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SURFACE MODIFICATION STRATEGIES TO REDUCE IMPLANT-RELATED INFECTIONS

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ABSTRACT

Dental implants have become the primary choice for repairing patients with tooth loss. The material used for implants has mostly been titanium and titanium alloys. These materials are known to have excellent mechanical properties and biocompatibility. However, the surface of titanium implants is easily invaded by pathogens, and infection is infected after implant surgery. After infection occurs around the implant, the alveolar bone is progressively destroyed, which in turn causes the implant to loosen and ultimately fall off. Therefore, there is a dire need for effective preventive measures to reduce the risk of implant-related infections. This article will systematically review passive antifouling anti-biofouling strategies, active bactericidal surface bactericidal modification strategies, and targeted dissipation strategies after biofilm formation, which is aimed at preventing implant infection. This article will systematically review passive antifouling strategies, active bactericidal surface bactericidal modification strategies, and targeted dissipation strategies after biofilm formation, which are all aimed at preventing implant infection.

Keywords: Implant-related Infection; Biological Contamination; Antimicrobial Peptides; Antibiotic Coating

INTRODUCTION

Medical implants usually have hydrophobic surfaces, which could lead to biofouling within a very short time after implantation. Biofouling generally refers to the process by which proteins and microorganisms adhere to and proliferate on implant surfaces [1]. Biofilms are defined as a protective collective of microorganisms that is enclosed in a stable structure; once formed, it is difficult to remove with common antibiotics and chemicals [2]. Therefore, anti-fouling modification of the implanted surface of medical devices can inhibit biofilm formation and improve implant surface biocompatibility [3], to ultimately solve the problem of implant infection from its source.

The main component of dental implants is titanium, which has exceptional physicochemical properties as well as good biocompatibility. However, the surface of traditional implants often lacks a functional surface [4]. Surface modification is to functionalize the surface of the implant with anti-biological contamination and bactericidal functions without changing the original

characteristics of the textured material. Nano-morphology [5], polymers [6], metal ions [7], biomaterials [8], etc. have been used to functionalize titanium surfaces to reduce surface bacterial adhesion and to kill the bacteria adhering to surfaces of implants. This review presents several strategies for the prevention and treatment of orthopedic implant infections through anti-biofouling strategies, antibacterial strategies, and targeted biofilm dissipation strategies (Figure 1).

