eliminate [10], finally resulting in chronic infections. Antibiotics as the traditionally most common strategy for treatment of infections are generally not effective for IRIs, because they cannot go into the biofilm. In addition, antibiotics may cause a series of problems such as cytotoxicity, and delayed bone regeneration. What's worse, the emergency of drug resistance and multi-drug resistance (MDR) may result from unreasonable antibiotic use, possibly leading to more severe infections [11–14]. As a result, implant replacement is frequently needed once IRIs occur. Besides further pain and economic burden, amputation or life-threatening consequences may occur in patients with serious IRIs.

It is necessary to prevent biofilm formation on the implant surface, among which endowing the implant with antibacterial properties is one of the important strategies [15,16]. Characterized by good surface properties and variable chemical structures, the surface coating technique can endow the implants with antibacterial properties to achieve efficient antibacterial effects, without affecting the overall material performance. Moreover, this technique can also improve the other surface properties required by the bone implants, such as wear resistance, scratch resistance, corrosion resistance, and suitable wettability. It is relatively easier to translate these techniques into clinical use as compared to other strategies [17,18]. Accordingly, the antibacterial coating techniques have attracted extensive attention recently, making it

* Corresponding author.
** Corresponding author.
*** Corresponding author.
E-mail addresses: shanxixian198001@163.com (J. Zhou), qianyu0272@163.com (Y. Qian), zhaolingzhou1983@hotmail.com (L. Zhao).

https://doi.org/10.1016/j.mtbio.2023.100586
Received 12 December 2022; Received in revised form 1 February 2023; Accepted 14 February 2023
Available online 15 February 2023

a remarkable field of research [19,20]. The exploitation of antibacterial coatings on implants has also motivated the progress of novel strategies to improve the implant. There are three major approaches for designing antibacterial coatings on the surface of orthopedic implants: anti-adhesion, contact-killing, and releasing-type [21]. The antibacterial cues have been expanded from antibiotics, low-molecular organic compounds, metal ions and nanoparticles, to natural or synthetic polymers.

It should be noted that the antibacterial surfaces should be biocompatible and bioactive since their main function is to form osseointegration. The surface of orthopedic implants should facilitate proper host cell adhesion and growth, while preventing bacterial adhesion and colonization. The balance between antimicrobial properties and biocompatibility is difficult to achieve because the surfaces that promote host cell adhesion are also helpful for bacteria that share some of the similar adhesive mechanisms as host cells [22–25]. The coatings that prevent infections *via* anti-adhesion or bacteria-repelling may also limit host cell adhesion and thus not facilitate integration with host tissues [26]. In addition, lacking bactericidal activity, the anti-adhesion or bacteria-repelling coating are inevitably contaminated once the bacteria break through the coatings during long-term use. For bactericidal coatings, they may be accompanied by the uncontrollable release of the bactericidal ions or antibiotics leading to possible toxicity [27]. Hence, in evaluating antibacterial coatings for orthopedic implants, it is urgent to comprehensively consider the design and mechanism of antimicrobial coatings to enhance antibacterial efficacy while maintaining biocompatibility and bioactivity as well as applicability in orthopedic implants [28,29].

In recent years, with the continuous development of material science and technology, especially biomaterials, diversified development has been achieved in the substrate materials of orthopedic implants. New ideas and new technologies for developing novel antibacterial coatings are emerging to hopefully prevent and treat IRIs, prolong the service life of implants, and better meet the patients' needs. In view of this, the research progress in antibacterial coatings on orthopedic implants in recent years was reviewed in this paper. The advantages and disadvantages of coatings based on different antibacterial mechanisms were clarified, and the further research direction was discussed with the focus on the synergistic multi-mechanism antibacterial coatings, multifunctional antibacterial coatings, and smart antibacterial coatings that are more potential for clinical use.

2. Infections associated with orthopedic implants

Ideal orthopedic implants should possess specific biological performances (e.g., biocompatibility, and bioactivity), and mechanical and chemical properties (e.g., hardness, durability, corrosion resistance, wear resistance and similar elastic modulus to that of human bones) [12,30,31]. While materials for orthopedic implants have advanced extensively, there are still a number of challenges and difficulties to overcome, such as infection and aseptic loosening which are deemed the major causes of failure of orthopedic implants [32,33]. In addition, the biocompatible and bioactive implant surface not only promotes the adhesion of host cells but also causes the adhesion and growth of microorganisms (bacteria) [34,35]. Infections in orthopedic implants are caused by bacterial adhesion and colonization acquired during surgery or the later functioning of the implants. It is inevitable that most implants will be colonized with bacteria [36]. Although tremendous advances in the quality of healthcare, the treatment of such infections remains a challenge [16]. At present, such infections are frequently treated with implant removal and replacement, which will increase the mental, physical, and economic pressure on patients [37,38]. Further, the infection may prolong patient suffering and another surgery may be needed for the implant to be removed. Acute and chronic infections can even result in death [39].

Bacterial adhesion, colonization, and growth into biofilms is the key cause of IRIs. Biofilms consist primarily of bacterial colonies and extracellular polymeric substances (EPS) such as polysaccharides, proteins, and deoxyribonucleic acid (DNA), with an extremely complex mechanism of formation. Generally, biofilm formation is divided into the following 5 stages [40–43]: (1) reversible bacterial adhesion, (2) irreversible adhesion, (3) initial biofilm formation, (4) biofilm maturation, and (5) release of toxins and free bacteria to start a new cycle of biofilm formation. In the first stage (initial bacterial adhesion), bacteria can freely crawl, gather, and stack on the surface of the implant, and at that time the bacterial adhesion is reversible. In the second stage, due to the specific and non-specific interaction between bacteria and the proteins adsorbed on the implant surface, proliferation and intercellular adhesion will start, and extracellular polymers will be gradually secreted, in which case the bacterial adhesion becomes irreversible, and the bacteria cannot move freely due to the restraint of secretions. In the third stage, bacteria constantly reproduce on the surface of the implant to form cell clusters of multilayers. Small colonies and water channel structures emerge, thereby initially forming the biofilm architecture. In the fourth stage, the small colonies further develop into large colonies, ultimately forming well-organized and intact three-dimensional (3D) matrix structures, i.e., bacterial biofilms [44]. In the fifth stage, with bacterial reproduction, the bacteria in the already formed biofilms are released and dispersed to prepare for new bacterial colonization and to start a new cycle, ultimately causing chronic infections.

It is difficult for the immune system or the antibacterial agents to effectively kill the bacteria in biofilms [45,46]. The sensitivity of bacteria in biofilms to antibiotics declines by about 1000 times as compared to that of planktonic ones. The antibacterial agents are easy to be blocked by EPS with poor permeability to biofilms [47–49]. Acidic and anaerobic conditions are generally present in biofilms, easily making antibacterial agents ineffective. What's more, the bacteria in biofilms also have tolerance to host immune responses, bactericidal agents, and disinfectants [50,51]. The bacteria in biofilms can reduce their metabolic rate, survive for a long time under an insufficient energy supply, and enhance their drug resistance and toxicity. Accordingly, the biofilms will become a chronic infection source [52], releasing toxins to directly harm the human body, and releasing dissociated bacteria to cause septicemia, toxemia, and bacteremia.

To sum up, the bacterial adhesion, colonization, and growth into biofilms on the surface of materials is the root cause of difficulty in treating IRIs. The key to solving IRIs lies in inhibiting bacterial adhesion and preventing bacterial biofilm formation on the surface of biomaterials. For antibiotics, the bacterial drug resistance is constantly enhanced and gradually evolves from single-drug resistance to MDR and even super-drug resistance, worsening the infections [53]. A variety of strategies have been presented by scholars in different countries to prevent bacterial adhesion and subsequent biofilm formation, most of which are based on coating design. The emphasis of research has shifted to the design of antibacterial coatings on the surface of implants to prevent IRIs [54].

3. Antibacterial coatings

3.1. Adhesion-resistant coatings

The root cause of IRIs is the initial bacterial colonization and adhesion and subsequent biofilm formation, the former of which is a key step in biofilm formation. Studies have revealed that bacterial adhesion on the surface of orthopedic implants is influenced with many factors. In the reversible adhesion stage, the bacterial adhesion is closely related to the surface hydrophilic/hydrophobic properties, surface energy, and electrical conductivity of materials. Regulatory films will be produced on the material surface due to non-specific adsorption of biomolecules such as proteins, which will mediate the bacterial adhesion ultimately forming biofilms. Therefore, tuning surface wettability and other physical and chemical characteristics of orthopedic implant materials to prevent

bacterial adhesion aboriginally are one of the important strategies for antibacterial coating development [55]. To this end, a large number of studies have been conducted.

Antifouling coatings on the material surface has become an important way to inhibit bacterial adhesion through steric exclusion [56]. In recent years, the immobilization of hydrophilic macromolecules on the surface of materials by surface grafting and layer-by-layer (LbL) self-assembly to construct the hydrophilic layer has become one of the most widely used strategies for resisting bacterial adhesion. Hydrophilic polymers represented by polyethylene glycol (PEG), zwitterionic polymer, hyaluronic acid (HA), and sodium alginate are characterized by strong activity and non-toxicity. They can be used to fabricate coatings with ideal water content, good hydrophilicity, and large exclusion volume, thereby effectively resisting bacterial adhesion on the material surface [57,58].

Among the antifouling strategies, surface modification by PEG is the most typical way. The hydrophilic groups of PEG can actively adsorb a large amount of water, thus forming a stable hydration layer, which can impede the adhesion of proteins and microorganisms [59]. The hydrophilicity of PEG, the dynamic movement of the PEG chains tethered to the surface, and the lack of binding sites make it difficult for bacteria and other microorganisms to adhere to the coating surface [60]. With the increase in PEG amount, the surface hydration reactivity is improved, and its bacterial adhesion resistant ability is also gradually enhanced, making PEG the most widely used antifouling material on the surface of orthopedic implants. For example, $PEGMA_{500}$-Phosmet and $PEGMA_{2000}$-Phosmer were coated on the surface of Ti6Al4V titanium (Ti) alloy by Cui et al. [61] using the affinity between phosphate groups and hydroxyapatite. It was proven that the adhesion rate of Staphylococcus epidermidis and Streptococcus mutans on the surface of the polymer coatings is less than 1%, displaying good bacterial adhesion resistant properties. In addition, $PEGMA_{500}$-Phosmet shows better responses to mouse osteoblast cells than $PEGMA_{2000}$-Phosmer and unmodified Ti alloy due to the grafted phosphate groups and the appropriate PEG brush length, which facilitate higher calcium deposition and fibronectin absorption. Thus, the coating possesses excellent application potential in the field of orthopedic implantation. PEGMA brushes were grafted by Chen et al. [62] on the silane coupling agent-activated Ti surface through surface-initiated atom transfer radical polymerization (SI-ATRP), and then surface functionalization with arginine-glycine-aspartate (RGD) was performed. It was verified that PEG-RGD brushes can not only effectively inhibit bacterial adhesion, but also facilitate osteoblast adhesion. Harris et al. synthesized dendrimer-like polymer coatings (PLL-g-PEG) on titanium surfaces with poly (L-lysine) and PEG and found they reduced the *Staphylococcus aureus* adhesion by 89–93% compared to titanium surfaces with no coating. It appears that bacteria-bacteria interactions were stronger than bacteria-surface interactions in the few bacteria that adhered to the surface. As such, the hosts' immune systems may be able to eliminate the bacteria before forming a biofilm and causing infections. Moreover, the coating also promotes the attachment, spread, and proliferation of fibroblasts and osteoblasts after it is functionalized with RGD [63,64]. Although PEG with good hydrophilic properties can achieve a good bacterial adhesion resistant effect, it has some inherent defects, e.g., it is prone to oxidative degradation in water environment, necessitating further improvement [65].

Zwitterionic polymers have greater surface hydration property and thus stronger anti-bacterial adhesion effect than the ion-free PEG. The polymer chains of Zwitterionic polymers have the same number of evenly distributed anionic and cationic groups at 1:1, whose isoelectric characteristics enable them to repel charged proteins and bacteria, thus showing excellent bacterial adhesion resistance. Cao et al. [66] argued that zwitterionic polymers Methacryloyl ethyl carboxyl betaine (CBMA) - and Sulfobetaine methacrylate ester (SBMA)-modified antibacterial coatings can prevent biofilm formation for a longer time *via* effectively inhibiting bacterial adhesion than PEG-modified coatings. Kang et al. [67] fabricated zwitterionic polymer coatings on the surface of hydroxyapatite materials based on the combination of calcium ions and phosphate monoester and found that the coating significantly reduces the adhesion of *Streptococcus mutans* on the material surface. Besides the steric hindrance of the hydration layer, the cationic groups such as quaternary ammonium salts, phosphorus, pyridine, and imidazole in the zwitterionic polymers can also kill bacteria, adding additional value to zwitterionic polymers as coating materials.

Due to the fact that polysaccharide not only can form coatings with a stable structure and a high hydration degree to effectively prevent bacterial adhesion, but also possesses excellent biological properties [68,69], such as biocompatibility, biodegradability, non-toxicity, and non-allergenicity. Polysaccharide coating and glycosyl biomimetic modification of implant materials is also an effective strategy to fabricate anti-adhesion coatings. For example, anionic polysaccharides such as hyaluronic acid (HA) can inhibit bacterial adhesion through electrostatic repulsion interactions, as most bacteria have negatively charged surfaces at physiological pH [70]. Researchers have paid lots of attention to mussel-inspired modification of polysaccharides in the last several years, which can endow polysaccharides with oxidation resistance, antibacterial property, bioactivity, and biological compatibility [71]. Many factors, such as polysaccharide adsorption and proteins involved in the process of adhesion may affect the inhibitory effect of polysaccharides on bacterial adhesion. In addition, the anti-adhesion mechanism of polysaccharides against bacteria needs more detailed study in the future [72].

Currently, hydrophilic polymer coatings able to inhibit bacterial adhesion due to their strong hydrophilic property have been widely studied on the surface of titanium implants [73]. However, *in vivo* experiments have proven that such hydrophilic surface coatings may also prevent cell adhesion, which is essential for osteogenesis and implant fixation [74]. Fortunately, the damaged cell functions can be restored or even improved by additional bioactive molecules such as sericin and RGD sequences while keeping good antibacterial ability [75]. The antifouling coatings may lack long-term stable bactericidal activity, as it was shown that bacteria will inevitably break through the hydration layer [76]. Hence, the long-term stability of the antifouling coatings needs special attention in the following studies. The common hydrophilic antibacterial coatings are shown in Table 1.

In addition to the above coatings, anti-adhesion coatings developed based on hydrophobic and super-hydrophobic surface characteristics inspired by self-cleaning surfaces such as sharkskin and lotus leaf in the nature have been increasingly studied [118]. For example, fluorine-containing polymer antifouling groups with low surface energy [119,120] have been applied to the fabrication of antifouling surfaces. Since such coatings can effectively resist the adsorption of pollutants such as proteins and bacteria, they have displayed strong anti-bacterial adhesion efficacy in the preclinical stage [121]. However, it is difficult for most of such coatings to completely resist bacterial adhesion, and their antibacterial effect is often unsatisfactory, especially in the complex *in vivo* environment containing multiple biomolecules. Bioinertness may be anticipated due to their protein adsorption resistant ability and protein adsorption is also crucial for host cell adhesion. In addition, their wear resistance also needs further improvement. Various common hydrophobic antibacterial coatings are shown in Table 2.

Other novel anti-adhesion strategies have also been explored, such as those based on the photocatalytic mechanism of TiO_2, CuO, ZnO, and other nano-metal oxides. Under light irradiation, a large amount of OH and O_2^- will be generated on the surface of metal oxides. When contacting these free radicals with strong chemical reactivity, the organic substances in microbes can be oxidized into carbon dioxide and water, thus displaying strong bactericidal ability. Among them, TiO_2 characterized by high oxidation activity, good chemical stability, no toxic and side effects on the human body, no pollution to the environment and low costs has attracted increasing attention in the antibacterial field [130,131]. For example, increasing the "spontaneous" hydrophilicity on the TiO_2 surface by direct ultraviolet irradiation can inhibit bacterial adhesion without affecting the osteogenic effect [132]. Jalvo et al. [133] studied the photooxidative damage of self-cleaning surface functionalized by

Table 1
Summary of common hydrophilic antibacterial coatings.

Type	Example	Antibacterial mechanism	Advantages and disadvantages
Hydrophilic polymer	PEG and its derivatives [77,78], polyhydroxypropyl methacrylate (PHPMA) [79], polyhydroxyethyl methacrylate (PHEMA) [80], poly (*N*-hydroxyethylacrylamide) (PHEAA) [81], etc.	The physical barrier is mainly formed by the interaction of spatial repulsion and surface hydration to reduce the adhesion of proteins and bacteria [82].	Advantages: Non-fouling and protein-resistant properties [83,84]. Excellent hydrophilicity contribute to the formation of a hydration layer [85]. Nanoparticles can be attached with PEG (PEGylation) to enhance their antibacterial properties [86–88]. Disadvantages: The non-biodegradable properties will cause it to accumulate in healthy cells' lysosomes [89,90]. Also, it can suffer oxidative damage in biological media and fluids, which restricts its use for long-term applications [91,92].
Zwitterionic polymer	Phosphatidylcholine type [93], carboxybetaine type [94], sulfobetaine type [95], sulfonium ion type (DMSP) [96], trimethylamine-*N*-oxide type (TMAO) [97].	Constructing a zwitterionic self-assembled monolayer, a zwitterionic polymer brush, and a hydrogel containing with zwitterionic groups [98–101].	Advantages: The charged species associated with zwitterionic appear even stronger hydration than PEG, which may enhance the antifouling properties [102,103]. Switchable surfaces can be made with zwitterionic materials that can shift between cationic, zwitterionic, and anionic states depending on the pH of the surrounding environment [104]. Zwitterionic can also be used in a variety of nanoparticulate coatings, including gold nanorods, silica nanoparticles, iron oxide nanoparticles, and so on [105–107]. Furthermore, cationic groups in zwitterionic polymers can kill bacteria by contact, adding additional value to zwitterionic. Disadvantages: The hydration layer will still rupture and cannot maintain hydrophilicity for a long time. Mechanical stability is lacking, and antibacterial activity is only sustained for a short period of time [108–111].
Polysaccharide	Hyaluronic acid (HA) [112], sodium alginate [113], agarose [114], etc.	It has good hydrophilicity with hydroxyl groups, can form a hydrogel structure with highly hydrated coating [115], and shows electrostatic repulsion [70].	Advantages: With excellent biocompatibility, biodegradability, and structural diversity, it can solve some key problems such as the poor biocompatibility of synthetic materials *in vivo* [116]. Disadvantages: Due to its high activity in the complex body fluid environment within the human body, it is prone to chemical reactions and loss of hydrophilicity [71,117].

Table 2
Summary of common hydrophobic antibacterial coatings.

Type	Example	Antibacterial mechanism	Advantages and disadvantages
Low surface energy coating	Polydimethylsiloxane [84], fluorinated polymers [122–124], etc.	Reduce the surface energy of the material and reduce the interaction between bacteria and the surface.	Advantages: Formation of a hydrophobic or superhydrophobic self-cleaning surface to effectively reduce or prevent the adhesion of bacteria and proteins. It is safe and will not cause pollution and side effects due to drug abuse. Disadvantages: There is usually limited duration of the anti-adhesion property. Bioinertness may be anticipated.
Bionic structure hydrophobic coating	Diamond functional coating [125], super anti-wetting nano coating [126], hierarchical nanostructured superhydrophobic antibacterial coatings [127], etc.	Formed the coating with microstructures and bionic structure inspired by self-cleaning surfaces such as sharkskin and lotus leaf in the nature [128]	Advantages: The bionic structure has certain mechanical properties and stability while enhancing resistance to bacterial adhesion. In addition, the surface can kill bacteria adhered to the surface effectively [129]. Disadvantages: Manufacturing bionic surfaces is a challenge for clinical application since physicochemical properties are critical parameters affecting their mechanical, chemical, and physiological stability [4].

TiO_2 photocatalytic nanoparticles to *Staphylococcus aureus* and *Pseudomonas putida*. After 2-h irradiation, it was found that the original hydrophobic surface is converted into a hydrophilic one. All irradiated samples loaded with TiO_2 induced cell membrane damage with a large amount of reactive oxygen species (ROS) produced in the cells, showing good antibacterial effect. TiO_2 nanotube coatings have a beneficial interplay with osteoblasts in addition to good antibacterial properties, which are of important significance in improving and promoting osseointegration, becoming a new direction for the development of anti-bacterial adhesion coatings in recent years [134,135].

Other strategies include the use of monolayer or multilayer film self-assembly, surface grafting or gelation, the preparation of biosurfactants and amphoteric microbes that resist bacterial adhesion, and hydrophobic/hydrophilic interpenetrating network hydrogels [136]. Interestingly, Dong et al. [137] combined the cell membrane and the implant surface using polyphenol layers [poly (tannic acid), pTA] as an intermediate to create controlled (patterned) and bioactive cell membrane coatings. To form the pTA coating on the surface of titanium, the substrates were first

immersed in a basic tannic acid solution to initiate tannic acid oxidative polymerization, and UV exposure was performed simultaneously to speed up this process. In the next step, the substrates coated with pTA were immersed in red blood cell membrane suspension (RBC). Ultimately, RBC's homogeneous membranes overlaid the PTA-coated substrate due to the strong interaction between the polyphenol coating and the membrane's biomolecules. The preparation process and mechanism are shown in Fig. 1. The coating, besides good anti-biofouling ability, can effectively prevent and control the non-specific adsorption of proteins (bovine serum albumin, fibrinogen, and lysozyme) and bacteria (*E. coli* and *S. aureus*). Studies have shown that the water contact angle (WCA) of the substrate material modified by pTA coatings declines from (78.83 ± 2.90)° to (47.00 ± 2.81)°, suggesting that pTA with many carbonyl groups observably improves the surface hydrophilicity. In addition, due to many hydrophilic heads of the phospholipid bilayer, the WCA further declines to (19.34 ± 2.23)° after the RBC membrane is coated on pTA (Fig. 2A). This coating with good hydrophilicity can help form a stable hydration shell in water environment, thereby resisting adhesion of proteins (Fig. 2B and C) and bacterial adhesion (Fig. 2D). The SEM images in Fig. 2D illustrate the nonstick properties of the coatings after incubation with *E. coli* and *S. aureus* for 24 h. It is believed that Ti-pTA-RBC is the best in resisting protein adsorption, and it is of great significance for developing anti-adhesion coatings. More importantly, Ti-pTA-RBC also has good biocompatibility and macrophage immunoregulatory capability. With high cell affinity of polyphenols, Ti-pTA-RBC coatings can be applied to different implants, so they have good prospects for clinical use.

Since no antibacterial agents and antibacterial drugs are used, and no chemical substances such as heavy metals and antibiotics are released during the antibacterial process, the anti-adhesion coatings are considered to be safe and will not cause pollution and side effects, so that complications may be effectively reduced. However, most of these coatings can only prevent bacterial adhesion to a certain extent but fail to inhibit the growth of pathogenic bacteria. The coating surface may become contaminated, and bacteria can continue to live and colonize on them to compromise its anti-adhesion properties [138]. In the complex environment containing multiple biomolecules in the human body, most of these coatings have no long-term stability. In addition, most anti-adhesion coatings may also have a detrimental impact on the adhesion and growth of normal human cells on their surface, thus impairing the tissue integration of orthopedic implants. Considering the demand for long-term use of orthopedic implants, it may be necessary to consider adopting methods that can kill bacteria or developing multi-mechanism antibacterial coatings combined with other antibacterial modes to achieve a more ideal antibacterial effect.

3.2. Contact bactericidal coatings

Using various antibacterial agents with bactericidal efficacy on the coating surface is also a common strategy for preparing antibacterial coatings on the surface of orthopedic implants, which destroy the cell membrane of bacteria *via* active substances in coatings, thereby inhibiting or killing the adhered bacteria. Contact bactericidal coatings are a method of killing bacteria in an “active attack” manner [139]. The bactericidal substance often is immobilized through covalent conjugation or physical adsorption in coatings and is not anticipated to be released from the coating surface, so a long-term bactericidal effect may be maintained theoretically. The antibacterial agents used in this respect range from natural biomolecules such as chitosan and antimicrobial peptides (AMPs) to synthetic chemicals such as quaternary ammonium compounds (QACs) [22,140].