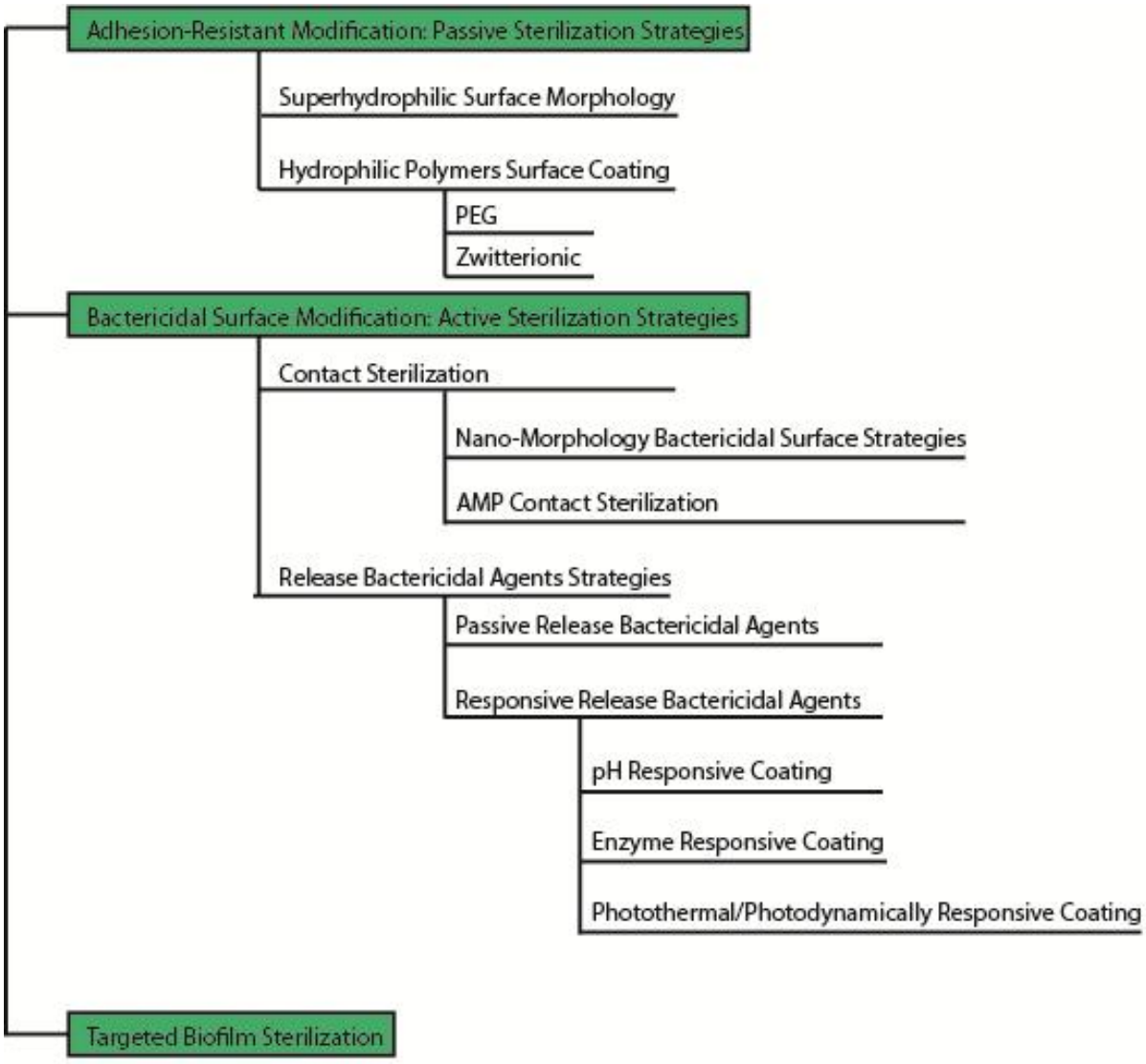

Figure 1. A general diagram of different strategies for the prevention and treatment of orthopedic implant infections.

1. Adhesion-Resistant Modification: Passive Sterilization Strategies

Bacterial adhesion is the first stage of bacterial biofilm formation and consists of three stages: transport of bacteria to surfaces, reversible bacterial adhesion, and irreversible bacterial adhesion [9]. Currently, the physical morphology and chemical modification of the implant surface to inhibit the initial attachment of bacteria, solving the problem of implant infection from the source, has become the research keystone of surface modification.

1.1 Superhydrophilic Surface Morphology

Many antifouling surfaces found in nature such as plant leaves [10], shark skin [11], and insect wings [12] in nature, contain surfaces with nanoscale features to minimize bacterial attachment and biofilm formation by reducing the contact area and surface wet ability.

Anil Mathew et al. [13] generated uniform micro-nano morphology on implants by hydrothermal method and found that this morphology has super-hydrophilic characteristics and high surface energy. Compared with acid-etched microscopic surfaces, the morphology method can reduce nearly 90% of bacterial adhesion *in vivo*, and can enhance osseointegration, and reduce the occurrence of peri-implantitis. On flowing hydrophobic surfaces, bacteria were shown to adhere less to hydrophobic nanopillar surfaces than to hydrophilic surfaces, and it can effectively reduce the number of bacteria adhered to the surface. However, long-term immersion of superhydrophobic surfaces in water will lead to coating destruction and reduced anti-adhesion effect, thus, its anti-fouling effect is only short-term [14].

1.2 Hydrophilic Polymers Surface Coating

The implant surface can be chemically grafted with a polymeric anti-adhesion coating to prevent protein and bacterial attachment. The antifouling principle of the hydrophilic layer is generally accepted based on the hydration barrier theory. The hydrophilic layer can combine with water to form a barrier, and bacteria and proteins would struggle to pass through the dense hydration layer to adhere to the surface of objects, thereby preventing primary adhesion and reducing the formation of biofilm [15]. Polyethylene glycol (PEG), amphiphilic fluoropolymers, and zwitterionic polymers are the most common hydrophilic polymers used as antifouling surface coatings. Although hydrophilic surface coatings are inherently passive antifouling strategies and are not biocidal, they are particularly effective at minimizing the initial attachment of bacteria to implants.

1.2.1 PEG

PEG is one of the earliest applied hydrophilic substances and is the gold standard for hydrophilicity evaluation [16]. The PEG molecular chain is considered to resist biofouling through two mechanisms: the steric repulsion caused by the surface tension of PEG, and the barrier effect of each hydrogen bond on the molecular chain binding two water molecules to form a hydration layer, the length of the chain and the thickness of the surface accumulation determines the effect of inhibiting bacterial adhesion [17]. He *et al.* developed a polydimethylsiloxane (PDMS) surface modification method using Tannic acid (TA) reduced gold nanoparticles (Au@TA NPs) and PEG; due to the unique antifouling properties of PEG and the photothermal conversion properties of AuNPs, an antibacterial application strategy combining antifouling and photothermal therapy (PTT) on the material surface was obtained [18]. Khoo XJ *et al.* grafted PEG onto implanted titanium via surface-binding peptides to form an antifouling surface that prevented nonspecific protein adhesion and bacterial colonization [19]. However, this surface is easily oxidized by free radicals and weakens its hydrophilicity, so it is often used in short-term antifouling and disposable antifouling devices, not suitable for long-term application in its antifouling performance.