Characterized by good biocompatibility, broad antibacterial spectrum, targeted specificity, and low drug resistance, AMPs are considered the most promising alternative to antibiotics [141], and one of the more promising measures for prevention and treatment of IRIs. It is generally thought that AMPs penetrate cell membranes or transport across cell membranes to attack bacterial cytoplasm mainly based on electrostatic adsorption on the bacterial surface, resulting in overflow of bacterial

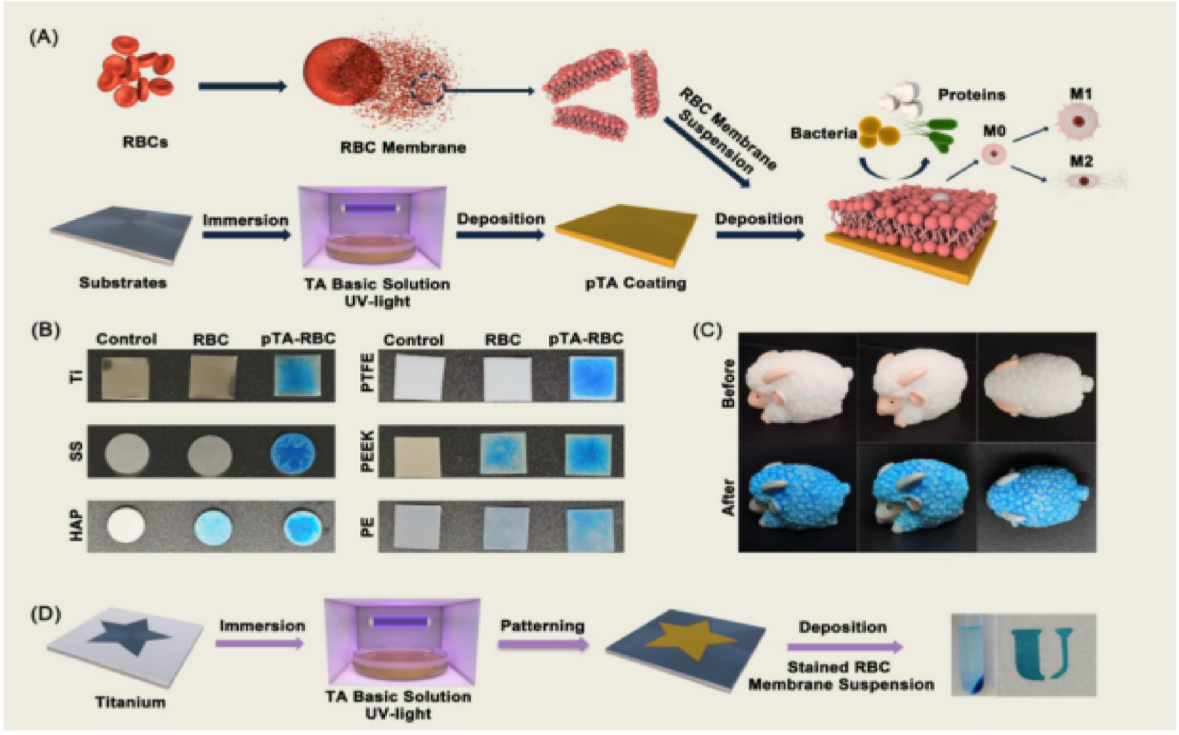

Fig. 1. (A) Schematic diagram of the fabrication process of the pTA-assisted cell membrane-based coating and its antifouling and macrophage immunoregulatory applications. Digital photographs of the DiD-stained cell membrane-based coating on the surface of (B) diverse materials and (C) irregular surface of a 3D model; (D) Schematic illustration of the patterning process of the coating and digital photographs of the DiD-stained RBC membrane used for patterning on a Ti substrate [137].

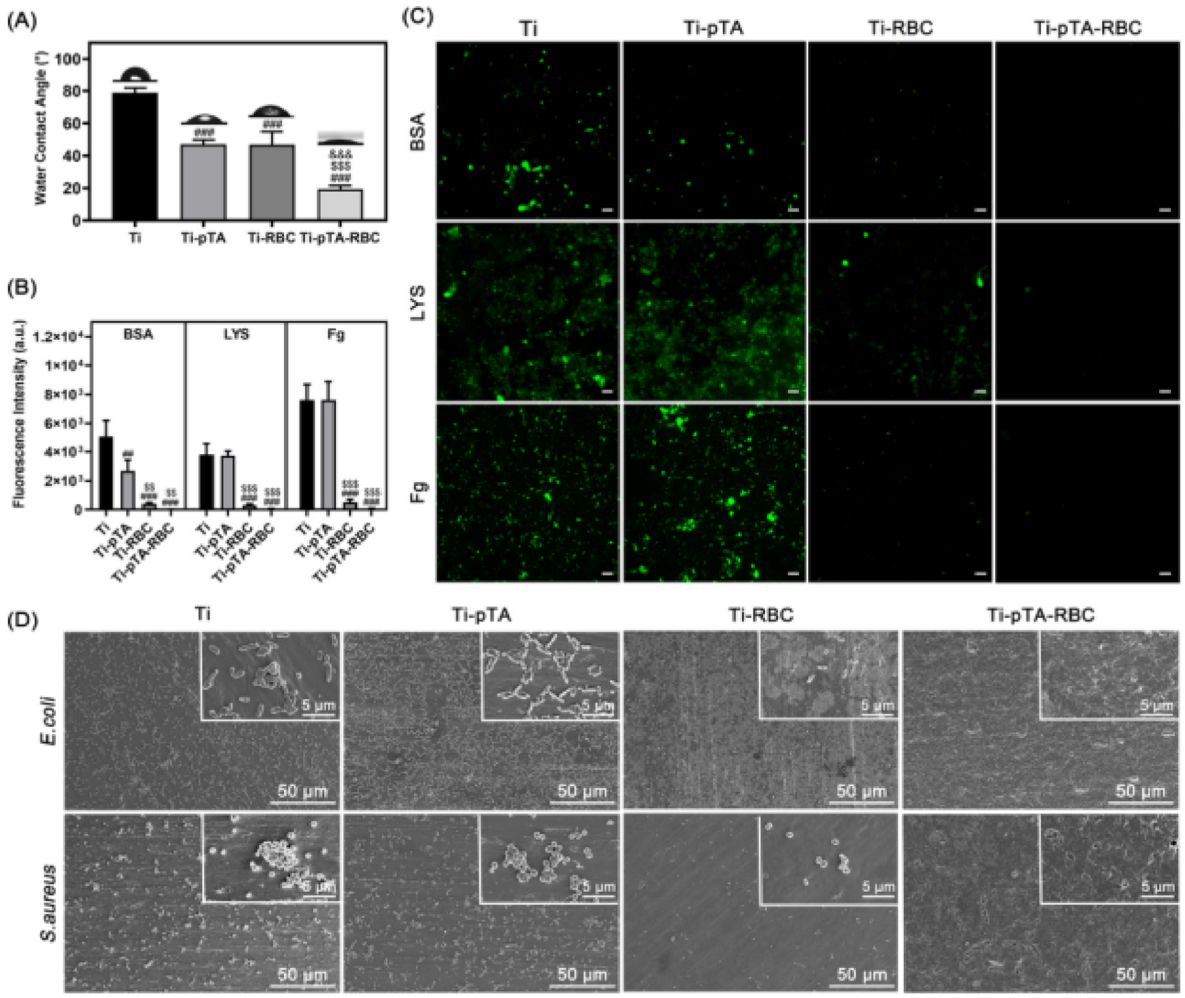

Fig. 2. Anti-biofouling performance: (A) WCA; (B) Fluorescence intensity; (C) Fluorescence images of anti-protein adsorption capacities [BSA, LYS, and Fg] (scale bar: 100 μm) ($^{\#}p < 0.05$, $^{\#\#}p < 0.01$, and $^{\#\#\#}p < 0.001$ *vs.* Ti group; $^{\$}p < 0.05$, $^{\$\$}p < 0.01$, and $^{\$\$\$}p < 0.001$ *vs.* Ti-pTA group; $^{\&}p < 0.05$, $^{\&\&}p < 0.01$, and $^{\&\&\&}p < 0.001$ *vs.* Ti-RBC group); (D) SEM images of the antibacterial (*E. coli* and *S. aureus*) abilities [137].

contents and bacterial death [142]. Due to such a rapid and non-specific antibacterial mechanism, bacterial drug resistance is relatively low, especially for synthetic AMPs [143,144]. Moreover, AMPs are effective against some super-bacteria that have developed great resistance to antibiotics [145]. Chen et al. [146] immobilized AMPs on the Ti-based surface *via* grafted PEG chains, with a grafting density of AMP up to (897.4 ± 67.3) ng/cm^2. The results showed that the antibacterial rate against *Staphylococcus aureus* and *Escherichia coli* was 90.2% and 88.1%, respectively. After 7-d degradation, 78.8% of *Staphylococcus aureus* can still be killed, with almost no cytotoxicity. Van et al. [147] used recombinant protein polymer obtained by biotechnology to directly immobilize AMPs on the Ti alloy surface. It was found that under dynamic biofilm culture conditions, this antibacterial coating still exhibits excellent antibacterial activity with good cell compatibility and low toxicity to mammalian cells. However, AMPs have relatively high costs and great instability during the preparation process [148,149], and their performance can be easily affected by the human body environment. In addition, the positive charge and hydrophobic group in coatings can facilitate the non-specific adsorption of proteins, greatly weakening the antibacterial effect of AMPs [150]. What's worse, it may not be possible to distinguish the membrane of normal cells and bacteria, thus greatly destroy the cell membrane.

Quaternary ammonium compounds (QACs) were found to be potential contact-killing antimicrobial materials for orthopedic implants and have drawn much interest since they have a broad antibacterial spectrum and low toxicity [151,152]. Its antimicrobial properties are attributed to its long lipophilic-C18H37 alkyl chain, which penetrates the walls and membranes of bacterial cells, causing autolysis and cell death of bacteria on contact [153]. Deb et al. [154] synthesized a dimethyacrylate quaternary amino iodine monomer and incorporated it as a comonomer in acrylic bone cement. Results indicate that bone cement has a broad range of destructive antimicrobial contact properties against *E. coli* and *S. aureus*. The antibacterial monomer works by eliminating bacteria by contact without releasing bioactive agents. Based on a large number of QA functionalities, Abid et al. [155] synthesized quaternary ammonium dendrimers of tripropylene glycol diacrylate (TPGDA) and demonstrated their potential efficacy as antimicrobial agents in bone cement. It can kill common hospital-derived bacteria such as *E. coli*, *S. aureus* and *P. aeruginosa* through contact with sustained bactericidal activity for 30 d. According to the MTT assay, the modified bone cement was not significantly cytotoxic. Thus, TPGDA is promising for clinical antimicrobial activity without sacrificing its mechanical properties. Similarly, quaternary ammonium polyethyleneimine (QPEI) nanoparticles have also been utilized to enhance the antimicrobial activity of bone cement because they possess positive antimicrobial activities and biosafety. Beyth et al. [156], found a strong antibacterial effect after aging for four weeks compared with bone cement without additives. In addition, the biocompatibility properties of bone cement were not affected by QPEI nanoparticles. Using QACs and adamantane, Wei et al. [157] developed a regenerative antibacterial coating that killed *S. aureus* and *E. coli via*

direct contact. Moreover, they found that the bactericidal activity of Ada-containing multilayer surfaces could be achieved by incorporating new QACs. However, it should be noted that QACs with positive charge also cause damage to mammalian cells. For good biocompatibility, it is necessary to control the modification amount, which makes the use of QACs more precise and safe.

Chitosan is a natural cationic polysaccharide with good biocompatibility and no cytotoxicity, whose positively charged amino groups can generate electrostatic interactions with negatively charged bacterial cell membranes, thereby altering the permeability of cell membranes and causing the lysis and death of bacteria. It has also been found that the metal chelation and water solubility of chitosan can also exert antibacterial effect, and the higher water solubility corresponds to the better antibacterial effect of chitosan and its derivatives and the stronger anti-adhesion ability of coatings [158]. Therefore, chitosan is expected to be a practical agent for preventing biofilm formation on the surface of orthopedic implants. Peng et al. [159] assessed the effect of hydroxypropyltrimethyl ammonium chloride chitosan (HACC) at three different component concentrations (6%, 18%, and 44%) in preventing biofilm formation on the surface of Ti implants by *in vitro* tests, and found that the three kinds of HACC, especially the latter two, can significantly inhibit the biofilm formation on the surface of Ti implants compared with control group, and also exert an effective therapeutic effect on previously formed mature biofilms.

In addition to AMPs, chitosan, and QACs, a variety of natural or synthetic antibacterial compounds, such as antibacterial enzymes and *N*-halamines, have also been applied to develop antibacterial coatings. However, whether the antibacterial coatings of natural or synthetic compounds can continuously remain stable *in vivo* and persistently exert an antibacterial effect remains to be clarified. Readers may refer to other reviews [160,161] for more information about antibacterial polymers.

Besides the above summarized contact-killing coatings with agents, new methods have been reported in recent years for creating contact-killing surfaces based on nanomaterials. Nanomaterials special in size and structure offer new directions for developing high-efficiency antibacterial coatings with enhanced biocompatibility. Nanomaterials with a diameter smaller than the mean size of bacteria (0.5–2 μm) can penetrate the cell membrane into bacteria to destroy the normal life activities of bacteria, achieving a bactericidal effect. They are demonstrated to resist common bacteria and drug-resistant bacteria, and effectively inhibit and eliminate biofilms [162,163]. For example, graphene materials can not only induce damage to bacterial cell membranes by oxidizing reduced glutathione in bacteria but also disrupt the integrity of bacterial cell membranes through the sharp nano-edges from graphene nanowalls or nanosheets, leading to pore formation and cell death [164]. Drawing inspiration from unique topographies studied in nature, numerous nanopillars, nanowires, and nanoblades have been developed to exert contact bactericidal effects [165,166]. In a recent study, Pandit et al. [167] found that arrays of graphene flakes grown perpendicularly to the surface by plasma-enhanced CVD can effectively prevent the formation of bacterial biofilm. By electron microscopy, it is revealed that the exposed edges of vertically aligned graphene flakes penetrate the bacterial membrane and drain the cytosol contents. According to them, graphene's orientation to the coated surface is the most significant factor for its contact-killing effect. It has been demonstrated that particles with a height of 60–100 nm are effective in killing bacteria while remaining completely harmless to mammalian cells. Ye et al. [168] prepared a ZnO nanorods-patterned coating on the Ti-based orthopedic implants, which exhibits intense bactericidal activity against adhered *S. aureus in vitro* and *in vivo*. According to the study, ZnO nanorods generated mechano-penetration and ROS, contributing significantly to killing adhered bacteria. Since the adhesion force of the bacterium to its underlying nano-stems continues to increase with time, the dominant bactericidal mechanism is believed to be mechano-penetration. Han et al. [169] have designed three arrays of Al_2O_3-wrapped nanorods. It was found that the difference in antibacterial activities was related to nanorod top sharpness rather than nanorod length, and the top-sharp nanorods were able to puncture S aureus with a 96% bactericidal effectiveness. A critical upper conic angle of 138 is identified for nanorods capable of perforating *S. aureus* from a finite element simulation. Moreover, the network of patterned nanorods has a favorable capacity for *in vitro* proliferation of rat bone marrow mesenchymal stem cells (rCSBMs). It shows a strong bactericidal activity in rat tibias infected with *S. aureus* by mechanical puncture activity.

Compared to adhesion-resistant coatings, contact bactericidal coatings can kill pathogens to restrain the development of bacterial infections. At present, great progress has been made in the research on such coatings in orthopedic implants, but many limitations are still present in their actual clinical use. On the one hand, contact-killing coatings can only kill bacteria that adhere to and make direct contact with the surface. With the accumulation of killed bacteria and intracellular components, active functional groups might be covered and the binding sites for subsequent biofilm formation are provided [170]. Once a barrier is formed between the functional surface and bacteria, the bactericidal effect is weakened [4]. On the other hand, it is difficult for bactericidal agents to kill all local bacteria, with a risk of drug resistance. In addition, long action time or high concentration is required for some bactericidal components to exert a good antibacterial effect, and bactericidal agents (as well as potential degradation products) may also cause some side effects on normal cells and tissues. Although some progress has been made in these antibacterial coatings, the focus is mostly placed on the short-term antibacterial property and a long-lasting antimicrobial activity for months or even years following surgery is still a major challenge. The stability of the coatings is crucial since their antibacterial effect is premised on the structural integrity of the coating and the tight connection to the implant surface.

3.3. Releasing-type antibacterial coatings

Another strategy for bactericidal antibacterial coatings to exert their efficacy is to load the antibacterial agents (e.g., antibiotics, nanoparticles, metal ions, and their oxides) into the implant surface coating and then release them ideally in a controlled mode. Coatings of this type can release bioactive agents at therapeutic doses to kill bacteria close to or far away from the surface. With the coating as a carrier, the antibacterial agent can be gradually released into the physiological environment through the diffusion and dissolution/degradation of molecules in the coating and the rupture of bonds between the coating and the antibacterial agent, thus achieving bactericidal effects *via* localized high concentration antibacterial agent [171–174]. Since the initial 24 h are the most critical period for biofilm formation, in most cases, successful resistance to biofilm colonization can be achieved when the antibacterial agent is released within a short period of time. This may be more effective in alleviating the infections associated with orthopedic implants compared to the coatings utilizing contact sterilization mode. Obviating systemic toxicity related to the antibacterial agent and usually displaying satisfactory antibacterial effect, releasing-type antibacterial coatings serve as a promising approach for preventing and treating IRIs [175,176].

3.3.1. Antibiotics releasing antibacterial coatings

Antibiotics that are important in preventing and treating infections associated with orthopedic implants and biofilm formation have been used as antibacterial agents in antibacterial coatings, including penicillin, chlortetracycline, streptomycin, vancomycin, and daptomycin [177]. As the most representative bactericidal agents, antibiotics have been essential for orthopedic implants for nearly a century. It is pertinent to note that systemic administration of antibiotics can have many potential disadvantages, including a relatively low level of drug concentration at the target site and possible systemic or organ-specific side effects. High efficacy can be achieved when antibiotics are administered to implant sites at high local doses without causing systemic toxicity.

Initially, Buchholz et al. [178] introduced polymethylmethacrylate (PMMA) bone cement with antibiotics as a local antibiotic prophylaxis prior to total joint replacement. Afterwards, some researchers loaded antibiotics onto titanium implants with porous hydroxyapatite (HA) coatings [179,180]. *In vivo* testing demonstrated that antibiotic-loaded hydroxyapatite coatings were significantly better in preventing infection than those that were not loaded with antibiotics, but there are still many unresolved issues pertaining to the optimal release kinetics and methodology for antibiotic inclusion in HA coatings [181]. Popat et al. [182] developed titanium nanotubular arrays that loaded gentamicin. They investigated gentamicin release kinetics from these nanotubes as well as their effect on *Staphylococcus epidermis* adhesion. It appears that the coating effectively decreases bacterial adhesion on the surface without compromising biocompatibility. Even so, gentamicin was still released too rapidly, and it will be completely released by soaking in phosphate buffer saline (PBS) for 50–150 min.

During a study by Antoci [183], vancomycin was covalently attached to a titanium alloy surface and the antibiotic derivatization can inhibit bacterial colonization and biofilm formation. The structure is stable and maintains its activity even when challenged multiple times. Similarly, layer-by-layer self-assembly coatings have also been proven to significantly slow the release of antibiotics [184,185]. However, the elution kinetics of antibiotics from the coating are still very fast, making it difficult to translate this method easily into the clinic [186]. In fact, there are a range of problems involved in the use of antibiotics in bactericidal coatings [187–189]. For example, a question is whether the bacteria around the implant are susceptible to antibiotics, and there has been some evidence that antibiotic-resistant bacteria can grow around implants [190], so picking the most effective antibiotic for coating preparation is crucial. IRIs are often accompanied by bacterial biofilms that can become resistant to antibiotics, resulting in prolonged infections [191, 192]. So far, the spread of antibiotic-resistant bacteria, such as methicillin-resistant *Staphylococcus aureus*, and vancomycin-resistant enterococci, has led to an increase in global morbidity and mortality. Also, the antibiotic-loaded coating should release the antibiotic within the effective concentrations, and then the antibiotic release should terminate immediately to avoid the development of antibiotic-resistant strains. While, it has been reported that gentamicin residue can still be detected five years after surgery in the tissue surrounding the antibiotic-loaded cement prosthesis which greatly increases the risk of resistant bacteria development [193]. Additionally, studies have shown that certain antibiotics compromise cellular function, despite antibiotics being considered highly biocompatible.

3.3.2. Metal ions releasing antibacterial coatings

While antibiotic-loaded coatings are associated with the risk of antibiotic resistance, alternatives without antibiotics become more appealing. Metal ions and metal oxides are commonly used in the releasing-type bactericidal coatings *via* loading in TiO_2, graphene, antibacterial polymers, etc. For example, well-known Ag^+, which can kill a variety of different bacteria, is a broad-spectrum antibacterial agent that is less likely to cause bacterial resistance. It is generally argued that the antibacterial mechanisms of Ag^+ involve such aspects as destroying the integrity of bacterial cell walls or cell membranes, inducing ROS, and inhibiting the bacterial metabolic process [194]. Since Ag^+ can kill Gram-positive and Gram-negative bacteria and even the drug-resistant bacteria, exert a long-lasting antibacterial effect, rarely cause bacterial drug resistance, and show no detrimental effects on the activity of osteoblasts used in lower dose, it has been well applied to various orthopedic implants. Jia et al. [195] developed a porous titanium scaffold entrapped in silver. After a 6-week durability test, strong yet sustained sterilization effects were achieved against both planktonic and adherent *S. aureus* bacteria. Researchers suggested that one of the antimicrobial properties was due to the durable topical Ag^+ release (a burst of 9.9% of total silver content was released initially, followed by steady release, with 40.6% remaining at 42 days).

Incorporating of Ag nanoparticles into polymer coatings to prepare nanocomposite antibacterial coatings is considered a practical method. Xie et al. [196] developed a coating consisting of HA, AgNPs, and CS on titanium implant. With polydopamine, they managed to prevent the fast release of silver ions, and the results were 91.7%, 89.5%, and 92% effective against *S. aureus*, Sepidermidis, and *E. coli*, respectively. Schlaich et al. [197] developed a mussel-inspired coating containing silver nanoparticles, which reduced bacterial attachment to the surface by >99.99%, but the release data showed that the coating was only capable of releasing silver ions for a short period of time (<7 days). In addition, methacrylate thermoset is a type of biomaterial commonly used in orthopedics. According to Bumgardner et al. [198], a nanocomposite coating composed of 1-deoxylactit-1-yl chitosan (Chitlac) and AgNPs was successfully designed based on methacrylate thermosets. A sufficiently high level of silver released at the beginning can effectively kill bacteria to prevent the development of resistant pathogens. It was observed under physiological conditions that silver was released slowly over time. Although the silver concentration decreased after 3 weeks, there was still effective protection against bacterial colonization, which may be explained by residual silver. Due to the special nanometer effect, however, nanoparticles tend to agglomerate and are difficult to uniformly disperse, seriously weakening their antibacterial effect. Therefore, how to effectively realize the uniform dispersion of nanoparticles in polymer substrate is still a difficult problem to be solved. To address this problem, researchers have also adopted surface modification and *in situ* generation of nanoparticles [199–204], but most of the methods involved are complicated and introduce other redundant substances, potentially harming the clinical use, and it is still difficult to achieve uniform dispersion in the real sense. Therefore, more effective and environmentally friendly methods that can realize uniform dispersion of metal nanoparticles remain to be studied. Among them, it is promising to design appropriate ionic ligands to achieve uniform dispersion of nanoparticles through electrostatic interactions with nanoparticles.

Though Ag loading biomaterials are widely studied, the close contact between silver-coated implants and bones raises concerns about the potentially harmful effects of Ag^+ entering bone and surrounding soft tissues [205]. In addition, bone healing following implantation of the implant is characterized by complex interactions among multiple cells and osteoconductive properties of materials, all of which might be influenced by Ag^+. Cytotoxicity may result from high-concentration Ag^+, and silver intolerance and Ag^+ allergy, although rare, may bring about safety problems. Moreover, the long-term impact of Ag^+ coatings on the metabolic status of adhered bacteria needs further study. Due to all the above problems, the use of Ag^+ releasing coatings is restricted to a certain extent [206,207].

Similarly, Zn^+ and Cu^+ are also metal ions commonly used in antibacterial coatings, which also display excellent antibacterial performance due to their ability to penetrate and destroy bacterial cell membranes. As reported, Zn^+ can also stimulate the proliferation and mineralization of osteocytes and contribute to the deposition of calcium in mesenchymal stem cells (MSCs), without inducing cytotoxicity [208]. Moreover, Zn is an essential trace element for multiple steps in bone formation and plays a positive role in enhancing osseointegration. According to Chu et al. a composite coating loaded with Zn/Ag was prepared by plasma immersion on the basis of titanium alloy loaded with Ag nanoparticles. Excellent antimicrobial ability was observed *in vivo* and the micro-CT and histological results reveal notable osseointegration. In addition, the calculation and simulation analysis showed that in the Zn/Ag composite coating, Ag nanoparticles can form a micro-current between Ag nanoparticles and Zn^{2+}, resulting in rapid release of Zn^{2+}, to produce the early antibacterial effect, while Ag^+ has a slow release effect, serving the long-term antibacterial effect [209]. Using a sol-gel method by spin-coating, Shen et al. [210] fabricated Zn-incorporated coatings on Micro-Ti and found that the Zn-incorporated samples (Ti–Zn0.08, Ti–Zn0.16, and Ti–Zn0.24) efficiently inhibited the adhesion of both Gram-positive (*Staphylococcus aureus*) and Gram-negative

(*Pseudomonas aeruginosa*) bacteria. The Ti–Zn0.16 sample was able to stimulate osteoblast proliferation as well as osteoclast differentiation *in vitro*. Furthermore, the Ti–Zn0.16 implant was efficient in promoting new bone formation *in vivo* after implantation for 4 and 12 weeks. Through plasma electrolytic oxidation, zinc was incorporated into TiO_2 coatings, according to Hu et al. [211]. In the antibacterial studies, results indicate that the coatings extremely inhibited the growth of *Staphylococcus aureus* and *Escherichia coli*, and their ability to inhibit bacteria can be improved by increasing the Zn content in the coatings. Zn-incorporated coatings were also demonstrated to significantly enhance the adhesion, proliferation, and differentiation of MSCs and no cytotoxicity was observed on any of the TiO_2 coatings. As well, MSCs exhibit an advanced level of alkaline phosphatase activity on the coating and are induced to differentiate into osteoblasts. According to the author, a significant reason for the excellent capabilities of the coatings is the ability to release Zn ions continuously and slowly. Similarly, in the study of Huo et al. [212], titania nanotubes (NTs) incorporated with zinc (NT-Zn) coatings are formed using anodization and hydrothermal treatment in Zn solution. NT10-Zn1, NT10-Zn3, NT40-Zn1, and NT40-Zn3 have total Zn contents of 1.2, 11.4, 3.4, and 60.2 mg, respectively as displayed in Fig. 3A, and then the Zn release kinetics was determined after immersing the samples in 5 mL of PBS for a month (Fig. 3B). Results showed that NT10-Zn1 and NT40-Zn1 released relatively small amounts of Zn (About 0.01 ppm Zn is detected on the first day, and nearly no Zn is detected one month later). By comparison, NT10-Zn3 delivers more Zn, while NT40-Zn3 generates the greatest amount. On the first day, Zn releases from NT40-Zn3 were 0.06 ppm and 0.05 ppm, respectively, and decreased rapidly over time. As a consequence, the antibacterial effectiveness of NT-Zn samples declines with time, in line with the Zn time-release profile (first a large amount of Zn is released, followed by a gradual decline over time). Particularly, NT40-Zn3 showed excellent antibacterial effects since its larger Zn loading capacity and increased Zn release. The optimal nanostructure of NT40-Zn3 also stimulates protein deposition enhancing cell function and Zn release, thereby enhancing osteogenic differentiation of MSCs.

As an essential trace element in many organisms, Cu is harmless to the environment and low-cost, and it adheres to the bacterial cell membrane in the form of Cu^{2+} and Cu^{+}, which can not only inhibit the breeding of a variety of bacteria and efficiently kill some drug-resistant bacteria, but also destroy ROS generated by cells and interfere with their proteins and lipids [213]. Besides, Cu can, through increasing the expression of vascular endothelial growth factor (VEGF), promote osteogenesis, so it has good prospects for use in antibacterial coatings of orthopedic implants. Liu et al. [214] immobilized Cu nanoparticles capable of killing bacteria on the surface of porous microstructural PEEK using the magnetron sputtering technique and confirmed that Cu nanoparticles can induce polarization of most macrophages and enhance the ability of macrophages to phagocytose *Staphylococcus aureus*, thereby increasing the antibacterial effect. Song et al. [215] demonstrated GO-Cu and GO-Cu-GO coatings through spin coatings and chemical in-situ methods. As a result, *E. coli* and *S. aureus* grew well on the pure GO coating, but their growth was significantly inhibited by the GO-Cu and GO-Cu-GO coatings. Pure GO coatings were found to support *E. coli* and *S. aureus* growth, while the GO-Cu and GO-Cu-GO coatings were significantly inhibitory. Also, the two coatings showed no evident toxicity when compared to the SiO_2 control in adhesion, viability, and proliferation tests on bone MSCs. GO-Cu coatings offer excellent antibacterial properties and high biocompatibility, making them suitable for use in biomedical implants.

Mg^{2+} with good antibacterial properties has also been applied to implants. Robinson et al. [216] believed that Mg^{2+} raises the pH value at the implantation site, altering the microenvironment of bacteria to exert an antibacterial effect. However, this view was revised by Wetteland [217] who thought that the improvement of antibacterial properties is attributed to the synergistic effect of multiple factors rather than regulation on pH only. Meanwhile, researchers developed composite coatings based on the synergistic effect of various antibacterial metal ions to further enhance the antibacterial effect. For example, Peng et al. [218] prepared PEO/Mg–Zn–Al layered double hydroxide composite coatings on the surface of Mg alloy, which not only possess excellent corrosion resistance but also enhance both antibacterial ability and osteogenic capability, having broad application prospects in orthopedic implants.

Besides, metal oxides (e.g., TiO_2, CuO, and ZnO) have also been widely introduced into the fabrication of antibacterial coatings [219–221]. For example, Li et al. [222] deposited a nano-ZnO film on the surface of 3D porous iron scaffolds using the atomic layer deposition technique, and then they found that the ZnO@Fe scaffolds display extremely strong antibacterial ability against both Gram-positive and Gram-negative bacteria and provide a better environment for cell adhesion, without affecting the cytocompatibility of porous scaffolds. In addition, the ZnO film greatly reduces the degradation rate of the scaffolds. Mantecca and co-workers [223] reported that sonochemically prepared CuO and ZnO nanoparticles exhibit highly crystalline structures after heat treatment, leading to higher ROS generation activity and thus stronger antibacterial performance than commercial metal oxides. Generally, metal ions/oxides antibacterial coatings are excellent in heat

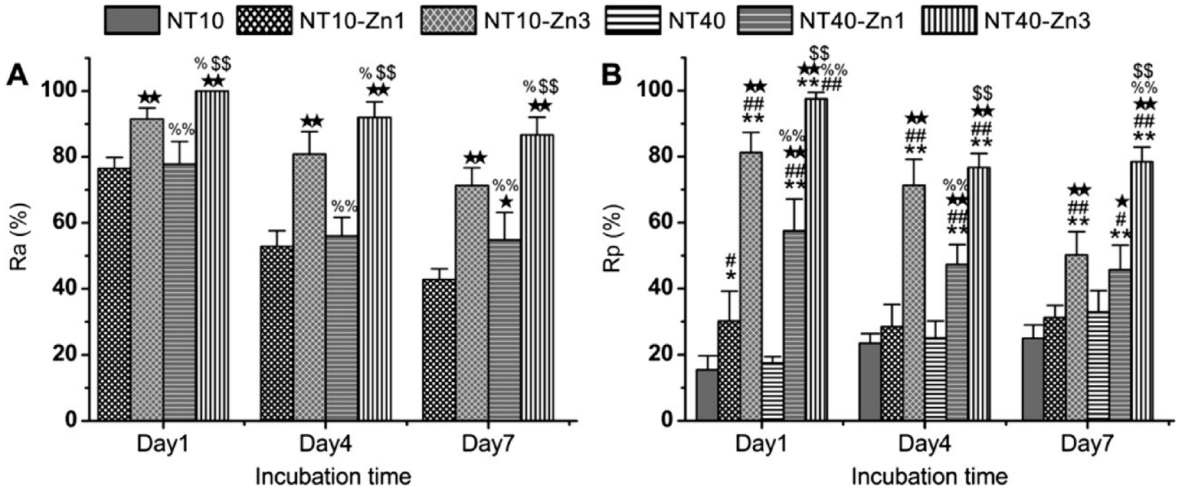

Fig. 3. (A) Antibacterial rates versus adherent bacteria on the specimen (Ra) and (B) Antibacterial rates against planktonic bacteria in the medium (Rp). *, **$p < 0.05$ and 0.01 vs NT10; #, ##$p < 0.05$ and 0.01 vs NT40; ★,★★$p < 0.05$ and 0.01 vs NT10-Zn1; %, %%$p < 0.05$ and 0.01 vs NT10-Zn3; $,$$ $p < 0.05$ and 0.01 vs NT40-Zn1 [212].

resistance and chemical stability and have a long effective antibacterial period and broad-spectrum antibacterial properties, which have thus been widely applied to the antibacterial coating of orthopedic implants. However, some problems need further consideration. For example, the action time needed between metal ions and bacteria is relatively long, and a good bactericidal effect can be achieved only upon long-time action and high concentration, thus missing the best time for inhibiting bacteria [224]. There is a study showing that the longer the culture time between metal ions and bacteria, the more significant the bactericidal effect. Drug-resistant bacteria can be effectively inhibited, and the biofilm formation can be reduced 24 h later, whereas it only takes dozens of minutes for bacteria to reproduce for one generation [225]. In addition, tissues and cells will be persistently stimulated by metal ions following orthopedic implantation, whose potential physiological toxicity remains unclear, and high-concentration metal ions used to achieve a good antibacterial effect may also produce toxicity to normal tissues [226].

3.3.3. Non-metallic ions releasing antibacterial coatings

In recent years, non-metallic materials used for antibacterial coatings have also been gradually studied. For example, the non-metallic element fluorine (F) is an essential trace element in biological activities, which plays an important role in bone growth and development and the maintenance of physiological structure and function of bones. Cooper et al. [227] showed that F^- can not only raise the antibacterial effect of materials, but also enhance the proliferation of human bone marrow-derived MSCs and the expression of differentiation genes. Cell differentiation can be promoted under a lower content of F^- but be inhibited under a higher content of F^-. Holinka et al. [228] covalently bonded selenium to the surface of Ti and Ti alloy implants and found that it can prevent the adherence of *Staphylococcus aureus* and *Staphylococcus epidermidis*, without affecting the viability of osteoblasts. Shirai et al. [229,230] incorporated iodine onto the Ti surface through anodic oxidation, which exerted effective antibacterial activity against *Staphylococcus aureus* and *Escherichia coli*, without *in vitro* (fibroblasts) or *in vivo* (rabbits) cytotoxicity. They also found that iodine-rich implants can reduce inflammation and infections and improve osseointegration. According to clinical trials, iodine displays good antibacterial activity without causing cytotoxicity or thyroid abnormalities, and 20–30% of it remains on the surface of materials 1 year after introduction [230]. Few reviews can be found on the fabrication of antibacterial coatings with non-metallic elements, so this topic deserves special attention and further exploration.

3.3.4. Development of carriers for ideal release mode of antibacterial agents

As reviewed above, numerous studies have been conducted on the use of releasable antibacterial agents for prevention of IRIs [231,232]. However, typically the release profiles follow first- or second-order kinetics [21]. There is often a burst release phase at the beginning of drug release, and then it is difficult for drug release to maintain above the minimum antibacterial concentration for a long period of time. Cytotoxicity and drug resistance may occur due to the unstable concentrations of drugs released. To solve the above problems, researchers have explored sustained-release antibacterial coatings [183,233]. Based on the electrostatic and hydrophobic interactions between nanostructures and drugs, Song et al. [234] designed antibacterial coatings consisting of a chitosan substrate of gelatin nanospheres and loaded with vancomycin or moxifloxacin, which can effectively control the antibiotic release. Using the collagen self-assembly and micro-sol electrospinning technique, Liang et al. [235] prepared a nanofibrous bionic periosteum with sustained releasing of VEGF, which is effective in promoting angiogenesis and bone tissue regeneration and, to some extent, contributes to addressing burst release of drugs and prolonging drug release time. However, since IRIs may occur at any time and chronic infections may even occur after 24 months, the drug release time is still not enough for effective prevention of infections associated with orthopedic implants, especially middle- and late-stage infections. Besides, proteins are rapidly deposited on the implant surface when the implant is implanted in the body, and due to uncontrollable drug release from the sustained-release coating, it is difficult for antibacterial agents at low release levels to penetrate the protein deposition layer to exert antibacterial effects. Thus, the development of coatings with high drug loading capacity, controlled release property and long-term antibacterial performance remains challenging.

With continuous research on controlled releasing-type antibacterial coatings assisted by nanotechnology and combining different preparation techniques (e.g., plasma electrolytic oxidation [236], electrophoresis [237], and LbL [238]) [239,240], multiple nano drug carriers have been developed. By virtue of the ability to enhance drug solubility, modulate drug release, and achieve targeted delivery of multiple drugs, in combination with the advantages of nanoparticles themselves such as small size and large specific surface area, these carriers (mainly including nanotubes, polymer nanocarriers, liposomes, and carbon-based nanocarriers) have become promising antibacterial drug carriers [241,242]. To further improve the bactericidal activity on the coating surface, two or more different types of bactericidal agents and bioactive elements are usually incorporated into one system. For example, Xie et al. [243] utilized chitosan to chelate silver ions, which were then *in situ* reduced into AgNPs by electrochemical methods, and heparin and bone morphogenetic protein 2 (BMP2) were compounded with the chitosan layer through electrostatic effects to form the coating that can stably release silver ions and BMP2 within 30 days and thus effectively repress bacterial growth and promote osteocyte growth. In a recent study, Zhao et al. [244] fabricated titania nanotubes that were incorporated with silver nanoparticles. Results show that the coating can kill all planktonic bacteria within a few days, and the coating's ability to prevent bacterial adhesion remains unchanged for more than 30 days without apparent decline. In spite of the fact that overdose of Ag^+ can cause some cytotoxicity, by controlling the release rate of Ag^+ the properties can be tailored for both long-term antibacterial activity and improved biointegration. Chen et al. [245] prepared TiO_2 nanotube arrays loaded with AgNPs using an anodic oxidation method based on TiAg films and used a hydrothermal method to load $SrTiO_3$. The samples still showed good antibacterial performance and osteoinductive ability after 60 days. Zeng et al. [246] reported good antibacterial effects of Ti nanotubes loaded with silver oxide nanoparticles (Ag_2O–TiO_2-NTS) against *Staphylococcus epidermidis* and *Staphylococcus aureus in vivo* and *in vitro* during the treatment of periprosthetic infections after artificial joint replacement. To better control the drug release rate, Zhong et al. [247] coated polymethacrylic acid onto norfloxacin-loaded TiO_2 nanotube arrays, which, in combination with biopolymer encapsulation, displayed a relatively small amount of burst release (34.4%) and relatively long sustained release time. Xu et al. [248] reported the incorporation of dexamethasone/minocycline (Dex/Mino)-loaded liposomes on the surface of PEEK material, and then obtained a releasing-type antibacterial coating that can effectively prevent the *in vitro* production of bacteria with marked antibacterial effects from the functional release of minocycline. Meanwhile, osteogenic differentiation of stem cells is notably improved due to the osteoinductive and osteoconductive abilities that are enhanced after the release of dexamethasone.

Owing to the loading amount 10 times higher than that of ordinary silica, excellent biocompatibility, high specific surface area, tunable pore structure and controllable pore size, mesoporous silica nanomaterials can load antibiotics and other drugs for targeted delivery and controlled release of antibacterial agents [249,250], which are considered to be high-quality nanocarriers for releasing-type antibacterial coatings and have been widely recognized in antibacterial coating applications. Using the nano-interfacial oriented assembly approach, Liu et al. [251] fabricated mesoporous silica coatings (MPSCs) with vertical and size-tunable mesochannels on titanium substrates, namely, Ti@MPSCs, which show excellent capacity for drug adsorption and sustained release. To be

specific, the saturation adsorption capacity can reach 0.544 μg cm^{-2} towards minocycline hydrochloride (MC-HCl) antibiotic molecules, which is 6.5 times higher than that of bare Ti substrate. The drug release time can be controlled within the range of 84–216 h, by changing the mesopore size, and the Ti@MPSCs can realize a higher antibacterial rate (95.9%) compared with the bare Ti (only 70.3%). These findings highlight the high potential of MPSCs for the long-term prevention and elimination of *peri*-implantitis.

In recent years, the use of nanotechnology-assisted loading of antibacterial agents has effectively controlled the release of antibacterial agents, and the amount of drugs required has been greatly diminished. Nano drug carrier loading, in particular, can enhance the antibacterial activity of drugs by accurately delivering drugs to the site of infection *via* specific recognition pathways [252], which not only achieves antibacterial effects against the target pathogen, but also reduces the occurrence of bacterial drug resistance and adverse drug reactions. However, nano drug carrier systems are still facing some problems to be addressed in the application, such as high production costs, system defects, and safety concerns [253]. Most of the relevant studies are currently at the experimental stage, and the animal experimental studies of drug carrier systems still need to be strengthened in the future to achieve better application on the orthopedic implants. Besides, special attention should be paid to the release of metal ion antibacterial agents with potential cytotoxicity.

Hydrogels (referred to as hydrophilic interpenetrating three-dimensional polymer networks), which can encapsulate antibacterial agents of different sizes and achieve different release profiles because intercommunicating pores can be modulated by varying the degree of cross-linking reactions [254], have also become a vital strategy for the construction of releasing-type antibacterial coatings in recent years. Ghimire et al. [255] designed a combination of polyethylene glycol dimethacrylate hydrogel coatings with vancomycin *via* covalent functionalization with the oligonucleotide sensitive to *Staphylococcus aureus* micrococcal nuclease (MN), namely, PEGDMA-Oligo-Vanco, which allows vancomycin to release in an appropriate amount for sterilization in the presence of *Staphylococcus aureus* on and around the implant surface. Moreover, the hydrogel coating, when used on the implant surface, may also suppress the attachment and colonization of *Staphylococcus aureus* on the surface, and inhibit or even eradicate bacteria in its vicinity. The implantation experiment also further confirmed the excellent antibacterial ability of the coating and its effectiveness in eliminating bacteria from the surface of the implant and the bone tissues surrounding the prosthesis. Although hydrogel antibacterial coatings have been reported to exhibit outstanding *anti*-biofilm performance and show great potential in preventing bacterial infections associated with orthopedic implants, their immobilization approaches, physicochemical properties (e.g., swelling, persistence, and stability), interfacial adhesion, and achievement of stable bactericidal activity remain challenging, and in-depth research still needs to be conducted [256].

By and large, proper releasing-type antibacterial coatings are effective in improving the controllability of drug release and achieving targeted bactericidal effects. The introduction of nanotechnology has particularly enhanced the preventive and therapeutic effectiveness of such coatings. Nonetheless, the antibacterial effect of single antibacterial agent release is still not ideal, and there are several problems that need to be further investigated. For instance, certain degradation and migration of antibacterial agents may occur over time, resulting in a gradual reduction in drug concentration and loss of antibacterial activity. The stability of some antibacterial agents is poor, giving rise to the difficulty in long-lasting release, and most studies are limited to *in vitro* experiments. Besides, most such coatings may release and spread antibacterial agents even in the absence of infection, affecting normal tissues around the implant and increasing the risk of drug-resistant bacteria. Therefore, further exploration of multi-mechanism antibacterial coatings and smart coatings showing antibacterial effect on demand is of great significance.

3.4. Synergistic multi-mechanism antibacterial coatings

Conventional designs of antibacterial surface coatings are mostly based on one of the two mechanisms of killing bacteria or preventing bacterial adhesion. Although great achievements and progress have been made in the research on single-mechanism antibacterial coatings, each approach has its inherent defects. Especially facing practical conditions (e.g., diversified clinical orthopedic implant substrate materials, diversified demands, and environmental differences at the implantation sites), the application of single-functional coatings is extremely limited. For this reason, endowing antibacterial coatings with multiple antibacterial mechanisms might be a direction of antibacterial coating development in the future. To avoid the inherent defects of single mechanism antibacterial coatings, an increasing number of researchers have attempted to construct dual- or multi-mechanism synergistic antibacterial coatings by incorporating different antibacterial strategies [257,258], whose antibacterial effects are more favorable than those of coatings with a single mechanism of action [259,260].

One example is the combination of anti-adhesive and bactericidal functions, thus endowing material surfaces with the dual mechanisms of resisting bacterial adhesion and killing adhered bacteria. As documented in several studies, hydrophilic polymers with good resistance to non-specific protein adsorption and anti-bacterial adhesion ability and zwitterionic polymer brushes with strong water-binding ability are utilized to bind to antibacterial agents with bactericidal effects to construct dual-mechanism synergistic antibacterial coatings with both anti-adhesive and bactericidal performances [261–265]. Antibacterial agents such as metal nanoparticles are loaded into anti-adhesive materials (e.g., PEG and zwitterionic polymers), and then multilayer films are developed by LbL to fabricate synergistic antibacterial coatings with a dual mechanism of resisting bacterial adhesion and killing bacteria [266–268].

Valverde et al. [269] prepared triclosan-containing hyaluronic acid/chitosan polyelectrolyte multilayers onto Ti–6Al–4V alloy surfaces. The coating displayed excellent stability and hydrophilicity, making it effective at resisting bacterial adhesion. Meanwhile, the multilayered coating system could release its main TRI content within 24 h and serves as a reservoir for bactericide for longer-term action. As a result, the coating is highly effective at inhibiting bacterial adhesion and proliferation after implantation.

However, during long-term use, bacterial colonization may inevitably appear on these biological surfaces that even have a dual mechanism of resisting bacterial adhesion and killing bacteria, which may be attributed to the fact that the anti-adhesive component of the coatings prevents initial adhesion of bacteria but cannot release attached dead bacteria from the surface. Ideal antibacterial surface coatings should not only have functions of resisting bacterial adhesion and killing bacteria but also be able to release dead bacteria and bacterial secretions [270]. To this end, numerous studies have been conducted by researchers. Cheng et al. [271] designed novel composite coatings, in which the bactericidal element can kill more than 99.9% of *Escherichia coli* within 1 h, followed with removal of the killed bacteria by an anti-adhesive surface formed by a zwitterionic polymer *via* hydrolyzing ester bonds. The transition from bactericidal coating to bacteriostatic coating controlled by regulating the rate of hydrolysis of ester bonds is relatively controllable. By combining the excellent antifouling property of polymers with the rapid antibacterial property of endolysins, Garay-Sarmiento et al. [272] prepared Kill-&Repel coatings composed of antifouling hybrid (LCI-eGFP-Polymer) and bactericidal hybrid (LCI-EndLys), which prevents bacterial debris from adhering while killing bacteria. The combination of two antibacterial mechanisms (killing bacteria and resisting bacterial adhesion) shall be efficient in enhancing the antibacterial effect and addressing the problem such as bacterial residues on anti-adhesion coatings.

Fan et al. [273] prepared a synergistic antibacterial coating (gentamicin (GS)/montmorillonite (MMT)) with mechanisms of sustained release, bacterial adsorption, and bactericidal performance on

biodegradable magnesium alloy. Based on this, the release time of GS is prolonged by the MMT sustained-release method, and the local availability of the drug is improved. The MMT with strong adsorption ability is used to adsorb bacteria, and the aminoglycoside gentamicin (a positively charged polymer of cationic nature) with broad-spectrum antibacterial effects binds to the anionic compound on the bacterial surface to destroy the permeability of bacterial cell membrane and thus achieve bactericidal effects. *In vitro* studies have indicated that the GS/MMT coating shows no toxic damage at the implantation site in addition to prominent inhibitory effects on *Escherichia coli* and *Staphylococcus aureus*. Additionally, due to the simple and convenient preparation process, the GS/MMT coating is expected to be an excellent candidate for addressing the problem of IRIs.

Wang et al. [274] designed multilayer Zn nanotopographic calcium phosphate (CaP) coatings by an antimicrobial trilogy strategy, with CaP (the top layer) nanotopographic features providing contact sterilization at the early stage of implantation. Zn^{2+} can be continuously released under physiological conditions with the hydrolytic degradation of CaP at the medium stage. Later on, Zn^{2+} from the bottom sodium titanate library offers contact-killing and release-killing modes to eradicate pathogens in bone or surrounding tissues. *In vivo* experiments in a rat femur model have shown the good biofilm removal capability of the graded antibacterial coating and that the sustained release of Sr^{2+} and Zn^{2+} can better promote bone fusion. This antimicrobial trilogy strategy is interesting for long-term infection preventing effect.

Fichman et al. [275] designed a novel peptide-based antibacterial adhesive hydrogel based on mussel foot protein-5 (Mfp-5) polypeptide. Lysine in the polypeptide possesses antibacterial activity, and 3,4-dihydroxy-L-phenylalanine (DOPA) residues in the polypeptide are easily oxidized to generate H_2O_2. Therefore, the dual mechanisms of contact induction and peroxide sterilization are achieved; specifically, the bacterial film is broken by surface contact and H_2O_2 is generated to achieve a bactericidal effect, which can be applied to antibacterial coatings for preventing IRIs.

In summary, synergistic antibacterial coatings with two or three mechanisms can effectively prevent bacterial colonization and biofilm formation on the implant surface, prolong the use of antibacterial coatings, and add other related bioactive functions. Great achievements have been made in relevant research. It should be noted, however, that the different antibacterial coating strategies may interfere with each other in practical applications. For instance, bactericidal strategies usually require contact between bacteria and the coating surface to play their roles, while bacteriostatic components often make the coating surface repel bacteria or reduce the adhesion between bacteria and the surface. In addition, most coatings have no surface self-cleaning function, so the residual bacteria and debris cannot be removed in a timely and effective manner, affecting the long-lasting antibacterial performance. Thus, to maintain long-lasting antibacterial activity and good biocompatibility, it is vital for exploring strategies to balance multiple antibacterial mechanisms.

3.5. Multi-functional antibacterial coatings

In clinical practice, the successful implantation and long-term use of orthopedic implants rely on not only antibacterial performance but also additional functions such as promoting osteocyte adhesion, proliferation and differentiation, and good stability, biocompatibility, and anticoagulation properties. Good mechanical performance, resistance to wear and corrosion, and load-bearing capacity may also be required [276]. Studies have shown that there is competition between bacteria and host osteoblasts during surface binding, and that reducing bacterial adhesion and improving osseointegration are essentially identical. If osteoblasts can win the competition on the surface, they can achieve long-term antibacterial actions. Hence, it is of great significance for endowing antibacterial coatings with additionally improved biological properties to achieve multi-performance and multi-functionalization and thus better clinical performance, which shall be the main direction of the future development of antibacterial coatings.

Han et al. [277] prepared multifunctional Ti/8DSS/PEG coatings with both antifouling and osteogenesis-promoting functions by the tannic acid-mediated LbL self-assembly, with an octa-complex (8DSS) of PEG and the biomineralization inducer aspartate-serine-serine as the functional raw materials (Fig. 4), which, in addition to having good anti-biofouling performance, can induce the formation of hydroxyapatite and thus promote the osteogenic differentiation of bone marrow-derived MSCs, facilitating visible osteogenesis around the implant and showing excellent biocompatibility *in vivo*. After implantation in rat femoral condyles for 4 weeks (Fig. 5a), the 3D reconstruction of new bone in growth within implants (Fig. 5b) and the quantitative analysis of femur and new bone growth (Fig. 5c) explicitly demonstrate the *in vivo* bone formation enhancing effect of Ti/8DSS/PEG. More importantly, this design is simple and easy to implement in clinical practice, serving as a promising option for the development of multifunctional antibacterial coatings with both anti-infection and osseointegration-promoting functions.

To exploit titanium implants with long-term antibacterial properties and superior biocompatibility. In a recent study, Chen et al. [278] integrated QACs, Ag nanoparticles, and TiO_2 nanotubes to produce a coating that kills bacteria by releasing Ag ions as well as killing bacteria when in contact with QACs (a non-leaching antibacterial agent). According to the results, TiO_2 nanotube-Ag-QAS coating has an antibacterial activity of around 99.9% after different time intervals of incubation. Moreover, it was found that the coating displayed good biocompatibility due to the low release rates of Ag nanoparticles which did not damage the cells, and the presence of a layer of QAS that enhanced the viability of the cells. Rao

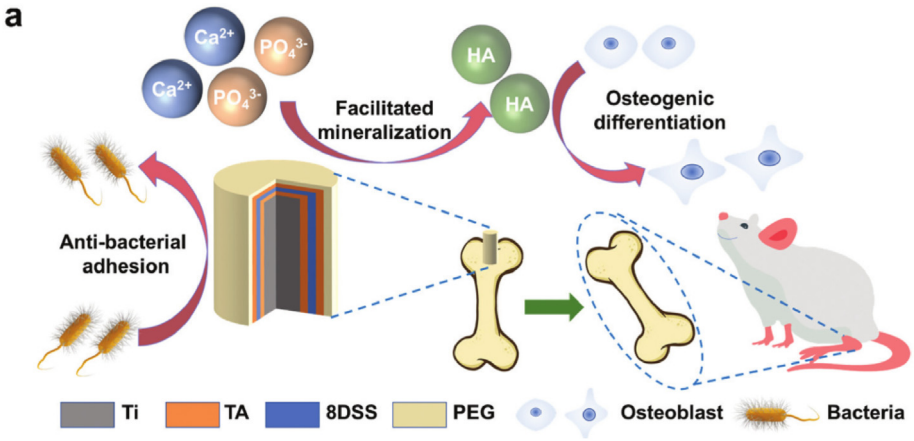

Fig. 4. Schematic illustration of anti-adhesion and osseointegration *via* Ti/8DSS/PEG [277].

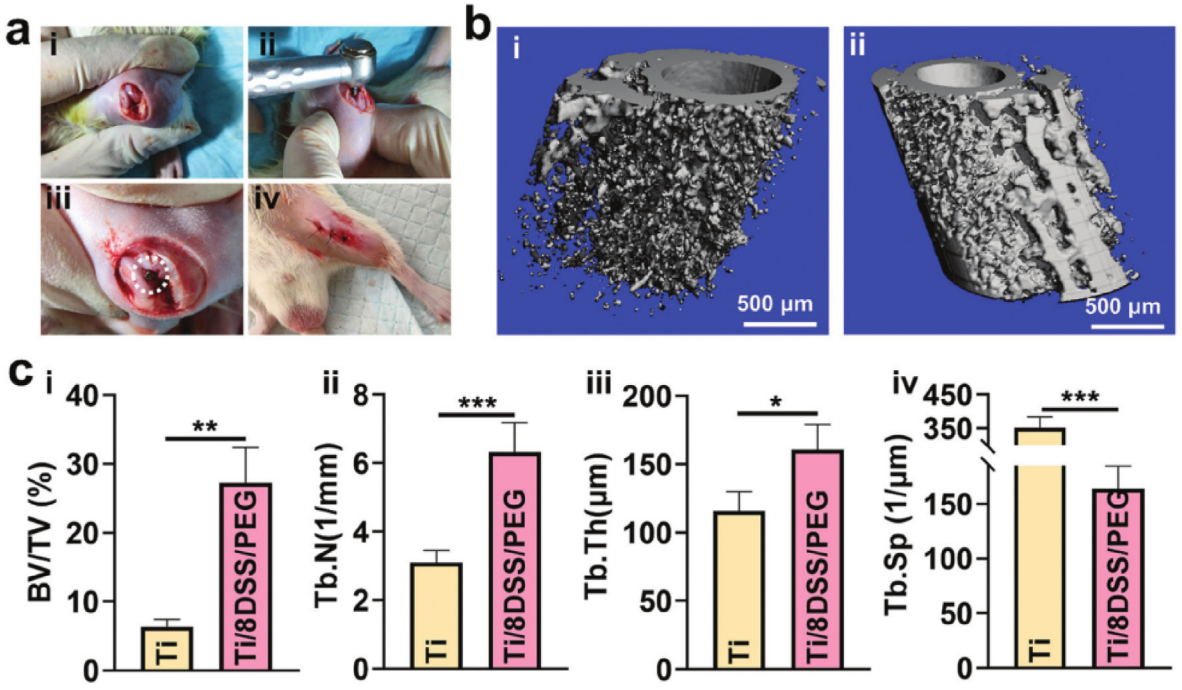

Fig. 5. *In vivo* experiments. (a) Digital photographs of *in vivo* experiment: (i) incision and exposure of the surgical area, (ii) implantation model formation, (iii) implant embedment, and (iv) suture of the surgical area; (b) 3D reconstruction images of new bone in growth within implants in rat femoral condyles: (i) Ti and (ii) Ti/8DSS/PEG; (c) Quantitative analysis of femoral and new bone in growth within the ROI at 4 weeks after implant surgery: (i) BV/TV, (ii) Tb.N, (iii) Tb.Th, and (iv) Tb. Sp. $*p < 0.05$, $**p < 0.01$, and $***p < 0.001$ [277].

et al. [279] prepared a dense and uniform Ag nanoparticle-modified layer on the surface of polyether-ether-ketone (PEEK), a typical material for orthopedic implants, which can not only effectively eliminate cytotoxicity resulting from an excessively high concentration of Ag^+, but also obviously enhance the antibacterial property of coatings due to the good hydrophobicity of Ag nanoparticles and the good bactericidal properties of Ag^+.

Mg alloys have attracted great attention in the field of biodegradable orthopedic implant materials due to their density and modulus of elasticity close to those of human bones, as well as non-toxic degradation [280]. However, magnesium degrades rapidly in the human body fluid environment and may cause detrimental effects (e.g., reduced strength, massive hydrogen precipitation, local alkalinization of body fluids, and bacterial infections [281,282]). Accordingly, Cui et al. [283] prepared a chitosan (CHI)/DNA multilayer film $(CHI/DNA)_5/Mg(OH)_2$ on the surface of NaOH-pretreated AZ31 magnesium alloy by the LbL assembly method and obtained a novel functional composite coating that improves corrosion resistance, antibacterial performance, and biocompatibility of magnesium alloy. $Mg(OH)_2$ as a physical barrier can prevent the penetration of corrosive ions, while $(CHI/DNA)_5$ can induce the formation of HA corrosion product film to protect substrates for a long period of time, and the contact sterilization effect of CHI endows coatings with good antibacterial activity. In addition, the good biomineralized effects of DNA and CHI compensate for the disadvantage that the outer polyelectrolyte multilayer film is relatively thin, thus exerting a positive effect on promoting bone growth. Yuan et al. [284] constructed a novel nanocomposite coating composed of $Mg(OH)_2$, GO, and hydroxyapatite ($Mg(OH)_2$/GO/HA) sequentially layered with a continuous interface and strong surface-interfacial bonding on the Mg-0.8Ca–5Zn-1.5Ag surface. *In vivo* and *in vitro* experiments indicated that the composite coating can slow down magnesium alloy degradation, suppress pathogenic bacteria, and promote bone regeneration, providing a new surface modification strategy for creating multifunctional Mg-based implants.

Rahnamaee et al. [285] designed a nanofibrillated chitosan-coated titania nanotube array/graphene nanocomposite multifunctional coating based on the biological and topological properties of chitosan nanofibers (CH) and graphene oxide (RGO) and found that the designed material features promote osteoblast cell viability, prolong antibiotic release profile, and inhibit bacterial biofilm formation. This design has fulfilled the need for an ideal implant with characteristics of osteoblast cell adhesion, bacterial adhesion resistance and bactericidal potency.

3.6. Smart antibacterial coatings

Fabricating coatings that can interchange multiple antibacterial mechanisms and possess the function of "surface regeneration" or smartly respond to certain stimuli is of great significance to achieve long-lasting controlled antibacterial effects. In recent years, smart antibacterial coatings have been developed, which not only integrate the functions such as resisting bacterial adhesion, killing bacteria, and releasing dead bacteria (namely "surface regeneration"), but also realize the controlled release of antibacterial agents through smart stimulation *via* physical and chemical approaches, thus achieving long-lasting effect and reducing the potential side effects. As such, smart antibacterial coatings are considered the most ideal antibacterial coatings. In general, smart antibacterial coatings can be divided into endogenous responsive and exogenous stimulating types [286].

3.6.1. Endogenous responsive type

Endogenous responsive coatings primarily involve the response to pH and bacterial secretions. The former is mainly stimulated by means of the acidification of the bacterial infection environment [287], whereas the latter refers to the response to various enzymes (such as phospholipase, hyaluronidase, cholesterol esterase and metalloprotease) or toxins secreted during the metabolic process [288,289]. Common pH responsive coatings are prepared based on electrostatic interactions. For example, negatively charged molecules and positively charged antibiotics are prepared by LbL self-assembly into neutrally stable coatings [290–293], or acid-sensing bonds (Schiff base bonds [294,295], metal coordination bonds [296], and borate ester bonds [297,298]) are introduced into preparation. In

addition, pH responsive coatings can also be prepared based on the reactive binding between nanoparticles and drugs and the responsive molecules such as polymethacrylic acid (PMAA) [240].

With the deepening of research, degradable smart responsive antibacterial coatings characterized by long-term stable antibacterial ability, good biocompatibility and an osteogenesis-promoting effect have been further explored. For example, Fang et al. [299] prepared vancomycin-modified specific demineralized extracellular cancellous bone matrix (Van-SDECM) coatings with a rapid response in an acidic environment and slow drug release in a physiological environment on the substrate of SDECM. With strong negative charge, SDECM can carry positively charged vancomycin by electrostatic adsorption to release drugs for quick sterilization in a pH-sensitive manner in an acidic environment at the early stage of infection, slowly release drugs for continuous sterilization in a physiological environment at the mid-late stage, and maintain a long-term sterilization ability to prevent recurrence of infections under an infection-free state. Moreover, SDECM possesses good biocompatibility and osteogenic ability, and its strong ability to kill bacterioplankton and adhesive bacteria has been demonstrated in bacteriological experiments *in vitro*. In general, such responsive coatings can effectively respond and release antibacterial agents to sterilize and reduce the generation of drug-resistant bacteria. Meanwhile, the preparation method is simple and applicable to a variety of bacteria, and it, effectively combined with other antibacterial mechanisms, can be used to obtain multifunctional coatings. However, such coatings may have poor stability under actual complex conditions.

As another common type of endogenous responsive coatings, the responsive antibacterial surface is designed based on multiple enzymes produced during bacterial metabolism [300]. With inherent biocompatibility, such coatings display good development prospects and are advantageous over pH responsive coatings in a biological environment. For example, through electrostatic LbL self-assembly of positively charged chitosan and negatively charged HA (a natural polysaccharide with good biocompatibility and strong modifiability) modified with AMPs on the substrate surface, hyaluronidase responsive antibacterial coatings can be obtained. Hyaluronidase released by bacteria can hydrolyze HA to release the antimicrobial component AMPs, thus killing bacteria [289, 301]. However, the enzymes secreted by different kinds of bacteria vary, so it is difficult to achieve a broad-spectrum antibacterial effect.

To further enhance the antibacterial effect, pH response, enzyme response or other modes are usually combined to achieve a dual/multiple-responsive synergistic antibacterial effect. For example, Wang et al. [302] prepared dual-responsive (hyaluronidase and pH) releasing-type antibacterial coatings. In situations where the Gram-positive bacterial infection occurs, the hyaluronate layer on the coating surface is rapidly enzymatically cleaved by the hyaluronidase secreted by bacteria, and the β-carboxyl group responds to the local microenvironment change such as bacterial acidification, leading to the rapid release of β-carboxyl-immobilized vancomycin to kill bacteria. This smart responsive coating shows precisely controlled release profile of the antibiotic by responding to the dual stimulation of hyaluronidase secreted by bacteria and pH, thus exhibiting better cytocompatibility and antibacterial performance.

Yang et al. [303] utilized two natural fabricating units, protocatechualdehyde (PA) and aminoglycosides (AGs), to achieve dynamic imine bond formation and enzyme-catalyzed polymerization reactions in the presence of the plant enzyme horseradish peroxidase and fabricated a non-surface-dependent highly efficient smart antibacterial coating. In addition to high-level drug loading and dynamic pH response performance, this coating has adjustable drug release profiles to achieve the on-demand release of antibiotics and efficient antibacterial activity, which provides an idea to fabricate powerful and smart antibacterial coatings using bionic materials.

By attaching an AMP with an osteogenic fragment to the surface of AgNPs *via* the hydrogen bond and carrying AgNP@AMP with collagen-structured filament (SF), Zhou et al. [304] prepared antibacterial coatings that can be triggered by infections. The results showed that the Ag@AP/SF has significant pH-responsive release properties. Under varying pH circumstances, the initial release amount increased by about ten times, and under neutral conditions, the release effect persisted for 28 days (Fig. 6a). Ag@AP/SF remained steady throughout the first two days, and Ag + emission was little, as seen in Fig. 6b. However, a sharp rise in Ag + release showed a release behavior driven by the infection when the pH decreased to 5.4 (simulating the scenario of bacterial infection). Changes in the external pH may lead to a shift in the conformation of the fibroin protein, with the α-helix structure changing to a β-sheet structure, attenuating the surface binding to AgNP@AMP complex and the dense nature of the coating, and ultimately, Ag^+ is released rapidly to achieve infection-triggered antibacterial effects. Moreover, Ag@AP/SF is effective in repressing bacterial adhesion and maintaining high bactericidal efficiency 1 month after implantation, without biofilm formation on the surface. In addition, Ag@AP/SF evidently slows down the release of Ag^+, while the low-concentration Ag^+ facilitates cell proliferation and osteogenic differentiation. Ag@AP/SF promotes not only osteogenesis but also osseointegration at the interface. Besides, *in vivo* implantation experiments further confirmed that the SF on the surface of Ag@AP/Ti implants is sufficient to withstand variable stress and friction (within 8 W) and that this multi-functional coating effectively ensures that Ag@AP/SF exerts its biological effects throughout the process of osteogenesis and bone healing (Fig. 7).

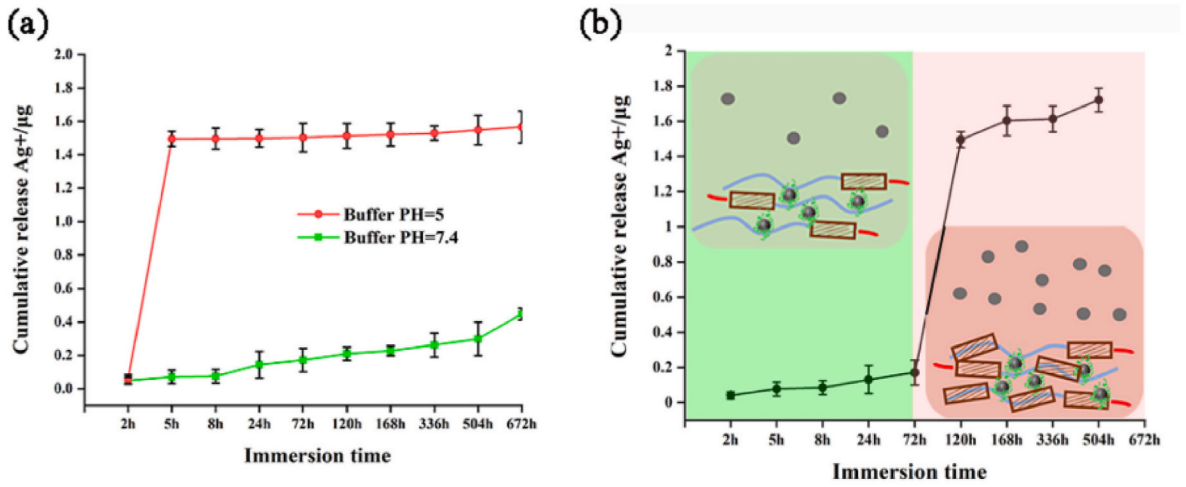

Fig. 6. (a) The cumulative release profile of Ag^+ at different pH conditions; (b) pH-controlled release of Ag^+ from Ag@AP/SF coatings [304].

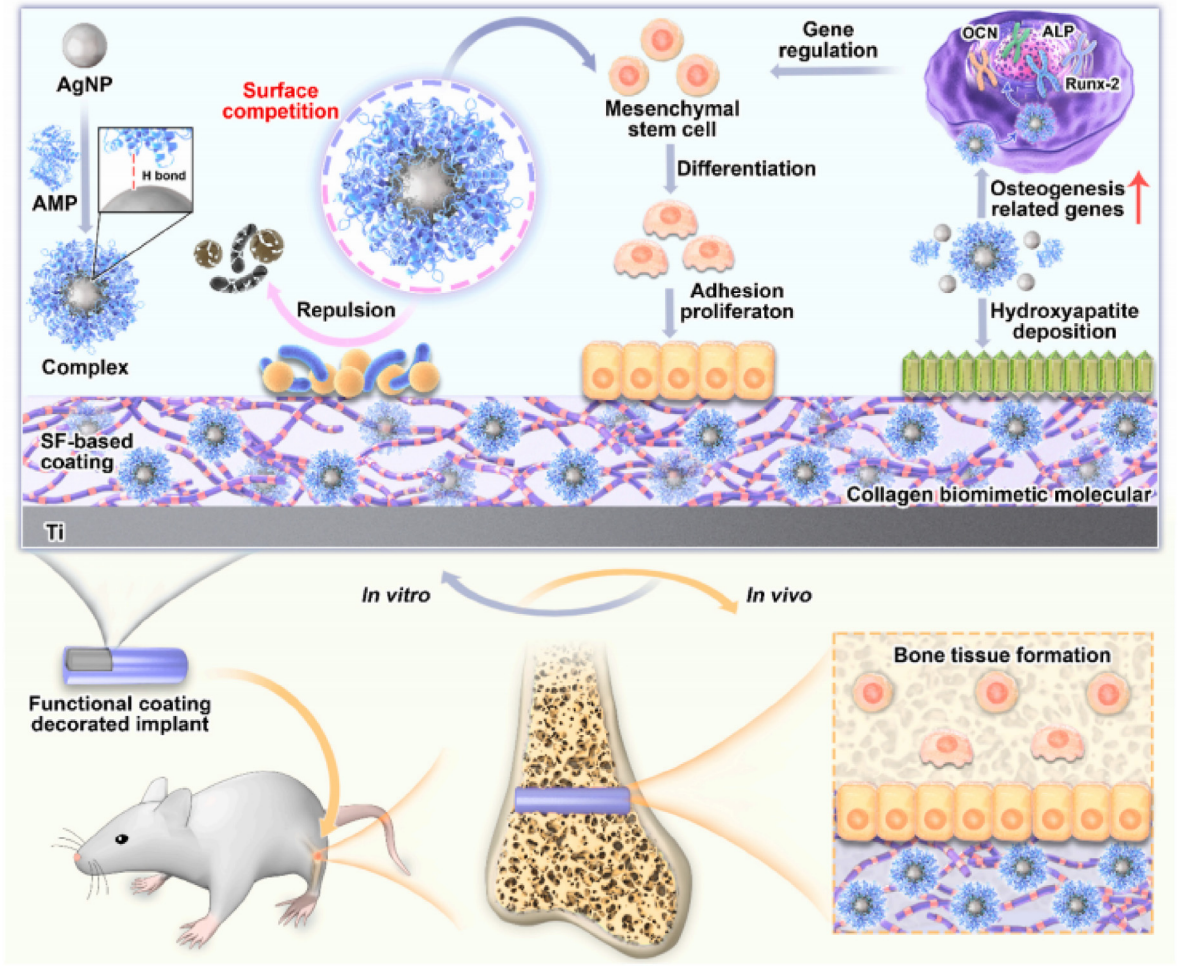

Fig. 7. Scheme illustration of antibacterial mechanism and osteogenesis mechanism of SF-based functional coatings [304].

3.6.2. *Exogenous stimulated type*

Exogenous stimulated coatings display antibacterial activity upon stimulation of external conditions. Such coatings can solve the problems of poor stability and uncontrollability of drug release and bacterial resistance existing in drug-loaded releasing-type antibacterial coatings, making them a safe and effective method. Exogenous stimulated coatings mainly cover the temperature control type, light control type, electric signal control type, and other stimulus responsive types. Among them, the light control type has temporal and spatial controllability, strong penetrability and small toxicity, and it can also be precisely controlled [305,306]. At present, photothermal therapy (PTT) and photodynamic therapy (PDT) have been the most widely studied methods for antibacterial application in bone implants. As compared to traditional treatment methods, such coatings work only when exposed to light, producing an interesting "switch effect", so that whether to kill bacteria can be determined according to demand, which has aroused great interest among researchers. Therein, antibacterial photothermal therapy (PTT) is a local thermal therapy to destroy bacterial integrity using photothermal converters (mainly including noble metal nanomaterials, metal sulfide/oxide nanomaterials, carbon-based nanomaterials, polymers, and organic small molecule-based nanomaterials [307]), characterized by a broad spectrum of bactericidal activity, no drug resistance, and few side effects [308]. The rapid development of photothermal materials in recent years has provided new ideas for the development of such antibacterial coatings [309]. Photodynamic therapy (PDT) is mainly based on the generation of ROS that are toxic to cells by light irradiation of photosensitizers to achieve bactericidal effects, which has also attracted wide attention because of effective eradication of pathogenic bacteria, advantages of repeated sterilization, avoidance of the emergence of drug-resistant bacteria, minimal invasiveness, and deep tissue penetration [310]. However, it is difficult to heat bacteria directly and specifically by PTT alone, and surrounding normal cells may be destroyed under prolonged heating at a certain temperature. Meanwhile, due to the short lifespan of light-excited ROS, PDT alone cannot effectively cure recurrent bacterial infections, and long-term irradiation may also cause damage to normal tissues. In addition, their clinical use is also restricted to some extent due to the lack of photothermal agents and photosensitive materials with excellent photothermal conversion efficiency.

In view of the above problems, other antibacterial modes have been introduced into phototherapy, or other antibacterial materials are effectively combined to achieve a synergistic and complementary antibacterial effect. For example, Wang et al. [311] connected the liposome-encapsulated photosensitizer (PS), IR780 and perfluorohexane (PFH) by covalent bonds onto the Ti implant surface and then induced a photodynamic antibacterial effect by near-infrared (NIR) light. With high oxygen capacity, PFH can overcome the problem of a low yield of ROS *in vivo*, and generate ROS through the NIR irradiation in the case of low oxygen content *in vivo*, thereby effectively enhancing the antibacterial effect. The results showed that the antibacterial rate of the modified implant surface against *Escherichia coli* and *Staphylococcus aureus* can be up to 99.62% and 99.63%, respectively, and good *in vitro* and *in vivo* bactericidal effects are also verified. Li et al. [312] developed a Ti-RP/PCP/RSNO composite hydrogel coating responding to NIR on the surface of Ti alloy, achieving a good synergistic antibacterial effect by

photothermal action and ROS. Moreover, the expression of osteogenic genes and osteogenic differentiation can be effectively strengthened by the slow release of NO and polarization of macrophages. Deng et al. [313] utilized sulfonated PEEK (sPEEK) with 3D network structures as a substrate and deposited GO with high photothermal conversion efficiency and good biocompatibility as well as polydopamine (PDA) layer on the surface of sPEEK by π-π-π stacking. Subsequently, adiponectin (APN) was grafted to generate an orthopedic implant coating with both efficient osteogenic induction performance and reproducible remote photo-controlled bactericidal performance. The results showed that this system can rapidly raise temperature to efficiently kill *Staphylococcus aureus* and *Escherichia coli*, and the bactericidal rate is still more than 95% after multiple cycles, exhibiting good, repeated photo-controlled bactericidal properties. In addition, the grafted APN can repair the tissue damage caused by local overheating during PTT and promote the oriented differentiation of osteoblasts. The results of animal experiments further proved that the sPEEK/GO/APN system facilitates osseointegration around the implant and promotes revascularization around the implant. Overall, this system successfully kills bacteria in a remote, controllable, repeatable, and efficient manner, which opens up a new direction for "exogenous" bactericidal actions to solve IRIs.

In clinic, iodine serves as an effective disinfectant with broad-spectrum antibacterial efficacy and no risk of drug resistance, but its poor volatility and solubility result in large limitations in clinical applications. Hence, Teng et al. [314] proposed a "synergistic anti-infection strategy" based on triggered iodine release and photodynamic effects. Specifically, based on the excellent absorption capacity and inherent photocatalytic properties of MOFs, iodine is loaded onto zeolitic imidazolate framework-8 (ZIF-8) using a vapor deposition process, which is then immobilized on microarc titanium oxide by hydrothermal method, thus achieving iodine-responsive release and oxidative exposure of intracellular ROS under NIR irradiation to achieve synergistic antibacterial effects. This combination prominently improves the antibacterial efficacy *in vivo* and *in vitro*. Moreover, this composite coating also supports osteogenic differentiation of bone marrow stromal cells and effectively improves osseointegration of the implant. The composite coating not only improves antibacterial efficacy without compromising the osteogenic potential of the implant but also successfully avoids the inherent defects of iodine, so it has become a novel strategy for resisting IRIs.

Such novel synergistic antibacterial coatings are also constructed by introducing photocatalytic sterilization and designing coating structures. For example, Hong et al. [315] designed a Bi_2S_3@Ag_3PO_4 heterojunction film on the surface of Ti alloy implant. Ag_3PO_4 can effectively improve the photocatalytic effect of bismuth sulfide without affecting its photothermal performance, thereby greatly raising the bactericidal effect of the material. In this way, the coating displays rapid and efficient sterilization and bacterial biofilm-eliminating ability by the synergistic effect of ROS and photothermal action under the NIR irradiation. Moreover, the trace silver ions slowly released by Ag_3PO_4 can suppress the biofilm, which provides a promising strategy for long-term and stable antibacterial coatings on the implant surface. Zhang et al. [316] prepared TiO_2 nanorod arrays based antibacterial coatings on the Ti implants with the synergistic bactericidal approaches (i.e., light-assisted therapy and nanostructures). The results manifested that the Ti implants exhibit efficient and excellent bactericidal actions and biofilm removal capabilities under exogenous NIR light irradiation (Fig. 8). Moreover, the nanorod structure of TiO_2 can also facilitate osteoblast adhesion, spread and differentiation, which promotes the development of new bones. Evaluation of osteogenic performance after one month of implantation is shown in Fig. 9. Synergistic effects of the photothermal technique, ROS, and nanorod puncture make the Ti implants display excellent antibacterial ability, effectively addressing bacterial infections and promoting osteogenesis.

This direction can guide the design of safe and efficient anti-infection interfaces in clinical applications. Similarly, Zhang et al. [317] designed a synergistic antibacterial system composed of F-Yb-Ho co-doped titanium dioxide nanorods (TiO_2NRs) and curcumin (Cur) on the Ti implant. TiO_2NRs can generate sufficient heat for photothermal therapy under the NIR irradiation, and its physical structure can kill attached microbial cells through the mechanical destructing mechanism. Meanwhile, up-conversion materials are formed by F-Yb-Ho doping, greatly improving the photocatalytic activity of TiO_2. In addition, Cur and BMP-2 are successively grafted to the surface of NRs through electrostatic binding, so that ROS required by PDT is supplemented to achieve a synergistic antibacterial effect, and both good osseointegration and relieved immune response are realized in the coating system. Cai et al. [318] prepared TiO_2/Ag photocatalytic nanofilms by the atomic layer deposition technique and *in situ* photoreduction process, which broadened the light absorption range from the UV light to the visible light. Due to the contact potential difference between TiO_2 and AgNPs, their combination at the surface interface formed a Schottky heterojunction, which generated ROS while hindering the electron-hole recombination rate, greatly improving the photocatalytic effect. *In vitro* visible light irradiation and tests have indicated that this coating has not only a rapid and good antibacterial effect but also favorable biocompatibility. Zhang et al. [319] designed photoactivated composite oxide of copper ferrite ($CuFe_2O_4$) heterojunction coatings on bioinert PEEK implants. The cycling heterojunction between two redox pairs of Fe(III)/Fe(II) and Cu(II)/Cu(I) in $CuFe_2O_4$ can continuously catalyze the production of bactericidal OH from H_2O_2 *via* the Fenton (-like) reaction in the bacterial infection microenvironment (IME), which not only produces photothermal and photodynamic effects under the NIR irradiation but also effectively improves the release of Cu and Fe ions to promote the osteogenic function. Besides, $CuFe_2O_4$/graphene oxide (GO) heterojunctions were also constructed by hybridizing 2D GO, further enhancing the NIR absorption of $CuFe_2O_4$ and the phototherapeutic effect.

In addition, studies have been conducted on the development of novel photosensitive materials with excellent conversion efficiency. Characterized by a good antibacterial effect due to high activity, excellent photoelectric properties, excellent ability to generate ROS under irradiation, unique shape and specific surface area, graphene, metal-based 2D materials, transition metal sulfides, black phosphorus (BP) [320], and other 2D nanomaterials have been paid extensive attention and received in-depth research [321]. For example, Chai et al. [322] first prepared porous TiO_2 coatings on the surface of Ti implant by micro-arc oxidation, and loaded graphene oxide on the coating surface by dopamine, which addressed the weaknesses of no antibacterial performance of porous TiO_2 coatings under the NIR irradiation. Upon 808 nm NIR laser irradiation, porous TiO_2 coatings are endowed with excellent photo-assisted antibacterial ability due to the synergistic effect of local overheating and ROS, which shows good potential in clinical use. Similarly, MoS_2 has good photosensitivity. Molybdenum is an essential trace element for the human body and it plays a highly important role in both physiological function and metabolism. MoS_2 is non-toxic and harmless, and it can also be well loaded with other biomolecules, becoming an ideal biomedical material, which has also been widely concerned [323,324]. Yuan et al. [325] prepared MoS_2/PDA-RGD coatings on the surface of Ti implant, which can not only exist *in vivo* for a long time, but also perform well in inhibiting *in-situ* bacterial infections and improving osseointegration, and they also verified by *in vivo* experiments that such coatings cause no damage to normal tissues.

Characterized by unique structure, physical and chemical properties, biocompatibility, biodegradability and low toxicity, BP is considered outstanding when used in the biomedical field. In particular, BP can work simultaneously as the carrier of metals (Ag, Au, *etc.*), *in-situ* green reducing agent and stabilizing agent [326] to directly reduce on its surface for uniform loading, avoiding introducing additional reducing agents as compared to other 2D materials such as graphene. Moreover, it can be degraded into phosphate (PO_4^{3-}) necessary for the human body under the action of water and oxygen. Due to the excellent NIR absorption, irradiation with NIR light not only promotes the breakdown of BP

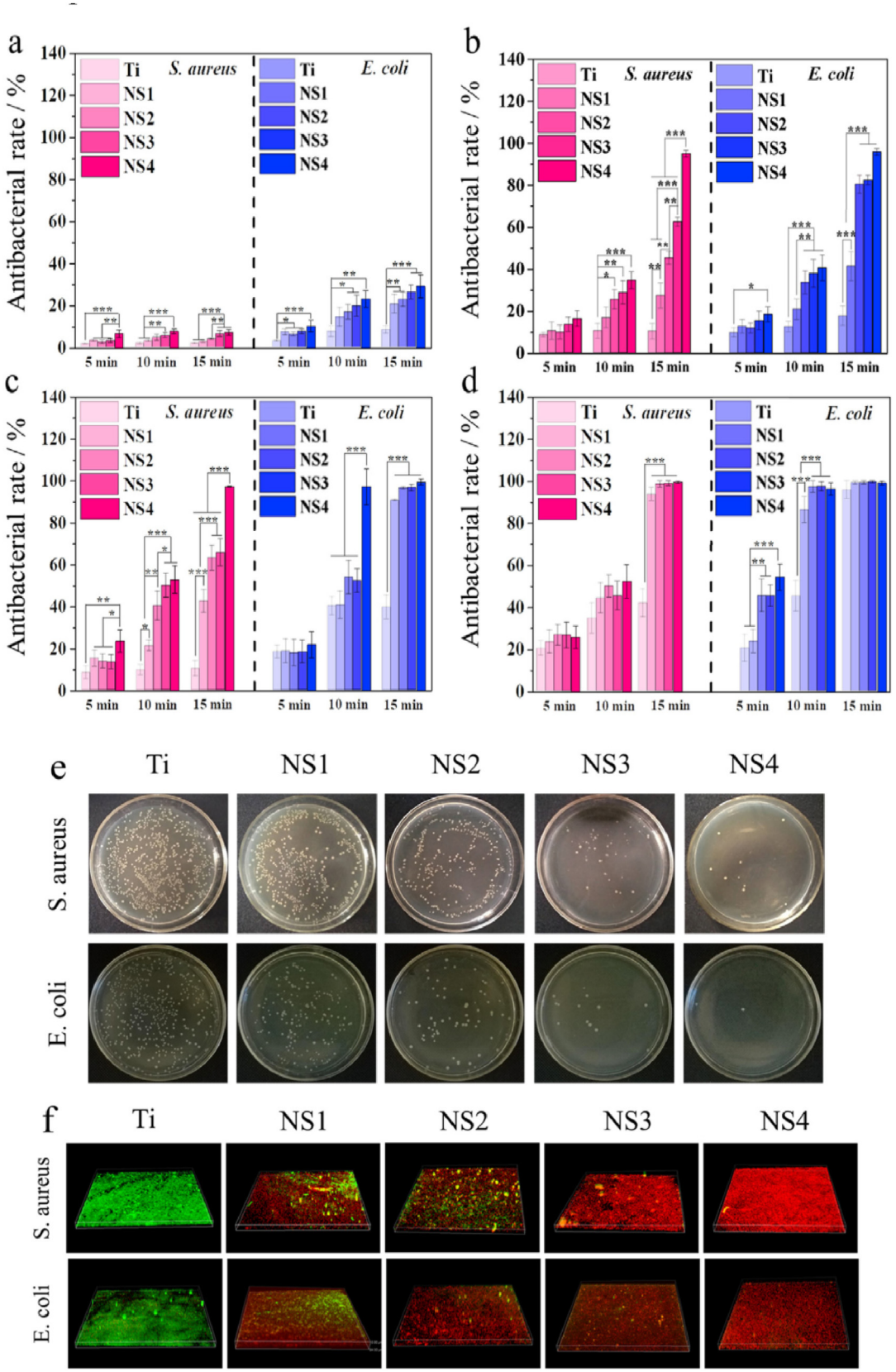

Fig. 8. Antibacterial performance: (a–d) Antibacterial rates of the Ti, NS1, NS2, NS3, and NS4 (Ti and TiO_2 nanostructures (1.0 × 1.0 cm^2) that immersed in 1 mL of phosphate buffer saline (PBS))under irradiation with 808 nm NIR light at 0.6, 0.8, 1.0 and 1.2 W cm^{-2}, respectively; (e) Bacteria colony images of different samples upon irradiation with 808 NIR light at 0.8 W cm^{-2} for 15 min; (f) *Anti*-biofilm performance of different samples under irradiation with 808 NIR light at 0.8 W cm^{-2} for 15 min (*$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$) [316].

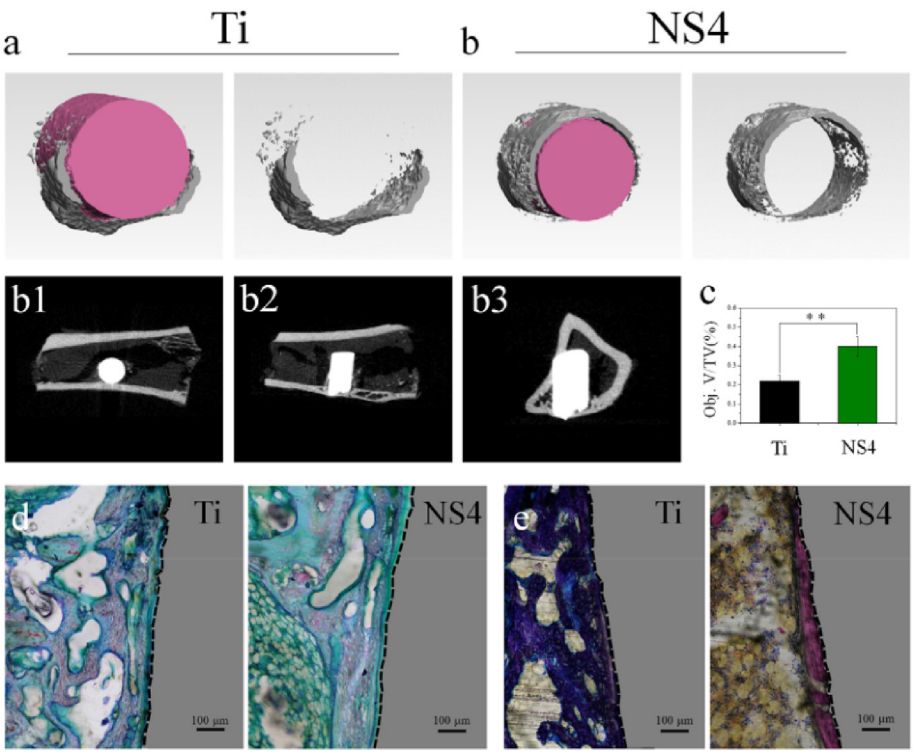

Fig. 9. *In vivo* osteogenic performance: (a, b) 3D images reconstructed by micro-CT in Ti and NS4 implants; (b1-b3) 2D micro-CT images of NS4 implants in tibia; (c) Quantitative analysis of bone volume/total volume (BV/TV) around the implants calculated from the micro-CT (**$p < 0.01$); (d) Safranin-O/Fast Green staining of the tissues around the implants after 1 month of implantation; (e) Methylene blue-acid fuchsin staining of the tissues around the implants after 1 month of implantation [316]. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

into PO_4^{3-}, but also increases chemical activity to speed up the reaction between PO_4^{3-} and Ca^{2+} and promote *in situ* biomineralization. Therefore, BP has great application potential in the biomaterial field, especially in tissue engineering [327]. Wu et al. [328] prepared ZnL_2-BPs with BP sheets (BPs) and zinc sulfonate ligands (ZnL_2) and integrated them on the surface of hydroxyapatite (HA) scaffold, obtaining ZnL_2-BPs@HAP. BPs have an excellent photothermal effect, and ZnL_2 can increase the thermal sensitivity of bacteria around the implant by inducing envelope stress. Under the NIR irradiation, the antibacterial capacity of ZnL_2-BPs@HAP is significantly improved due to the photothermal effect, and it also develops good stability and biological safety. Zn^{2+} and PO_4^{3-} are gradually released in the later stage to benefit later osteogenesis, thereby achieving a sustained photothermal antibacterial effect and promoting bone regeneration. In addition, *in vivo* studies have demonstrated that there is almost no inflammatory cell infiltration and bacterial contamination around the implant, and no severe damage is caused after the NIR irradiation, displaying good potential in clinical use. However, BPs often have defects such as fast photo-induced electron-hole recombination and weak and narrow light absorption in the photocatalytic process. In view of this, Liang et al. [329] designed a novel AgNP-doped BP composite coating. With the introduction of AgNPs, efficient action sites are provided for the adsorption and activation of O_2 on the composite material during the photocatalytic process, greatly facilitating the generation of ROS. Besides, AgNPs can accelerate the separation and transport of electron hole, thus suppressing photo-induced electron-hole recombination, enhancing the light utilization, and exhibiting an overall good antibacterial effect, which provides a new idea for further BP-based biomedical research.

3.6.3. Other categories of smart coatings

Researchers are also working on the development of some novel smart coatings by means of the process and characteristics of bacterial infections. Some interesting examples are described here.

Fu et al. [330] prepared HA/MoS_2 modified coatings on the surface of Ti implant by laser cladding and CVD. When bacteria adhered to HA/MoS_2 coating, the electrons from bacterial membranes were transferred to the coating due to the potential difference between the coating and bacteria. This coating utilizes the energy generated during the metabolic process of *Staphylococcus aureus* and *Escherichia coli* to trigger its antibacterial activity without additional energy, thereby creating an infection-triggered self-activated antibacterial process. Moreover, this coating also shows broad-spectrum antibacterial performance and strong ability of osteogenic differentiation, which may effectively solve the implant osseointegration problem.

Cao et al. [331] introduced antimicrobial inert metals (e.g. silver) and osteogenesis-promoting active metals (e.g. calcium) simultaneously onto the Ti surface to construct a "bifunctional microbattery" based on the "proton coupled electron transfer" theory. The proton motive force (PMF) on which the bacterial energy synthesis depends is "disrupted" by cathodic hydrogen evolution reaction of the "microbattery", and the anodic corrosion (ion release) of "microbattery" "attracts" bacteria to "store" active ions (energy consumption). With such a synergistic effect of the two above, bacteria are placed in a serious "stress" state, so that the antibacterial surface with cell selection features can be successfully prepared, which provides a new direction for the research and application of "antibacterial + osteogenic" implant.

Chu et al. [332] demonstrated the adjustable antibacterial activity of *para*-mercaptobenzoic acid (pMBA)-capped gold nanoclusters (GNCs). The anionic amphiphilic GNCs are thought to disrupt the structural integrity of the phospholipid bilayer, increasing membrane permeability and causing leakage of essential intracytoplasmic contents, the antibacterial activity of which is closely related to the protonation level of pMBA ligands. Under a lower pH environment with more ligands protonated, the GNCs show enhanced antibacterial activity while keeping minimal cell cytotoxicity. Afterwards, the authors constructed GNCs based mixed-metal metal-organic network (MM-MON) film on the Ti substrate by metal-ligand coordination-driven and solvent evaporation-induced self-assembly as antibacterial nanocoatings. The heterobimetallic MM-MON films enable the bacteria-trigged release of Cu^{2+} while maintaining structural integrity. The *in vitro* and *in vivo* data demonstrated a bacteria-triggered release character and contact-killing ability of the self-defensive MM-MON film nanocoatings. This system integrates the

smart bacterial-responsive character of GNCs and excellent chemical stability, and significantly enhances the antibacterial activity *via* the introduction of antibacterial ions, finally killing adherent bacteria and launching a self-defensive function, thus providing a novel technique and feasible protocol for the development of smart antibacterial coatings.

With MMT, polylysine (PLL), and a chlorhexidine (CHX) as raw materials, Liao et al. [333] prepared a bacteria-responsive antibacterial coating loaded with enzyme (i.e., MMT/PLL-CHX) on the surface of orthopedic implants through LbL assembly technique. The results implied that after being incubated with *Staphylococcus aureus* and chymotrypsin (CMS) solution, the (MMT/PLL-CHX)10 multilayer film structures were gradually destroyed and displayed excellent concentration-dependent degradation features. High levels of bactericidal activity were demonstrated in protein leakage tests and bacterial inhibition rate measurements. The (MMT/PLL-CHX)10 multilayer films also have perfectly biocompatible, according to the CCK-8 examination. Moreover, the implant coated with multilayer films showed lower infection and inflammation rates *in vivo* antibacterial tests than the unmodified group, and all parameters were similar to those in the sham group.

With in-depth research on smart coatings, those with self-healing functions have been constructed to further strengthen the antibacterial effects. Wang et al. [334] obtained decyl-polyethyleneimine (DPEI) using alkyl side chain polyethyleneimine (PEI) with good hydrophobic performance, and then used DPEI micelles and polyacrylic acid (PAA) to prepare smart antibacterial coatings that can self-heal in a short period by LbL self-assembly. The results showed that this coating can effectively prevent bacterial adhesion (more than 90%) and biofilm formation in a short period. More importantly, based on the reversible interaction force between molecules and molecular mobility, this coating can achieve rapid self-healing under wet conditions, effectively reducing bacterial adhesion and contamination in the scratch damage area of the implant and thus ensuring a long-lasting antibacterial effect.

In a word, these smart responsive coatings can incorporate the functions of killing bacteria (contact sterilization), releasing dead bacteria, and resisting bacterial adhesion, and can also repeatedly switch among these functions. They can respond to specific stimuli to achieve controlled rapid and long-term bactericidal actions. In particular, the introduction of PTT and PDT contributes to avoiding the use of relevant drug-based antibacterial agents and effectively ameliorating or solving the problems such as cytotoxicity and drug resistance. However, the current studies are basically in the preliminary stage, and the implant may not effectively use external triggers in practice to alter the antibacterial mode for achieving a truly smart antimicrobial effect. It will be one important trend in the future to develop antibacterial coating that can rapidly respond to local bacteria *in vivo*, thus realizing self-triggering and greatly improving the flexibility and specificity of smart antibacterial coatings.

4. Conclusion

IRIs have been a vexing problem to be solved in the medical field, negatively affecting the clinical use of implants. The development and application of various types of antibacterial coatings have provided promising and innovative strategies to address this problem. In particular, advances in material science and technology and the continuous development of novel preparation techniques have further propelled the research and development of multiple antibacterial coatings. This paper summarizes the mainstream types of coatings (including anti-adhesion coatings, contact bactericidal coatings, releasing-type bactericidal coatings, multi-mechanism antibacterial coatings, multifunctional coatings, and smart antibacterial coatings) currently applied to orthopedic implants based on different mechanisms and functions. Significant progress has been made regarding these coatings in recent years, which are expected to play vital roles in the prevention and treatment of infections associated with orthopedic implants in the future. Nonetheless, various types of coatings have not yet been widely used in the clinic due to some limitations and drawbacks. For instance, the safety, effectiveness, long-term and stability of antibacterial coatings when applied to implant surfaces remain challenging in terms of techniques. In most studies, coatings are tested for only short-term antibacterial properties, with no systematic evaluations of their biointegration, long-term antibacterial effects, toxicity, and so on.

Briefly, the development of antibacterial coatings for orthopedic implants is in the preclinical research stage, and there is still a gap in their clinical. It is widely accepted that the ability of host defense around the implant is the ultimate means against infections. Thus, we hold that the development of antibacterial coatings should not only emphasize the antibacterial performance of implants but neglect their properties such as biocompatibility and osteoinductive ability. Only endowing implant surface with antibacterial performance is far from adequate for clinical practical demands, and the osteogenic, biocompatible, wear-resistant, load-bearing, and other performances of coatings must be taken into account. Thus, the ideal orthopedic implant coatings should be "smart" and multi-functional, which not only has great application potential and research value but also will be the main direction of research on antibacterial coatings in the future. Nevertheless, determining the balance and the "optimal protocol" in the development of multifunctional coatings will be challenging in the future. It is believed that with the advancement of research, smart multi-functional coatings of orthopedic implants will be widely applied in clinical orthopedics.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Acknowledgements

This work was financially supported by the National Natural Science Foundation of China (No. 82072075), Key Scientific Research Plan of Shaanxi Provincial Department of Education (No. 22JC001), and Key R&D Plan of Shaanxi Province with Shaanxi Provincial Department of Science and Technology, china (2022SF-179,2023YBSF255).

References

[1] M.M. Bikbov, R.R. Fayzrakhmanov, G.M. Kazakbaeva, et al., Frequency and associated factors of bone fractures in Russians: the Ural eye and medical study, Sci. Rep. 8 (1) (2018) 1–9.
[2] W. Wang, K.W.K. Yeung, Bone grafts and biomaterials substitutes for bone defect repair: a review, Bioact. Mater. 2 (4) (2017) 224–247.
[3] K.A. Kravanja, M. Finšgar, A review of techniques for the application of bioactive coatings on metal-based implants to achieve controlled release of active ingredients, Mater. Des. (2022), 110653.
[4] Z. Wu, B. Chan, J. Low, et al., Microbial resistance to nanotechnologies: an important but understudied consideration using antimicrobial nanotechnologies in orthopaedic implants, Bioact. Mater. 16(2022)249-270.
[5] C. Guder, S. Gravius, C. Burger, et al., Osteoimmunology: a current update of the interplay between bone and the immune system, Front. Immunol. 11 (2020) 58.
[6] R.O. Darouiche, Treatment of infections associated with surgical implants, N. Engl. J. Med. 350 (14) (2004) 1422–1429.
[7] A.J. Tande, R. Patel, Prosthetic joint infection, Clin. Microbiol. Rev. 27 (2) (2014) 302–345.
[8] B.H. Kapadia, R.A. Berg, J.A. Daley, et al., Periprosthetic joint infection, Lancet 387 (10016) (2016) 386–394.
[9] S. Hogan, N.T. Stevens, H. Humphreys, et al., Current and future approaches to the prevention and treatment of staphylococcal medical device-related infections, Curr. Pharmaceut. Des. 21 (1) (2015) 100–113.
[10] J.D. Denstedt, T.A. Wollin, G. Reid, Biomaterials used in urology: current issues of biocompatibility, infection, and encrustation, J. Endourol. 12 (6) (1998) 493–500.
[11] J.S. Fernandes, P. Gentile, R.A. Pires, et al., Multifunctional bioactive glass and glass-ceramic biomaterials with antibacterial properties for repair and regeneration of bone tissue, Acta Biomater. 59 (2017) 2–11.

[12] U. Filipović, R.G. Dahmane, S. Ghannouchi, et al., Bacterial adhesion on orthopedic implants, Adv. Colloid Interface Sci. 283 (2020), 102228.
[13] C. Zhao, W. Liu, M. Zhu, et al., Bioceramic-based scaffolds with antibacterial function for bone tissue engineering: a review, Bioact. Mater.18 (2022)383-398.
[14] M. Vallet-Regí, D. Lozano, B. González, et al., Biomaterials against bone infection, Advanced healthcare materials 9 (13) (2020), 2000310.
[15] Z. Yuan, Y. He, C. Lin, et al., Antibacterial surface design of biomedical titanium materials for orthopedic applications, J. Mater. Sci. Technol. 78 (2021) 51–67.
[16] H.Y. Ahmadabadi, K. Yu, J.N. Kizhakkedathu, Surface modification approaches for prevention of implant associated infections, Colloids Surf. B Biointerfaces 193 (2020), 111116.
[17] A. Nana, S.B. Nelson, A. McLaren, et al., What's new in musculoskeletal infection: update on biofilms, JBJS 98 (14) (2016) 1226–1234.
[18] Y. Jin, Z. Zhu, L. Liang, et al., A facile heparin/carboxymethyl chitosan coating mediated by polydopamine on implants for hemocompatibility and antibacterial properties, Appl. Surf. Sci. 528 (2020), 146539.
[19] W. Xi, V. Hegde, S.D. Zoller, et al., Point-of-care antimicrobial coating protects orthopaedic implants from bacterial challenge, Nat. Commun. 12 (1) (2021) 1–15.
[20] R. Ramalhete, R. Brown, G. Blunn, et al., A novel antimicrobial coating to prevent periprosthetic joint infection, Bone & Joint Research 9 (12) (2020) 848–856.
[21] M. Cloutier, D. Mantovani, F. Rosei, Antibacterial coatings: challenges, perspectives, and opportunities, Trends Biotechnol. 33 (11) (2015) 637–652.
[22] I.V. Sukhorukova, A.N. Sheveyko, P.V. Kiryukhantsev-Korneev, et al., Toward bioactive yet antibacterial surfaces, Colloids Surf. B Biointerfaces 135 (2015) 158–165.
[23] E.S. Permyakova, A.M. Manakhov, P.V. Kiryukhantsev-Korneev, et al., Different concepts for creating antibacterial yet biocompatible surfaces: adding bactericidal element, grafting therapeutic agent through COOH plasma polymer and their combination, Appl. Surf. Sci. 556 (2021), 149751.
[24] S. Duan, R. Wu, Y.H. Xiong, et al., Multifunctional antimicrobial materials: from rational design to biomedical applications, Prog. Mater. Sci. 125 (2022), 100887.
[25] J. Raphel, M. Holodniy, S.B. Goodman, et al., Multifunctional coatings to simultaneously promote osseointegration and prevent infection of orthopaedic implants, Biomaterials 84 (2016) 301–314.
[26] S.B. Goodman, Z. Yao, M. Keeney, et al., The future of biologic coatings for orthopaedic implants, Biomaterials 34 (13) (2013) 3174–3183.
[27] Y. Zou, Y. Zhang, Q. Yu, et al., Dual-function antibacterial surfaces to resist and kill bacteria: painting a picture with two brushes simultaneously, J. Mater. Sci. Technol. 70 (2021) 24–38.
[28] Z. Pang, Q. Li, Y. Jia, et al., Controlling the pyridinium–zwitterionic ligand ratio on atomically precise gold nanoclusters allowing for eradicating Gram-positive drug-resistant bacteria and retaining biocompatibility, Chem. Sci. 12 (44) (2021) 14871–14882.
[29] C. Zhou, J. Zhou, X. Ma, et al., Robust anti-infective multilayer coatings with rapid self-healing property, Mater. Sci. Eng. C 121 (2021), 111828.
[30] Y. Tang, C. Wu, Z. Wu, et al., Fabrication and in vitro biological properties of piezoelectric bioceramics for bone regeneration, Sci. Rep. 7 (1) (2017) 1–12.
[31] Y. Li, Y. Ding, K. Munir, et al., Novel β-Ti35Zr28Nb alloy scaffolds manufactured using selective laser melting for bone implant applications, Acta Biomater. 87 (2019) 273–284.
[32] B.G.X. Zhang, D.E. Myers, G.G. Wallace, et al., Bioactive coatings for orthopaedic implants—recent trends in development of implant coatings, Int. J. Mol. Sci. 15 (7) (2014) 11878–11921.
[33] H. Chouirfa, H. Bouloussa, V. Migonney, et al., Review of titanium surface modification techniques and coatings for antibacterial applications, Acta Biomater. 83 (2019) 37–54.
[34] S. Johansson, G. Svineng, K. Wennerberg, et al., Fibronectin-integrin interactions, Frontiers in Bioscience-Landmark 2 (4) (1997) 126–146.
[35] T. Fowler, E.R. Wann, D. Joh, et al., Cellular invasion by Staphylococcus aureus involves a fibronectin bridge between the bacterial fibronectin-binding MSCRAMMs and host cell β1 integrins, Eur. J. Cell Biol. 79 (10) (2000) 672–679.
[36] W. Zimmerli, A. Trampuz, P.E. Ochsner, Prosthetic-joint infections, N. Engl. J. Med. 351 (16) (2004) 1645–1654.
[37] V. Traykov, M.G. Bongiorni, G. Boriani, et al., Clinical practice and implementation of guidelines for the prevention, diagnosis and management of cardiac implantable electronic device infections: results of a worldwide survey under the auspices of the European Heart Rhythm Association, EP Europace 21 (8) (2019) 1270–1279.
[38] J.A. Browne, J.M. Cancienne, W.M. Novicoff, et al., Removal of an infected hip arthroplasty is a high-risk surgery: putting morbidity into context with other major nonorthopedic operations, J. Arthroplasty 32 (9) (2017) 2834–2841.
[39] M. Kumar, R. Kumar, S. Kumar, Coatings on orthopedic implants to overcome present problems and challenges: a focused review, Mater. Today Proc. 45 (2021) 5269–5276.
[40] M.E. Cortés, J.C. Bonilla, R.D. Sinisterra, Biofilm formation, control and novel strategies for eradication, Sci Against Microbial Pathog Commun Curr Res Technol Adv 2 (2011) 896–905.
[41] E.K. Riga, M. Vöhringer, V.T. Widyaya, et al., Polymer-based surfaces designed to reduce biofilm formation: from antimicrobial polymers to strategies for long-term applications, Macromol. Rapid Commun. 38 (20) (2017), 1700216.
[42] Z.K. Zander, M.L. Becker, Antimicrobial and Antifouling Strategies for Polymeric Medical Devices, 2018.
[43] C.R. Arciola, D. Campoccia, L. Montanaro, Implant infections: adhesion, biofilm formation and immune evasion, Nat. Rev. Microbiol. 16 (7) (2018) 397–409.
[44] H.S. Vasavi, H.V. Sudeep, H.B. Lingaraju, et al., Bioavailability-enhanced Resveramax™ modulates quorum sensing and inhibits biofilm formation in Pseudomonas aeruginosa PAO1, Microb. Pathog. 104 (2017) 64–71.
[45] S. Gatadi, Y.V. Madhavi, S. Nanduri, Nanoparticle drug conjugates treating microbial and viral infections: a review, J. Mol. Struct. 1228 (2021), 129750.
[46] S. Fulaz, S. Vitale, L. Quinn, et al., Nanoparticle–biofilm interactions: the role of the EPS matrix, Trends Microbiol. 27 (11) (2019) 915–926.
[47] P. Gilbert, P.J. Collier, M.R. Brown, Influence of growth rate on susceptibility to antimicrobial agents: biofilms, cell cycle, dormancy, and stringent response, Antimicrob. Agents Chemother. 34 (10) (1990) 1865–1868.
[48] A.W. Smith, Biofilms and antibiotic therapy: is there a role for combating bacterial resistance by the use of novel drug delivery systems? Adv. Drug Deliv. Rev. 57 (10) (2005) 1539–1550.
[49] D. Davies, Understanding biofilm resistance to antibacterial agents, Nat. Rev. Drug Discov. 2 (2) (2003) 114–122.
[50] S.L. Percival, L. Suleman, C. Vuotto, et al., Review Healthcare-associated infections, medical devices and biofilms: risk, tolerance and control, J. Med. Microbiol. 64 (2015) 323–334.
[51] G. Topka-Bielecka, A. Dydecka, A. Necel, et al., Bacteriophage-derived depolymerases against bacterial biofilm, Antibiotics 10 (2) (2021) 175.
[52] D. Sharma, L. Misba, A.U. Khan, Antibiotics versus biofilm: an emerging battleground in microbial communities, Antimicrob. Resist. Infect. Control 8 (1) (2019) 1–10.
[53] R. Chen, M.D.P. Willcox, K.K.K. Ho, et al., Antimicrobial peptide melimine coating for titanium and its in vivo antibacterial activity in rodent subcutaneous infection models, Biomaterials 85 (2016) 142–151.
[54] H.J. Busscher, H.C. van der Mei, G. Subbiahdoss, et al., Biomaterial-associated infection: locating the finish line in the race for the surface, Sci. Transl. Med. 4 (153) (2012), 153rv10-153rv10.
[55] I. Banerjee, R.C. Pangule, R.S. Kane, Antifouling coatings: recent developments in the design of surfaces that prevent fouling by proteins, bacteria, and marine organisms, Adv. Mater. 23 (6) (2011) 690–718.
[56] A. Maan, A.H. Hofman, W.M.D. Vos, et al., Recent Developments and Practical Feasibility of Polymer Ⅲased Antifouling Coatings, Advanced Functional Materials, 2020.
[57] T. Chen, L. Zhao, Z. Wang, et al., Hierarchical surface inspired by geminized cationic amphiphilic polymer brushes for super-antibacterial and self-cleaning properties, Biomacromolecules 21 (12) (2020).
[58] G. Lu, S. Tian, J. Li, et al., Fabrication of bio-based amphiphilic hydrogel coating with excellent antifouling and mechanical properties, Chem. Eng. J. 409 (3) (2020), 128134.
[59] L.C. Xu, Z. Li, Z. Tian, et al., A new textured polyphosphazene biomaterial with improved blood coagulation and microbial infection responses, Acta Biomater. 67 (2018) 87–98.
[60] K. Page, M. Wilson, I.P. Parkin, Antimicrobial surfaces and their potential in reducing the role of the inanimate environment in the incidence of hospital-acquired infections, J. Mater. Chem. 19 (23) (2009) 3819–3831.
[61] X. Cui, Y. Koujima, H. Seto, et al., Inhibition of bacterial adhesion on hydroxyapatite model teeth by surface modification with PEGMA-phosmer copolymers, ACS Biomater. Sci. Eng. 2 (2) (2016) 205–212.
[62] Q. Chen, D. Liu, Y. Gong, et al., Modification of titanium surfaces via surface-initiated atom transfer radical polymerization to graft PEG-RGD polymer brushes to inhibit bacterial adhesion and promote osteoblast cell attachment, J. Wuhan Univ. Technol.-Materials Sci. Ed. 32 (5) (2017) 1225–1231.
[63] L.G. Harris, S. Tosatti, M. Wieland, et al., Staphylococcus aureus adhesion to titanium oxide surfaces coated with non-functionalized and peptide-functionalized poly (L-lysine)-grafted-poly (ethylene glycol) copolymers, Biomaterials 25 (18) (2004) 4135–4148.
[64] L. Liu, H. He, R. Liang, et al., ROS-inducing micelles sensitize tumor-associated macrophages to TLR3 stimulation for potent immunotherapy, Biomacromolecules 19 (6) (2018) 2146–2155.
[65] J. Ulbricht, R. Jordan, R. Luxenhofer, On the biodegradability of polyethylene glycol, polypeptoids and poly (2-oxazoline) s, Biomaterials 35 (17) (2014) 4848–4861.
[66] Zhiqiang Cao, Shaoyi Jiang, Super-hydrophilic zwitterionic poly(carboxybetaine) and amphiphilic non-ionic poly(ethylene glycol) for stealth nanoparticles, Nano Today 7 (5) (2012).
[67] S. Kang, M. Lee, M. Kang, et al., Development of anti-biofouling interface on hydroxyapatite surface by coating zwitterionic MPC polymer containing calcium-binding moieties to prevent oral bacterial adhesion, Acta Biomater. 40 (2016) 70–77.
[68] C. Valotteau, C. Calers, S. Casale, et al., Biocidal properties of a glycosylated surface: sophorolipids on Au (111), ACS Appl. Mater. Interfaces 7 (32) (2015) 18086–18095.
[69] M. Li, D. Mitra, E.T. Kang, et al., Thiol-ol chemistry for grafting of natural polymers to form highly stable and efficacious antibacterial coatings, ACS Appl. Mater. Interfaces 9 (2) (2017) 1847–1857.
[70] G. Pitarresi, F.S. Palumbo, F. Calascibetta, et al., Medicated hydrogels of hyaluronic acid derivatives for use in orthopedic field, Int. J. Pharm. 449 (1–2) (2013) 84–94.
[71] F. Liu, X. Liu, F. Chen, et al., Mussel-inspired chemistry: a promising strategy for natural polysaccharides in biomedical applications, Prog. Polym. Sci. 123 (2021), 101472.
[72] Z. Wang, Q. Sun, H. Zhang, et al., Insight into antibacterial mechanism of polysaccharides: a review, LWT (Lebensm.-Wiss. & Technol.) 150 (2021), 111929.

[73] C.L. Romanò, S. Scarponi, E. Gallazzi, et al., Antibacterial coating of implants in orthopaedics and trauma: a classification proposal in an evolving panorama, J. Orthop. Surg. Res. 10 (1) (2015) 1–11.
[74] K.G. Neoh, X. Hu, D. Zheng, et al., Balancing osteoblast functions and bacterial adhesion on functionalized titanium surfaces, Biomaterials 33 (10) (2012) 2813–2822.
[75] Seunghan Oh, Kyung Suk Moon, Seoung Hoon Lee, Effect of RGD peptide-coated TiO2 nanotubes on the attachment, proliferation, and functionality of bone-related cells, J. Nanomater. 2013(2013)9-9.
[76] C. Liu, T. Zhang, Y. Luo, et al., Multifunctional polyurethane sponge coatings with excellent flame retardant, antibacterial, compressible, and recyclable properties, Compos. B Eng. 215 (2021), 108785.
[77] D. Shang, X. Sun, X. Shen, et al., Effects of PEG-TMS on the stability and antifouling performances of hydrocarbon-modified amphiphilic xerogel coatings, Prog. Org. Coating 121 (2018) 142–150.
[78] Z. Zhou, D.R. Calabrese, W. Taylor, et al., Amphiphilic triblock copolymers with PEGylated hydrocarbon structures as environmentally friendly marine antifouling and fouling-release coatings, Biofouling 30 (5) (2014) 589–604.
[79] C. Zhao, L. Li, J. Zheng, Achieving highly effective nonfouling performance for surface-grafted poly (HPMA) via atom-transfer radical polymerization, Langmuir 26 (22) (2010) 17375–17382.
[80] C. Zhao, L. Li, Q. Wang, et al., Effect of film thickness on the antifouling performance of poly (hydroxy-functional methacrylates) grafted surfaces, Langmuir 27 (8) (2011) 4906–4913.
[81] C. Zhao, X. Li, L. Li, et al., Dual functionality of antimicrobial and antifouling of poly (N-hydroxyethylacrylamide)/salicylate hydrogels, Langmuir 29 (5) (2013) 1517–1524.
[82] J.A.D. Olmo, L. Ruiz-Rubio, L. Pérez-Alvarez, et al., Antibacterial coatings for improving the performance of biomaterials, Coatings 10 (2) (2020) 139.
[83] B. Ran, C. Jing, C. Yang, et al., Synthesis of efficient bacterial adhesion-resistant coatings by one-step polydopamine-assisted deposition of branched polyethylenimine-g-poly (sulfobetaine methacrylate) copolymers, Appl. Surf. Sci. 450 (2018) 77–84.
[84] W. Zheng, Y. Jia, W. Chen, et al., Universal coating from electrostatic self-assembly to prevent multidrug-resistant bacterial colonization on medical devices and solid surfaces, ACS Appl. Mater. Interfaces 9 (25) (2017) 21181–21189.
[85] S. Lowe, N.M. O'Brien-Simpson, L.A. Connal, Antibiofouling polymer interfaces: poly (ethylene glycol) and other promising candidates, Polym. Chem. 6 (2) (2015) 198–212.
[86] T. Gillich, C. Acikgöz, L. Isa, et al., PEG-stabilized core–shell nanoparticles: impact of linear versus dendritic polymer shell architecture on colloidal properties and the reversibility of temperature-induced aggregation, ACS Nano 7 (1) (2013) 316–329.
[87] L.A. Connal, C.R. Kinnane, A.N. Zelikin, et al., Stabilization and functionalization of polymer multilayers and capsules via thiol− ene click chemistry, Chem. Mater. 21 (4) (2009) 576–578.
[88] E.D. Pressly, R.A. Pierce, L.A. Connal, et al., Nanoparticle PET/CT imaging of natriuretic peptide clearance receptor in prostate cancer, Bioconjugate Chem. 24 (2) (2013) 196–204.
[89] E. Ostuni, R.G. Chapman, R.E. Holmlin, et al., A survey of structure− property relationships of surfaces that resist the adsorption of protein, Langmuir 17 (18) (2001) 5605–5620.
[90] L. Li, S. Chen, S. Jiang, Protein interactions with oligo (ethylene glycol)(OEG) self-assembled monolayers: OEG stability, surface packing density and protein adsorption, J. Biomater. Sci. Polym. Ed. 18 (11) (2007) 1415–1427.
[91] K. Knop, R. Hoogenboom, D. Fischer, et al., Poly (ethylene glycol) in drug delivery: pros and cons as well as potential alternatives, Angew. Chem. Int. Ed. 49 (36) (2010) 6288–6308.
[92] R. Duncan, R. Gaspar, Nanomedicine (s) under the microscope, Mol. Pharm. 8 (6) (2011) 2101–2141.
[93] K. Ishihara, Blood-compatible surfaces with phosphorylcholine-based polymers for cardiovascular medical devices, Langmuir 35 (5) (2018) 1778–1787.
[94] P. Cabanach, A. Pena-Francesch, D. Sheehan, et al., Zwitterionic 3D-printed non-immunogenic stealth microrobots, Adv. Mater. 32 (42) (2020), 2003013.
[95] P. Liu, J.D. Skelly, J. Song, Three-dimensionally presented anti-fouling zwitterionic motifs sequester and enable high-efficiency delivery of therapeutic proteins, Acta Biomater. 10 (10) (2014) 4296–4303.
[96] R. Imamura, H. Mori, Synthesis of zwitterionic polymers containing a tertiary sulfonium group for protein stabilization, Biomacromolecules 20 (2) (2018) 904–915.
[97] B. Li, P. Jain, J. Ma, et al., Trimethylamine N-oxide–derived zwitterionic polymers: a new class of ultralow fouling bioinspired materials, Sci. Adv. 5 (6) (2019), eaaw9562.
[98] G. Cheng, G. Li, H. Xue, et al., Zwitterionic carboxybetaine polymer surfaces and their resistance to long-term biofilm formation, Biomaterials 30 (28) (2009) 5234–5240.
[99] G. Cheng, Z. Zhang, S. Chen, et al., Inhibition of bacterial adhesion and biofilm formation on zwitterionic surfaces, Biomaterials 28 (29) (2007) 4192–4199.
[100] G. Li, G. Cheng, H. Xue, et al., Ultra low fouling zwitterionic polymers with a biomimetic adhesive group, Biomaterials 29 (35) (2008) 4592–4597.
[101] G. Cheng, H. Xue, G. Li, et al., Integrated antimicrobial and nonfouling hydrogels to inhibit the growth of planktonic bacterial cells and keep the surface clean, Langmuir 26 (13) (2010) 10425–10428.
[102] Z. Cao, S. Jiang, Super-hydrophilic zwitterionic poly (carboxybetaine) and amphiphilic non-ionic poly (ethylene glycol) for stealth nanoparticles, Nano Today 7 (5) (2012) 404–413.
[103] C. Leng, K.A. Gibney, Y. Liu, et al., In situ probing the surface restructuring of antibiofouling amphiphilic polybetaines in water, ACS Macro Lett. 2 (11) (2013) 1011–1015.
[104] H.S. Sundaram, J.R. Ella-Menye, N.D. Brault, et al., Reversibly switchable polymer with cationic/zwitterionic/anionic behavior through synergistic protonation and deprotonation, Chem. Sci. 5 (1) (2014) 200–205.
[105] X. Chen, J. Lawrence, S. Parelkar, et al., Novel zwitterionic copolymers with dihydrolipoic acid: synthesis and preparation of nonfouling nanorods, Macromolecules 46 (1) (2013) 119–127.
[106] G. Jia, Z. Cao, H. Xue, et al., Novel zwitterionic-polymer-coated silica nanoparticles, Langmuir 25 (5) (2009) 3196–3199.
[107] L. Zhang, H. Xue, C. Gao, et al., Imaging and cell targeting characteristics of magnetic nanoparticles modified by a functionalizable zwitterionic polymer with adhesive 3, 4-dihydroxyphenyl-l-alanine linkages, Biomaterials 31 (25) (2010) 6582–6588.
[108] I. Buzzacchera, M. Vorobii, N.Y. Kostina, et al., Polymer brush-functionalized chitosan hydrogels as antifouling implant coatings, Biomacromolecules 18 (6) (2017) 1983–1992.
[109] M.J. Jensen, A. Peel, R. Horne, et al., Antifouling and mechanical properties of photografted zwitterionic hydrogel thin-film coatings depend on the cross-link density, ACS Biomater. Sci. Eng. 7 (9) (2021) 4494–4502.
[110] Y. Zhang, L. Chen, Z. Lin, et al., Highly sensitive dissolved oxygen sensor with a sustainable antifouling, antiabrasion, and self-cleaning superhydrophobic surface, ACS Omega 4 (1) (2019) 1715–1721.
[111] W. Yu, J. Koc, J.A. Finlay, et al., Layer-by-layer constructed hyaluronic acid/chitosan multilayers as antifouling and fouling-release coatings, Biointerphases 14 (5) (2019), 051002.
[112] F.S. Palumbo, A.B. Volpe, M.G. Cusimano, et al., A polycarboxylic/amino functionalized hyaluronic acid derivative for the production of pH sensible hydrogels in the prevention of bacterial adhesion on biomedical surfaces, Int. J. Pharm. 478 (1) (2015) 70–77.
[113] D. Alves, T. Sileika, P.B. Messersmith, et al., Polydopamine-mediated immobilization of alginate lyase to prevent P. aeruginosa adhesion, Macromol. Biosci. 16 (9) (2016) 1301–1310.
[114] L. Xu, D. Pranantyo, K.G. Neoh, et al., Tea stains-inspired antifouling coatings based on tannic acid-functionalized agarose, ACS Sustain. Chem. Eng. 5 (4) (2017) 3055–3062.
[115] J. Zhou, G. Romero, E. Rojas, et al., Layer by layer chitosan/alginate coatings on poly (lactide-co-glycolide) nanoparticles for antifouling protection and Folic acid binding to achieve selective cell targeting, J. Colloid Interface Sci. 345 (2) (2010) 241–247.
[116] A. Fallacara, E. Baldini, S. Manfredini, et al., Hyaluronic acid in the third millennium, Polymers 10 (7) (2018) 701.
[117] C. Huang, C. You, R. Xiong, et al., Research progress of natural polysaccharide in the application of biomedical materials, J. For. Eng 6 (2021) 1–8.
[118] T. Darmanin, F. Guittard, Recent advances in the potential applications of bioinspired superhydrophobic materials, J. Mater. Chem. 2 (39) (2014) 16319–16359.
[119] ABC triblock copolymers antibacterial materials consisting of fluoropolymer and polyethylene glycol antifouling block and quaternary ammonium salt sterilization block, ACS Appl. Bio Mater. 4 (4) (2021) 3166–3177.
[120] W. Li, H. Zhang, X. Li, et al., Multifunctional antibacterial materials comprising water dispersible random copolymers containing a fluorinated block and their application in catheters, ACS Appl. Mater. Interfaces 12 (6) (2020) 7617–7630.
[121] H. Zhu, Z. Guo, W. Liu, Adhesion behaviors on superhydrophobic surfaces, Chem. Commun. 50 (30) (2014) 3900–3913.
[122] J. Wang, J. Sun, J. Zhou, et al., Fluorinated and thermo-cross-linked polyhedral oligomeric silsesquioxanes: new organic–inorganic hybrid materials for high-performance dielectric application, ACS Appl. Mater. Interfaces 9 (14) (2017) 12782–12790.
[123] Z. Wang, H. Zuilhof, Self-healing superhydrophobic fluoropolymer brushes as highly protein-repellent coatings, Langmuir 32 (25) (2016) 6310–6318.
[124] X. Xu, Y. Shao, W. Wang, et al., Fluorinated polyhedral oligomeric silsesquioxanes end-capped poly (ethylene oxide) giant surfactants: precise synthesis and interfacial behaviors, Polymer 186 (2020), 122055.
[125] T. Wang, L. Huang, Y. Liu, et al., Robust biomimetic hierarchical diamond architecture with a self-cleaning, antibacterial, and antibiofouling surface, ACS Appl. Mater. Interfaces 12 (21) (2020) 24432–24441.
[126] S. Pan, R. Guo, M. Björnmalm, et al., Coatings super-repellent to ultralow surface tension liquids, Nat. Mater. 17 (11) (2018) 1040–1047.
[127] R. Jiang, L. Hao, L. Song, et al., Lotus-leaf-inspired hierarchical structured surface with non-fouling and mechanical bactericidal performances, Chem. Eng. J. 398 (2020), 125609.
[128] X. Zhu, D. Jańczewski, S. Guo, et al., Polyion multilayers with precise surface charge control for antifouling, ACS Appl. Mater. Interfaces 7 (1) (2015) 852–861.
[129] J. Hasan, S. Raj, L. Yadav, et al., Engineering a nanostructured "super surface" with superhydrophobic and superkilling properties, RSC Adv. 5 (2015) 44953–44959.
[130] V. Etacheri, C. Di Valentin, J. Schneider, et al., Visible-light activation of TiO2 photocatalysts: advances in theory and experiments, J. Photochem. Photobiol. C Photochem. Rev. 25 (2015) 1–29.
[131] A. Raghunath, E. Perumal, Metal oxide nanoparticles as antimicrobial agents: a promise for the future, Int. J. Antimicrob. Agents 49 (2) (2017) 137–152.
[132] R. Shirai, T. Miura, A. Yoshida, et al., Antimicrobial effect of titanium dioxide after ultraviolet irradiation against periodontal pathogen, Dent. Mater. J. 35 (3) (2016) 511–516.

[133] B. Jalvo, M. Faraldos, A. Bahamonde, et al., Antimicrobial and antibiofilm efficacy of self-cleaning surfaces functionalized by TiO2 photocatalytic nanoparticles against Staphylococcus aureus and Pseudomonas putida, J. Hazard Mater. 340 (2017) 160–170.
[134] K.C. Popat, L. Leoni, C.A. Grimes, et al., Influence of engineered titaniananotubular surfaces on bone cells, Biomaterials 28 (21) (2007) 3188–3197.
[135] Z. Peng, J. Ni, K. Zheng, et al., Dual effects and mechanism of TiO2 nanotube arrays in reducing bacterial colonization and enhancing C3H10T1/2 cell adhesion, Int. J. Nanomed. 8 (2013) 3093.
[136] L. Rodrigues, I.M. Banat, J. Teixeira, et al., Biosurfactants: potential applications in medicine, J. Antimicrob. Chemother. 57 (4) (2006) 609–618.
[137] Zhiyun Dong, Ke Xiang, Shuxian Tang, Shuai Wu, Wei Wu, Xingyu Chen, Jiaojiao Yang, Jing Xie, Jun Luo, Jianshu Li, A stable cell membrane-based coating with antibiofouling and macrophage immunoregulatory properties for implants at the macroscopic level, Chem. Mater. 33 (20) (2021).
[138] Z.X. Voo, M. Khan, K. Narayanan, et al., Antimicrobial/antifouling polycarbonate coatings: role of block copolymer architecture, Macromolecules 48 (4) (2015) 1055–1064.
[139] A. Kugel, S. Stafslien, B.J. Chisholm, Antimicrobial coatings produced by "tethering" biocides to the coating matrix: a comprehensive review, Prog. Org. Coating 72 (3) (2011) 222–252.
[140] X. Yuan, L. Ouyang, Y. Luo, et al., Multifunctional sulfonated polyetheretherketone coating with beta-defensin-14 for yielding durable and broad-spectrum antibacterial activity and osseointegration, Acta Biomater. 86 (2019) 323–337.
[141] F. Costa, I.F. Carvalho, R.C. Montelaro, et al., Covalent immobilization of antimicrobial peptides (AMPs) onto biomaterial surfaces, Acta Biomater. 7 (4) (2011) 1431–1440.
[142] M.N. Melo, R. Ferre, M.A.R.B. Castanho, Antimicrobial peptides: linking partition, activity and high membrane-bound concentrations, Nat. Rev. Microbiol. 7 (3) (2009) 245–250.
[143] J.V. Carratalá, N. Serna, A. Villaverde, et al., Nanostructured antimicrobial peptides: the last push towards clinics, Biotechnol. Adv. 44 (2020), 107603.
[144] N. Mookherjee, M.A. Anderson, H.P. Haagsman, et al., Antimicrobial host defence peptides: functions and clinical potential, Nat. Rev. Drug Discov. 19 (5) (2020) 311–332.
[145] S.A. Onaizi, S.S.J. Leong, Tethering antimicrobial peptides: current status and potential challenges, Biotechnol. Adv. 29 (1) (2011) 67–74.
[146] J. Chen, Y. Zhu, M. Xiong, et al., Antimicrobial titanium surface via click-immobilization of peptide and its in vitro/vivo activity, ACS Biomater. Sci. Eng. 5 (2) (2018) 1034–1044.
[147] M.E. van Gent, M. Ali, P.H. Nibbering, et al., Current advances in lipid and polymeric antimicrobial peptide delivery systems and coatings for the prevention and treatment of bacterial infections, Pharmaceutics 13 (11) (2021) 1840.
[148] M. Kazemzadeh-Narbat, H. Cheng, R. Chabok, et al., Strategies for antimicrobial peptide coatings on medical devices: a review and regulatory science perspective, Crit. Rev. Biotechnol. 41 (1) (2021) 94–120.
[149] S. Atefyekta, M. Pihl, C. Lindsay, et al., Antibiofilm elastin-like polypeptide coatings: functionality, stability, and selectivity, Acta Biomater. 83 (2019) 245–256.
[150] R. Wang, K.G. Neoh, E.T. Kang, Integration of antifouling and bactericidal moieties for optimizing the efficacy of antibacterial coatings, J. Colloid Interface Sci. 438 (2015) 138–148.
[151] Y. Jiao, L. Niu, S. Ma, et al., Quaternary ammonium-based biomedical materials: state-of-the-art, toxicological aspects and antimicrobial resistance, Prog. Polym. Sci. 71 (2017) 53–90.
[152] L. Cheng, K. Zhang, N. Zhang, et al., Developing a new generation of antimicrobial and bioactive dental resins, J. Dent. Res. 96 (8) (2017) 855–863.
[153] B. Ahlström, R.A. Thompson, L. Edebo, The effect of hydrocarbon chain length, pH, and temperature on the binding and bactericidal effect of amphiphilic betaine esters on Salmonella tvphimurium, Apmis 107 (1-6) (1999) 318–324.
[154] S. Deb, R. Doiron, L. DiSilvio, et al., PMMA bone cement containing a quaternary amine comonomer with potential antibacterial properties, J. Biomed. Mater. Res. Part B: Applied Biomaterials: An Official Journal of The Society for Biomaterials, The Japanese Society for Biomaterials, and The Australian Society for Biomaterials and the Korean Society for Biomaterials 85 (1) (2008) 130–139.
[155] C.K.V.Z. Abid, S. Jain, R. Jackeray, et al., Formulation and characterization of antimicrobial quaternary ammonium dendrimer in poly (methyl methcarylate) bone cement, J. Biomed. Mater. Res. B Appl. Biomater. 105 (3) (2017) 521–530.
[156] S. Beyth, D. Polak, C. Milgrom, et al., Antibacterial activity of bone cement containing quaternary ammonium polyethyleneimine nanoparticles, J. Antimicrob. Chemother. 69 (3) (2014) 854–855.
[157] T. Wei, W. Zhan, L. Cao, et al., Multifunctional and regenerable antibacterial surfaces fabricated by a universal strategy, ACS Appl. Mater. Interfaces 8 (44) (2016) 30048–30057.
[158] X. Hu, K.G. Neoh, Z. Shi, et al., An in vitro assessment of titanium functionalized with polysaccharides conjugated with vascular endothelial growth factor for enhanced osseointegration and inhibition of bacterial adhesion, Biomaterials 31 (34) (2010) 8854–8863.
[159] Z.X. Peng, B. Tu, Y. Shen, et al., Quaternized chitosan inhibits icaA transcription and biofilm formation by Staphylococcus on a titanium surface, Antimicrob. Agents Chemother. 55 (2) (2011) 860–866.
[160] F. Siedenbiedel, J.C. Tiller, Antimicrobial polymers in solution and on surfaces: overview and functional principles, Polymers 4 (1) (2012) 46–71.
[161] L. Timofeeva, N. Kleshcheva, Antimicrobial polymers: mechanism of action, factors of activity, and applications, Appl. Microbiol. Biotechnol. 89 (3) (2011) 475–492.
[162] Z. Chen, H. Ji, C. Liu, et al., A multinuclear metal complex based DNase-mimetic artificial enzyme: matrix cleavage for combating bacterial biofilms, Angew. Chem. 128 (36) (2016) 10890–10894.
[163] M. Natan, F. Edin, N. Perkas, et al., Two are better than one: combining ZnO and MgF2 nanoparticles reduces Streptococcus pneumoniae and Staphylococcus aureus biofilm formation on cochlear implants, Adv. Funct. Mater. 26 (15) (2016) 2473–2481.
[164] V.T.H. Pham, V.K. Truong, M.D.J. Quinn, et al., Graphene induces formation of pores that kill spherical and rod-shaped bacteria, ACS Nano 9 (8) (2015) 8458–8467.
[165] M. van de Lagemaat, A. Grotenhuis, B. van de Belt-Gritter, et al., Comparison of methods to evaluate bacterial contact-killing materials, Acta Biomater. 59 (2017) 139–147.
[166] A. Tripathy, P. Sen, B. Su, et al., Natural and bioinspired nanostructured bactericidal surfaces, Adv. Colloid Interface Sci. 248 (2017) 85–104.
[167] S. Pandit, Z. Cao, V.R.S.S. Mokkapati, et al., Vertically aligned graphene coating is bactericidal and prevents the formation of bacterial biofilms, Adv. Mater. Interfac. 5 (7) (2018), 1701331.
[168] J. Ye, B. Li, M. Li, et al., Formation of a ZnO nanorods-patterned coating with strong bactericidal capability and quantitative evaluation of the contribution of nanorods-derived puncture and ROS-derived killing, Bioact. Mater. 11 (2022) 181–191.
[169] J. Ye, B. Li, Y. Zheng, et al., Eco-friendly bacteria-killing by nanorods through mechano-puncture with top selectivity, Bioact. Mater. 15 (2022) 173–184.
[170] J. Tian, Y. Liu, S. Miao, et al., Amyloid-like protein aggregates combining antifouling with antibacterial activity, Biomater. Sci. 8(24)(2020) 6903-6911.
[171] M.H. Xiong, Y. Bao, X.Z. Yang, et al., Delivery of antibiotics with polymeric particles, Adv. Drug Deliv. Rev. 78 (2014) 63–76.
[172] V. Castelletto, C.J.C. Edwards-Gayle, I.W. Hamley, et al., Peptide-stabilized emulsions and gels from an arginine-rich surfactant-like peptide with antimicrobial activity, ACS Appl. Mater. Interfaces 11 (10) (2019) 9893–9903.
[173] Z. Sadrearhami, T.K. Nguyen, R. Namivandi-Zangeneh, et al., Recent advances in nitric oxide delivery for antimicrobial applications using polymer-based systems, J. Mater. Chem. B 6 (19) (2018) 2945–2959.
[174] S. Tang, J. Zheng, Antibacterial activity of silver nanoparticles: structural effects, Advanced healthcare materials 7 (13) (2018), 1701503.
[175] J. Cai, R. Liu, Introduction to antibacterial biomaterials, Biomater. Sci. 8 (24) (2020) 6812–6813.
[176] R. Agarwal, A.J. García, Biomaterial strategies for engineering implants for enhanced osseointegration and bone repair, Adv. Drug Deliv. Rev. 94 (2015) 53–62.
[177] N.J. Hickok, I.M. Shapiro, Immobilized antibiotics to prevent orthopaedic implant infections, Adv. Drug Deliv. Rev. 64 (12) (2012) 1165–1176.
[178] H.W. Buchholz, H. Engelbrecht, Depot effects of various antibiotics mixed with Palacos resins, Der Chirurg; Zeitschrift fur alle Gebiete der operativen Medizen 41 (11) (1970) 511–515.
[179] D. Jahoda, O. Nyc, D. Pokorný, et al., Antibiotic treatment for prevention of infectious complications in joint replacement, Acta Chir. Orthop. Traumatol. Cech. 73 (2) (2006) 108–114.
[180] L. Engesæter, S.A. Lie, B. Espehaug, et al., Antibiotic prophylaxis in total hip arthroplasty Effects of antibiotic prophylaxis systemically and in bone cement on the revision rate of 22,170 primary hip replacements followed 0-14 years in the Norwegian Arthroplasty Register, Acta Orthop. Scand. 74 (6) (2003) 644–651.
[181] V. Alt, A. Bitschnau, J. Österling, et al., The effects of combined gentamicin–hydroxyapatite coating for cementless joint prostheses on the reduction of infection rates in a rabbit infection prophylaxis model, Biomaterials 27 (26) (2006) 4627–4634.
[182] K.C. Popat, M. Eltgroth, T.J. LaTempa, et al., Decreased Staphylococcus epidermis adhesion and increased osteoblast functionality on antibiotic-loaded titania nanotubes, Biomaterials 28 (32) (2007) 4880–4888.
[183] V. Antoci Jr., C.S. Adams, J. Parvizi, et al., The inhibition of Staphylococcus epidermidis biofilm formation by vancomycin-modified titanium alloy and implications for the treatment of periprosthetic infection, Biomaterials 29 (35) (2008) 4684–4690.
[184] O. Guillaume, X. Garric, J.P. Lavigne, et al., Multilayer, degradable coating as a carrier for the sustained release of antibiotics: preparation and antimicrobial efficacy in vitro, J. Contr. Release 162 (3) (2012) 492–501.
[185] Y. Tang, Y. Zhao, H. Wang, et al., Layer-by-layer assembly of antibacterial coating on interbonded 3D fibrous scaffolds and its cytocompatibility assessment, J. Biomed. Mater. Res. 100 (8) (2012) 2071–2078.
[186] S. Radin, P. Ducheyne, Controlled release of vancomycin from thin sol–gel films on titanium alloy fracture plate material, Biomaterials 28 (9) (2007) 1721–1729.
[187] H. Sun, Y. Hong, Y. Xi, et al., Synthesis, self-assembly, and biomedical applications of antimicrobial peptide–polymer conjugates, Biomacromolecules 19 (6) (2018) 1701–1720.
[188] B.P. Gibb, M. Hadjiargyrou, Bacteriophage therapy for bone and joint infections: an instructional review, The bone & joint journal 103 (2) (2021) 234–244.
[189] J.K. Smith, J.D. Bumgardner, H.S. Courtney, et al., Antibiotic-loaded chitosan film for infection prevention: a preliminary in vitro characterization, J. Biomed. Mater. Res. B Appl. Biomater. 94 (1) (2010) 203–211.
[190] M.M. Tunney, G. Ramage, S. Patrick, et al., Antimicrobial susceptibility of bacteria isolated from orthopedic implants following revision hip surgery, Antimicrob. Agents Chemother. 42 (11) (1998) 3002–3005.

[191] E. Tshibangu-Kabamba, Y. Yamaoka, Helicobacter pylori infection and antibiotic resistance—from biology to clinical implications, Nat. Rev. Gastroenterol. Hepatol. 18 (9) (2021) 613–629.
[192] E. Rossi, R. La Rosa, J.A. Bartell, et al., Pseudomonas aeruginosa adaptation and evolution in patients with cystic fibrosis, Nat. Rev. Microbiol. 19 (5) (2021) 331–342.
[193] H. Wahlig, E. Dingeldein, Antibiotics and bone cements: experimental and clinical long-term observations, Acta Orthop. Scand. 51 (1–6) (1980) 49–56.
[194] X. Tian, X. Jiang, C. Welch, et al., Bactericidal effects of silver nanoparticles on lactobacilli and the underlying mechanism, ACS Appl. Mater. Interfaces 10 (10) (2018) 8443–8450.
[195] Z. Jia, W. Zhou, J. Yan, et al., Constructing multilayer silk protein/Nanosilver biofunctionalized hierarchically structured 3D printed Ti6Al4 V scaffold for repair of infective bone defects, ACS Biomater. Sci. Eng. 5 (1) (2018) 244–261.
[196] K. Xie, Z. Zhou, Y. Guo, et al., Long-term prevention of bacterial infection and enhanced osteoinductivity of a hybrid coating with selective silver toxicity, Advanced healthcare materials 8 (5) (2019), 1801465.
[197] C. Schlaich, M. Li, C. Cheng, et al., Mussel-inspired polymer-based universal spray coating for surface modification: fast fabrication of antibacterial and superhydrophobic surface coatings, Adv. Mater. Interfac. 5 (5) (2018), 1701254.
[198] J.D. Bumgardner, P. Adatrow, W.O. Haggard, et al., Emerging antibacterial biomaterial strategies for the prevention of peri-implant inflammatory diseases, Int. J. Oral Maxillofac. Implants 26 (3) (2011).
[199] P. Boomi, J.A. Raj, S.P. Palaniappan, et al., Improved conductivity and antibacterial activity of poly (2-aminothiophenol)-silver nanocomposite against human pathogens, J. Photochem. Photobiol. B Biol. 178 (2018) 323–329.
[200] A. Celebioglu, F. Topuz, Z.I. Yildiz, et al., One-step green synthesis of antibacterial silver nanoparticles embedded in electrospun cyclodextrin nanofibers, Carbohydr. Polym. 207 (2019) 471–479.
[201] M.J. Monerris, M.F. Broglia, E.I. Yslas, et al., Antibacterial Polymeric Nanocomposites Synthesized by In-Situ Photoreduction of Silver Ions without Additives inside Biocompatible Hydrogel Matrices Based on N-Isopropylacrylamide and Derivatives, 2017.
[202] L. Du, Y.J. Wang, K. Wang, et al., In situ dispersion of oil-based Ag nanocolloids by microdroplet coalescence and their applications in SERS detection, RSC Adv. 6 (64) (2016) 59639–59647.
[203] M. Hao, W. Zhao, R. Li, et al., Surface modification of as-prepared silver-coated silica microspheres through mussel-inspired functionalization and its application properties in silicone rubber, Ind. Eng. Chem. Res. 57 (22) (2018) 7486–7494.
[204] X. Chen, F. Liang, W. Lu, et al., High permittivity nanocomposites embedded with Ag/TiO2 core–shell nanoparticles modified by phosphonic acid, Polymers 10 (6) (2018) 586.
[205] H.C. Fischer, W.C.W. Chan, Nanotoxicity: the growing need for in vivo study, Curr. Opin. Biotechnol. 18 (6) (2007) 565–571.
[206] K. Zhang, V.C.H. Lui, Y. Chen, et al., Delayed application of silver nanoparticles reveals the role of early inflammation in burn wound healing, Sci. Rep. 10 (1) (2020) 1–12.
[207] J. Parvizi, P. Alijanipour, E.F. Barberi, et al., Novel developments in the prevention, diagnosis, and treatment of periprosthetic joint infections, JAAOS-Journal of the American Academy of Orthopaedic Surgeons 23 (suppl) (2015) S32–S43.
[208] L.A.B. Santana, P.H.O. Junior, C. Damia, et al., Bioactivity in SBF versus trace element effects: the isolated role of Mg2+ and Zn2+ in osteoblast behavior, Mater. Sci. Eng. C 118 (2021), 111320.
[209] G. Jin, H. Qin, H. Cao, et al., Zn/Ag micro-galvanic couples formed on titanium and osseointegration effects in the presence of S. aureus, Biomaterials 65 (2015) 22–31.
[210] X. Shen, Y. Hu, G. Xu, et al., Regulation of the biological functions of osteoblasts and bone formation by Zn-incorporated coating on microrough titanium, ACS Appl. Mater. Interfaces 6 (18) (2014) 16426–16440.
[211] H. Hu, W. Zhang, Y. Qiao, et al., Antibacterial activity and increased bone marrow stem cell functions of Zn-incorporated TiO2 coatings on titanium, Acta Biomater. 8 (2) (2012) 904–915.
[212] K. Huo, X. Zhang, H. Wang, et al., Osteogenic activity and antibacterial effects on titanium surfaces modified with Zn-incorporated nanotube arrays, Biomaterials 34 (13) (2013) 3467–3478.
[213] A. Jacobs, G. Renaudin, C. Forestier, et al., Biological properties of copper-doped biomaterials for orthopedic applications: a review of antibacterial, angiogenic and osteogenic aspects, Acta Biomater. 117 (2020) 21–39.
[214] X. Liu, K. Gan, H. Liu, et al., Antibacterial properties of nano-silver coated PEEK prepared through magnetron sputtering, Dent. Mater. 33 (9) (2017) e348–e360.
[215] X. Song, L. Xie, M. Zhang, et al., Cu-decorated graphene oxide coatings with enhanced antibacterial activity for surface modification of implant, Mater. Res. Bull. 141 (2021), 111345.
[216] D.A. Robinson, R.W. Griffith, D. Shechtman, et al., In vitro antibacterial properties of magnesium metal against Escherichia coli, Pseudomonas aeruginosa and Staphylococcus aureus, Acta Biomater. 6 (5) (2010) 1869–1877.
[217] C.L. Wetteland, N.Y.T. Nguyen, H. Liu, Concentration-dependent behaviors of bone marrow derived mesenchymal stem cells and infectious bacteria toward magnesium oxide nanoparticles, Acta Biomater. 35 (2016) 341–356.
[218] F. Peng, D. Wang, D. Zhang, et al., PEO/Mg–Zn–Al LDH composite coating on Mg alloy as a Zn/Mg ion-release platform with multifunctions: enhanced corrosion resistance, osteogenic, and antibacterial activities, ACS Biomater. Sci. Eng. 4 (12) (2018) 4112–4121.
[219] J. Liu, Y. Wang, J. Ma, et al., A review on bidirectional analogies between the photocatalysis and antibacterial properties of ZnO, J. Alloys Compd. 783 (2019) 898–918.
[220] A.A. Oun, S. Shankar, J.W. Rhim, Multifunctional nanocellulose/metal and metal oxide nanoparticle hybrid nanomaterials, Crit. Rev. Food Sci. Nutr. 60 (3) (2020) 435–460.
[221] J. Gallo, M. Holinka, C.S. Moucha, Antibacterial surface treatment for orthopaedic implants, Int. J. Mol. Sci. 15 (8) (2014) 13849–13880.
[222] Y.L. Li, J. He, H.X. Ye, et al., Atomic layer deposition of zinc oxide onto 3D porous iron scaffolds for bone repair: in vitro degradation, antibacterial activity and cytocompatibility evaluation, Rare Met. 41 (2) (2022) 546–558.
[223] I. Perelshtein, A. Lipovsky, N. Perkas, et al., The influence of the crystalline nature of nano-metal oxides on their antibacterial and toxicity properties, Nano Res. 8 (2) (2015) 695–707.
[224] J. Milenkovic, J. Hrenovic, D. Matijasevic, et al., Bactericidal activity of Cu-, Zn-, and Ag-containing zeolites toward Escherichia coli isolates, Environ. Sci. Pollut. Control Ser. 24 (25) (2017) 20273–20281.
[225] R. Lotha, B.R. Shamprasad, N.S. Sundaramoorthy, et al., Biogenic phytochemicals (cassinopin and isoquercetin) capped copper nanoparticles (ISQ/CAS@ CuNPs) inhibits MRSA biofilms, Microb. Pathog. 132 (2019) 178–187.
[226] C. Ning, X. Wang, L. Li, et al., Concentration ranges of antibacterial cations for showing the highest antibacterial efficacy but the least cytotoxicity against mammalian cells: implications for a new antibacterial mechanism, Chem. Res. Toxicol. 28 (9) (2015) 1815–1822.
[227] L.F. Cooper, Y. Zhou, J. Takebe, et al., Fluoride modification effects on osteoblast behavior and bone formation at TiO2 grit-blasted cp titanium endosseous implants, Biomaterials 27 (6) (2006) 926–936.
[228] J. Holinka, M. Pilz, B. Kubista, et al., Effects of selenium coating of orthopaedic implant surfaces on bacterial adherence and osteoblastic cell growth, The bone & joint journal 95 (5) (2013) 678–682.
[229] T. Shirai, T. Shimizu, K. Ohtani, et al., Antibacterial iodine-supported titanium implants, Acta Biomater. 7 (4) (2011) 1928–1933.
[230] H. Tsuchiya, T. Shirai, H. Nishida, et al., Innovative antimicrobial coating of titanium implants with iodine, J. Orthop. Sci. 17 (5) (2012) 595–604.
[231] S. Liu, K. Fukushima, S. Venkataraman, et al., Supramolecular nanofibers self-assembled from cationic small molecules derived from repurposed poly (ethylene teraphthalate) for antibiotic delivery, Nanomed. Nanotechnol. Biol. Med. 14 (1) (2018) 165–172.
[232] Z. Jia, P. Xiu, M. Li, et al., Bioinspired anchoring AgNPs onto micro-nanoporous TiO2 orthopedic coatings: trap-killing of bacteria, surface-regulated osteoblast functions and host responses, Biomaterials 75 (2016) 203–222.
[233] Biomaterials, Studies from University of Pennsylvania Yield New Information about Biomaterials (Percutaneous external fixator pins with bactericidal micron-thin sol-gel films for the prevention of pin tract infection), Journal of Technology & Science 62(2015)95-105.
[234] J. Song, Q. Chen, Y. Zhang, et al., Electrophoretic deposition of chitosan coatings modified with gelatin nanospheres to tune the release of antibiotics, ACS Appl. Mater. Interfaces 8 (22) (2016) 13785–13792.
[235] Liang Wu, Yong Gu, Lili Liu, Jincheng Tang, Jiannan Mao, Kun Xi, Zhirong Jiang, Yidi Zhou, Yun Xu, Lianfu Deng, Liang Chen, Wenguo Cui, Hierarchical micro/nanofibrous membranes of sustained releasing VEGF for periosteal regeneration, Biomaterials 227 (C) (2020).
[236] M. Thukkaram, R. Coryn, M. Asadian, et al., Fabrication of microporous coatings on titanium implants with improved mechanical, antibacterial, and cell-interactive properties, ACS Appl. Mater. Interfaces 12 (27) (2020) 30155–30169.
[237] F. Ordikhani, E. Tamjid, A. Simchi, Characterization and antibacterial performance of electrodeposited chitosan–vancomycin composite coatings for prevention of implant-associated infections, Mater. Sci. Eng. C 41 (2014) 240–248.
[238] L. Séon, P. Lavalle, P. Schaaf, et al., Polyelectrolyte multilayers: a versatile tool for preparing antimicrobial coatings, Langmuir 31 (47) (2015) 12856–12872.
[239] H. Sun, L. Lv, Y. Bai, et al., Nanotechnology-enabled materials for hemostatic and anti-infection treatments in orthopedic surgery, Int. J. Nanomed. 13 (2018) 8325.
[240] H. Wei, X. Song, P. Liu, et al., Antimicrobial coating strategy to prevent orthopaedic device-related infections: recent advances and future perspectives, Biomaterials Advances (2022), 212739.
[241] R. Lakshminarayanan, E. Ye, D.J. Young, et al., Recent advances in the development of antimicrobial nanoparticles for combating resistant pathogens, Advanced healthcare materials 7 (13) (2018), 1701400.
[242] M. Kumar, A. Curtis, C. Hoskins, Application of nanoparticle technologies in the combat against anti-microbial resistance, Pharmaceutics 10 (1) (2018) 11.
[243] C.M. Xie, X. Lu, K.F. Wang, et al., Silver nanoparticles and growth factors incorporated hydroxyapatite coatings on metallic implant surfaces for enhancement of osteoinductivity and antibacterial properties, ACS Appl. Mater. Interfaces 6 (11) (2014) 8580–8589.
[244] L. Zhao, H. Wang, K. Huo, et al., Antibacterial nano-structured titania coating incorporated with silver nanoparticles, Biomaterials 32 (24) (2011) 5706–5716.
[245] Chen Y. Antibacterial, Osteogenic and Angiogenic Activities of SrTiO3 Nanotube Arrays Embedded with Ag2O Nanoparticles[D].Taiyuan: Taiyuan University of Technology, 2017.
[246] Z.P. Zeng, B.Q. Tan, X. He, et al., Titanium oxide nanotubes embedded with silver dioxide nanoparticles for treatment of prosthetic joints infections in vivo and *in vitro* in rabbit, Met. Funct. Mater. 26 (2019) 42–48, https://doi.org/10.13228/j.boyuan.issn1005-8192.2019015, 04.
[247] S. Zhong, L. Huang, J. Chen, et al., New J. Chem. 43 (4) (2018) 1827–1837.

[248] X. Xu, Y. Li, L. Wang, et al., Triple-functional polyetheretherketone surface with enhanced bacteriostasis and anti-inflammatory and osseointegrative properties for implant application, Biomaterials 212 (2019) 98–114.
[249] K. He, Z. Zeng, A. Chen, et al., Advancement of Ag–graphene based nanocomposites: an overview of synthesis and its applications, Small 14 (32) (2018), 1800871.
[250] X. Wang, W. Sun, W. Yang, et al., Mesoporous silica-protected silver nanoparticle disinfectant with controlled Ag+ ion release, efficient magnetic separation, and effective antibacterial activity, Nanoscale Adv. 1 (2) (2019) 840–848.
[251] M. Liu, F. Huang, C.T. Hung, et al., An implantable antibacterial drug-carrier: mesoporous silica coatings with size-tunable vertical mesochannels, Nano Res. 15 (5) (2022) 4243–4250.
[252] S. Maslanka Figueroa, D. Fleischmann, S. Beck, et al., Nanoparticles mimicking viral cell recognition strategies are superior transporters into mesangial cells, Adv. Sci. 7 (11) (2020), 1903204.
[253] A. Ghose, B. Nabi, S. Rehman, et al., Development and evaluation of polymeric nanosponge hydrogel for terbinafine hydrochloride: statistical optimization, in vitro and in vivo studies, Polymers 12 (12) (2020) 2903.
[254] A. Barik, N. Chakravorty, Targeted drug delivery from titanium implants: a review of challenges and approaches, Trends in Biomedical Research (2019) 1–17.
[255] A. Ghimire, J.D. Skelly, J. Song, Micrococcal-nuclease-triggered on-demand release of vancomycin from intramedullary implant coating eradicates Staphylococcus aureus infection in mouse femoral canals, ACS Cent. Sci. 5 (12) (2019) 1929–1936.
[256] M. Fu, Y. Liang, X. Lv, et al., Recent advances in hydrogel-based anti-infective coatings, J. Mater. Sci. Technol. 85 (2021) 169–183.
[257] X. Hao, W.H. Wang, Z. Yang, et al., pH responsive antifouling and antibacterial multilayer films with Self-healing performance, Chem. Eng. J. 356 (2019) 130–141.
[258] Y. Li, N. Li, J. Ge, et al., Biodegradable thermal imaging-tracked ultralong nanowire-reinforced conductive nanocomposites elastomers with intrinsical efficient antibacterial and anticancer activity for enhanced biomedical application potential, Biomaterials 201 (2019) 68–76.
[259] L. Mi, S. Jiang, Integrated antimicrobial and nonfouling zwitterionic polymers, Angew. Chem. Int. Ed. 53 (7) (2014) 1746–1754.
[260] Q. Yu, Z. Wu, H. Chen, Dual-function antibacterial surfaces for biomedical applications, Acta Biomater. 16 (2015) 1–13.
[261] S. Zhang, X. Yang, B. Tang, et al., New insights into synergistic antimicrobial and antifouling cotton fabrics via dually finished with quaternary ammonium salt and zwitterionic sulfobetaine, Chem. Eng. J. 336 (2018) 123–132.
[262] Z. Li, W. Hu, Y. Zhao, et al., Integrated antibacterial and antifouling surfaces via cross-linking chitosan-g-eugenol/zwitterionic copolymer on electrospun membranes, Colloids Surf. B Biointerfaces 169 (2018) 151–159.
[263] Q. Zeng, Y. Zhu, B. Yu, et al., Antimicrobial and antifouling polymeric agents for surface functionalization of medical implants, Biomacromolecules 19 (7) (2018) 2805–2811.
[264] X. Xin, P. Li, Y. Zhu, et al., Mussel-inspired surface functionalization of PET with zwitterions and silver nanoparticles for the dual-enhanced antifouling and antibacterial properties, Langmuir 35 (5) (2018) 1788–1797.
[265] Y. Fu, Y. Yang, S. Xiao, et al., Mixed polymer brushes with integrated antibacterial and antifouling properties, Prog. Org. Coating 130 (2019) 75–82.
[266] A. Vaterrodt, B. Thallinger, K. Daumann, et al., Antifouling and antibacterial multifunctional polyzwitterion/enzyme coating on silicone catheter material prepared by electrostatic layer-by-layer assembly, Langmuir 32 (5) (2016) 1347–1359.
[267] Y. Xie, L. Chen, X. Zhang, et al., Integrating zwitterionic polymer and Ag nanoparticles on polymeric membrane surface to prepare antifouling and bactericidal surface via Schiff-based layer-by-layer assembly, J. Colloid Interface Sci. 510 (2018) 308–317.
[268] M. He, Q. Wang, W. Zhao, et al., A substrate-independent ultrathin hydrogel film as an antifouling and antibacterial layer for a microfiltration membrane anchored via a layer-by-layer thiol–ene click reaction, J. Mater. Chem. B 6 (23) (2018) 3904–3913.
[269] A. Valverde, L. Pérez-Álvarez, L. Ruiz-Rubio, et al., Antibacterial hyaluronic acid/chitosan multilayers onto smooth and micropatterned titanium surfaces, Carbohydr. Polym. 207 (2019) 824–833.
[270] A.B. Asha, Y. Chen, H. Zhang, et al., Rapid mussel-inspired surface zwitteration for enhanced antifouling and antibacterial properties, Langmuir 35 (5) (2018) 1621–1630.
[271] G. Cheng, H. Xue, Z. Zhang, et al., A switchable biocompatible polymer surface with self-sterilizing and nonfouling capabilities, Angew. Chem. 120 (46) (2008) 8963–8966.
[272] M. Garay-Sarmiento, L. Witzdam, M. Vorobii, et al., Kill&repel coatings: the marriage of antifouling and bactericidal properties to mitigate and treat wound infections, Adv. Funct. Mater. 32 (9) (2022), 2106656.
[273] L. Fan, W. Sun, Y. Zou, et al., Enhanced corrosion resistance, antibacterial activity and biocompatibility of gentamicin-montmorillonite coating on Mg alloy-in vitro and in vivo studies, J. Mater. Sci. Technol. 111 (2022) 167–180.
[274] Y. Wang, W. Teng, Z. Zhang, et al., A trilogy antimicrobial strategy for multiple infections of orthopedic implants throughout their life cycle, Bioact. Mater. 6 (7) (2021) 1853–1866.
[275] X. Liao, X. Yu, H. Yu, et al., Development of an anti-infective coating on the surface of intraosseous implants responsive to enzymes and bacteria, J. Nanobiotechnol. 19 (1) (2021) 1–16.
[276] T. Xiao, L. Fan, R. Liu, et al., Fabrication of dexamethasone-loaded dual-metal–organic frameworks on polyetheretherketone implants with bacteriostasis and angiogenesis properties for promoting bone regeneration, ACS Appl. Mater. Interfaces 13 (43) (2021) 50836–50850.
[277] M. Han, Z. Dong, J. Li, et al., Mussel-inspired self-assembly engineered implant coatings for synergistic anti-infection and osteogenesis acceleration, J. Mater. Chem. B 9 (40) (2021) 8501–8511.
[278] N.H. Rao, N. Lakshmidevi, S.V.N. Pammi, et al., Green synthesis of silver nanoparticles using methanolic root extracts of Diospyros paniculata and their antimicrobial activities, Mater. Sci. Eng. C 62 (2016) 553–557.
[279] X. Chen, K. Cai, J. Fang, et al., Dual action antibacterial TiO2 nanotubes incorporated with silver nanoparticles and coated with a quaternary ammonium salt (QAS), Surf. Coating. Technol. 216 (2013) 158–165.
[280] H.S. Han, I. Jun, H.K. Seok, et al., Biodegradable magnesium alloys promote angio-osteogenesis to enhance bone repair, Adv. Sci. 7 (15) (2020), 2000800.
[281] D. Zhao, T. Wang, J. Kuhlmann, et al., In vivo monitoring the biodegradation of magnesium alloys with an electrochemical H2 sensor, Acta Biomater. 36 (2016) 361–368.
[282] A. Salhotra, H.N. Shah, B. Levi, et al., Mechanisms of bone development and repair, Nat. Rev. Mol. Cell Biol. 21 (11) (2020) 696–711.
[283] L.Y. Cui, L. Gao, J.C. Zhang, et al., In vitro corrosion resistance, antibacterial activity and cytocompatibility of a layer-by-layer assembled DNA coating on magnesium alloy, Journal of Magnesium and Alloys 9 (1) (2021) 266–280.
[284] B. Yuan, H. Chen, R. Zhao, et al., Construction of a magnesium hydroxide/graphene oxide/hydroxyapatite composite coating on Mg–Ca–Zn–Ag alloy to inhibit bacterial infection and promote bone regeneration, Bioact. Mater. 18 (2022) 354–367.
[285] S.Y. Rahnamaee, R. Bagheri, H. Heidarpour, et al., Nanofibrillated chitosan coated highly ordered titania nanotubes array/graphene nanocomposite with improved biological characters, Carbohydr. Polym. 254 (2021), 117465.
[286] A.P. Blum, J.K. Kammeyer, A.M. Rush, et al., Stimuli-responsive nanomaterials for biomedical applications, J. Am. Chem. Soc. 137 (6) (2015) 2140–2154.
[287] J. Zhang, L. Liu, L. Wang, et al., pH responsive zwitterionic-to-cationic transition for safe self-defensive antibacterial application, J. Mater. Chem. B 8 (38) (2020) 8908–8913.
[288] T. Wei, Q. Yu, H. Chen, Responsive and synergistic antibacterial coatings: fighting against bacteria in a smart and effective way, Advanced healthcare materials 8 (3) (2019), 1801381.
[289] G. Cado, R. Aslam, L. Séon, et al., Self-defensive biomaterial coating against bacteria and yeasts: polysaccharide multilayer film with embedded antimicrobial peptide, Adv. Funct. Mater. 23 (38) (2013) 4801–4809.
[290] J. Ye, X. Zhang, W. Xie, et al., An enzyme-responsive prodrug with inflammation-triggered therapeutic drug release characteristics, Macromol. Biosci. 20 (9) (2020), 2000116.
[291] N.G. Fischer, X. Chen, K. Astleford-Hopper, et al., Antimicrobial and enzyme-responsive multi-peptide surfaces for bone-anchored devices, Mater. Sci. Eng. C 125 (2021), 112108.
[292] F. Hizal, I. Zhuk, S. Sukhishvili, et al., Impact of 3D hierarchical nanostructures on the antibacterial efficacy of a bacteria-triggered self-defensive antibiotic coating, ACS Appl. Mater. Interfaces 7 (36) (2015) 20304–20313.
[293] L. Sutrisno, S. Wang, M. Li, et al., Construction of three-dimensional net-like polyelectrolyte multilayered nanostructures onto titanium substrates for combined antibacterial and antioxidant applications, J. Mater. Chem. B 6 (32) (2018) 5290–5302.
[294] Y. Bu, L. Zhang, J. Liu, et al., Synthesis and properties of hemostatic and bacteria-responsive in situ hydrogels for emergency treatment in critical situations, ACS Appl. Mater. Interfaces 8 (20) (2016) 12674–12683.
[295] X. Jin, Y.H. Xiong, X.Y. Zhang, et al., Self-adaptive antibacterial porous implants with sustainable responses for infected bone defect therapy, Adv. Funct. Mater. 29 (17) (2019), 1807915.
[296] T. Wang, X. Liu, Y. Zhu, et al., Metal ion coordination polymer-capped pH-triggered drug release system on titania nanotubes for enhancing self-antibacterial capability of Ti implants, ACS Biomater. Sci. Eng. 3 (5) (2017) 816–825.
[297] T. Liu, S. Yan, R. Zhou, et al., Self-adaptive antibacterial coating for universal polymeric substrates based on a micrometer-scale hierarchical polymer brush system, ACS Appl. Mater. Interfaces 12 (38) (2020) 42576–42585.
[298] Y. Zou, K. Lu, Y. Lin, et al., Dual-functional surfaces based on an antifouling polymer and a natural antibiofilm molecule: prevention of biofilm formation without using Biocides, ACS Appl. Mater. Interfaces 13 (38) (2021) 45191–45200.
[299] B. Fang, P. Qiu, C. Xia, et al., Extracellular matrix scaffold crosslinked with vancomycin for multifunctional antibacterial bone infection therapy, Biomaterials 268 (2021), 120603.
[300] Y.J. Wang, X.L. Huang, J.J. Chen, et al., Bacterial infection-microenvironment responsive polymeric materials for the treatment of bacterial infectious diseases: a review, Materials Reports 33 (2019) 5–15.
[301] B. Wang, H. Liu, L. Sun, et al., Construction of high drug loading and enzymatic degradable multilayer films for self-defense drug release and long-term biofilm inhibition, Biomacromolecules 19 (1) (2018) 85–93.
[302] X. Wang, L. Song, J. Zhao, et al., Bacterial adaptability of enzyme and pH dual-responsive surface for infection resistance, J. Mater. Chem. B 6 (46) (2018) 7710–7718.
[303] L. Yang, C. Wang, L. Li, et al., Bioinspired integration of naturally occurring molecules towards universal and smart antibacterial coatings, Adv. Funct. Mater. 32 (4) (2022), 2108749.
[304] W. Zhou, T. Bai, L. Wang, et al., Biomimetic AgNPs@ antimicrobial peptide/silk fibroin coating for infection-trigger antibacterial capability and enhanced osseointegration, Bioact. Mater. 20 (2023) 64–80.

[305] L. Zhang, Y. Wang, J. Wang, et al., Photon-responsive antibacterial nanoplatform for synergistic photothermal-/pharmaco-therapy of skin infection, ACS Appl. Mater. Interfaces 11 (1) (2018) 300–310.
[306] Q. Wu, G. Wei, Z. Xu, et al., Mechanistic insight into the light-irradiated carbon capsules as an antibacterial agent, ACS Appl. Mater. Interfaces 10 (30) (2018) 25026–25036.
[307] Y. Chen, Y. Gao, Y. Chen, et al., Nanomaterials-based photothermal therapy and its potentials in antibacterial treatment, J. Contr. Release 328 (2020) 251–262.
[308] Y. Zou, Y. Zhang, Q. Yu, et al., Photothermal bactericidal surfaces: killing bacteria using light instead of biocides, Biomater. Sci. 9 (1) (2021) 10–22.
[309] W. Lei, K. Ren, T. Chen, et al., Polydopamine nanocoating for effective photothermal killing of bacteria and fungus upon near-infrared irradiation, Adv. Mater. Interfac. 3 (22) (2016), 1600767.
[310] H. Zhu, P. Cheng, P. Chen, et al., Recent progress in the development of near-infrared organic photothermal and photodynamic nanotherapeutics, Biomater. Sci. 6 (4) (2018) 746–765.
[311] X. Wang, L. Tan, X. Liu, et al., Construction of perfluorohexane/IR780@ liposome coating on Ti for rapid bacteria killing under permeable near infrared light, Biomater. Sci. 6 (9) (2018) 2460–2471.
[312] Y. Li, X. Liu, B. Li, et al., Near-infrared light triggered phototherapy and immunotherapy for elimination of methicillin-resistant Staphylococcus aureus biofilm infection on bone implant, ACS Nano 14 (7) (2020) 8157–8170.
[313] Y. Deng, X. Gao, X.L. Shi, et al., Graphene oxide and adiponectin-functionalized sulfonated poly (etheretherketone) with effective osteogenicity and remotely repeatable photodisinfection, Chem. Mater. 32 (5) (2020) 2180–2193.
[314] W. Teng, Z. Zhang, Y. Wang, et al., Iodine immobilized metal–organic framework for NIR-triggered antibacterial therapy on orthopedic implants (small 35/2021), Small 17 (35) (2021), 2170180.
[315] L. Hong, X. Liu, L. Tan, et al., Rapid biofilm elimination on bone implants using near-infrared-activated inorganic semiconductor heterostructures, Advanced Healthcare Materials 8 (19) (2019), 1900835.
[316] X. Zhang, G. Zhang, M. Chai, et al., Synergistic antibacterial activity of physical-chemical multi-mechanism by TiO2 nanorod arrays for safe biofilm eradication on implant, Bioact. Mater. 6 (1) (2021) 12–25.
[317] G. Zhang, Y. Yang, J. Shi, et al., Near-infrared light II-assisted rapid biofilm elimination platform for bone implants at mild temperature, Biomaterials 269 (2021), 120634.
[318] P.F. Cai, J. Li, X.B. Wu, et al., ALD-induced TiO2/Ag nanofilm for rapid surface photodynamic ion sterilization, Rare Met. (2022) 1–11.
[319] J. Zhang, X. Gao, D. Ma, et al., Copper ferrite heterojunction coatings empower polyetheretherketone implant with multi-modal bactericidal functions and boosted osteogenicity through synergistic photo/Fenton-therapy, Chem. Eng. J. 422 (2021), 130094.
[320] R. Kurapati, K. Kostarelos, M. Prato, et al., Biomedical uses for 2D materials beyond graphene: current advances and challenges ahead, Adv. Mater. 28 (29) (2016) 6052–6074.
[321] A. Kouloumpis, A.V. Chatzikonstantinou, N. Chalmpes, et al., Germanane monolayer films as antibacterial coatings, ACS Appl. Nano Mater. 4 (3) (2021) 2333–2338.
[322] M.Z. Chai, M.W. An, X.Y. Zhang, et al., In vitro and in vivo antibacterial activity of graphene oxide-modified porous TiO2 coatings under 808-nm light irradiation, Rare Met. 41 (2) (2022) 540–545.
[323] W. Yin, J. Yu, F. Lv, et al., Functionalized nano-MoS2 with peroxidase catalytic and near-infrared photothermal activities for safe and synergetic wound antibacterial applications, ACS Nano 10 (12) (2016) 11000–11011.
[324] B. Zhang, S. Zou, R. Cai, et al., Highly-efficient photocatalytic disinfection of Escherichia coli under visible light using carbon supported Vanadium Tetrasulfide nanocomposites, Appl. Catal. B Environ. 224 (2018) 383–393.
[325] Z. Yuan, B. Tao, Y. He, et al., Biocompatible MoS2/PDA-RGD coating on titanium implant with antibacterial property via intrinsic ROS-independent oxidative stress and NIR irradiation, Biomaterials 217 (2019), 119290.
[326] J. Ouyang, R.Y. Liu, W. Chen, et al., A black phosphorus based synergistic antibacterial platform against drug resistant bacteria, J. Mater. Chem. B 6 (39) (2018) 6302–6310.
[327] J. Shao, C. Ruan, H. Xie, et al., Photochemical activity of black phosphorus for near-infrared light controlled in situ biomineralization, Adv. Sci. 7 (14) (2020), 2000439.
[328] Y. Wu, Q. Liao, L. Wu, et al., ZnL2-BPs integrated bone scaffold under sequential photothermal mediation: a win–win strategy delivering antibacterial therapy and fostering osteogenesis thereafter, ACS Nano 15 (11) (2021) 17854–17869.
[329] M. Liang, M. Zhang, S. Yu, et al., Silver-laden black phosphorus nanosheets for an efficient in vivo antimicrobial application, Small 16 (13) (2020), 1905938.
[330] J. Fu, W. Zhu, X. Liu, et al., Self-activating anti-infection implant, Nat. Commun. 12 (1) (2021) 1–13.
[331] H. Cao, K. Tang, X. Liu, Bifunctional galvanics mediated selective toxicity on titanium, Mater. Horiz. 5 (2) (2018) 264–267.
[332] G. Chu, C. Zhang, Y. Liu, et al., A gold nanocluster constructed mixed-metal metal–organic network film for combating implant-associated infections, ACS Nano 14 (11) (2020) 15633–15645.
[333] G. Fichman, C. Andrews, N.L. Patel, et al., Antibacterial gel coatings inspired by the cryptic function of a mussel byssal peptide, Adv. Mater. 33 (40) (2021), 2103677.
[334] Q. Wang, L. Wang, L. Gao, et al., Stable and self-healable LbL coating with antibiofilm efficacy based on alkylated polyethyleneimine micelles, J. Mater. Chem. B 7 (24) (2019) 3865–3875.