1.2.2 Zwitterionic

Zwitterions are materials characterized by an equal number of positively and negatively charged groups, maintaining overall electrical neutrality. Zwitterions commonly used are: polysulfobetaine methacrylate (PSBMA) [20-22], polycarboxybetaine methacrylate (PCBMA) [23], poly (2-methylacyloxyethylphosphorylcholine Alkali) (PMPC) and other polymers [24], due to their excellent hydrophilicity, self-cleaning, and biocompatibility, have been widely used in the surface modification of various medical devices. Zwitterionic anti-fouling surfaces are electrostatically induced hydration layers that are more stable and firmer than those formed by PEG using hydrogen bonds [25, 26], therefore zwitterions are ideal candidates for surface biocompatibility [27].

Unfortunately, the effect of using anti-adhesion coating alone is limited, and it is difficult to achieve the ideal anti-fouling effect. Cheng et al. [28] further used the cationic precursor of PCBMA to successfully prepare a switchable polymer surface coating with antifouling and bactericidal functions; it's able to release 98% of dead bacteria from surfaces. Utilizing bactericidal and anti-adhesive functions of zwitterionic polymer derivative materials with self-adaptive functions combines the advantages of bactericidal, self-cleaning, and long-term biocompatibility; this is especially suitable for the coating of implantable biomedical devices. Currently, the most novel strategy is the smart responsive zwitterionic coating [29].

2. Bactericidal Surface Modification: Active Sterilization Strategies

2.1 Contact Sterilization

2.1.1 Nano-Morphology Bactericidal Surface Strategies

With an increase in the number of antimicrobial resistances, physical antimicrobial surfaces utilizing nano-morphology have received greater attention. Micro-nano morphology modification is divided into nanotubes, nanowires, nanodots, and nanocrystal deposits, etc. [30].Diu *et al*. [31] first studied the formation of a bactericidal surface with a nanowire structure directly on the surface of titanium through the alkaline hydrothermal method. They also found that motile bacteria are more likely to be killed than motionless bacteria, and Gram-negative bacteria are more likely to be killed than Gram-positive bacteria. Yi *et al*. [32] developed a switchable bioinspired nanopillar surface with mechano-bactericidal and release effects by grafting zwitterionic polymer PSBMA on zinc oxide nanopillars, which ensured long-term effects of antimicrobial properties.

Templating, hydrothermal, and anodic oxidation methods are often developed for the formation of titania nanotubes (TNTs) [33]. Studies have shown that TNT can effectively inhibit the initial adhesion of bacteria through the anodic oxidation group, and it is this delayed initial adhesion that enhances the sterilization of bacteria in the logarithmic growth phase; the dissipation function of bacterial biofilm then becomes the key to anti-infection [34]. One of the antibacterial mechanisms of TNT is its ability to stretch bacterial membranes [35], and the morphology of TNT will cause the damage to the bacterial cell membrane, the leakage of the content and the death of the bacteria.

2.1.2 AMP Contact Sterilization

Antimicrobial peptide (AMP) is composed of hydrophilic and hydrophobic parts, and their positively charged hydrophilic parts can interact with the negatively charged bacterial cell wall surface, Hydrophobic residues can insert into the bacterial membrane and come into contact with its lipophilic part, resulting in cell lysis; this antimicrobial mechanism makes AMP less prone to drug resistance [37]. Antimicrobial peptides have been explored as a promising alternative to combat implant-associated infections because of their broad-spectrum antimicrobial activity against a variety of bacteria, fungi, and viruses and their low propensity to develop antimicrobial resistance [38].

Godoy-Gallardo M *et al*. [39] was able to prepare polymer brushes via silanization and surface-initiated atom transfer radical polymerization (ATRP) and covalently immobilized lactoferrin-derived hLf1-11 antimicrobial peptides on titanium surfaces. *In vitro* antibacterial experiments found that these AMP-modified surfaces had a significant inhibitory effect on the attachment and biofilm formation of *Streptococcus sanguinis* and *Lactobacillus salivarius*. Compared with silanization, the titanium surface modified by the ATRP method showed less bacterial attachment. This may be due to the use of polymer brushes enabling more peptides to be immobilized on surfaces as well as the antifouling properties of polymer PDMA segments. Host defense peptides (HDPs) are important components of the innate immune system, which protect against microbial infections and modulate host immune responses. To overcome the shortcomings of HDPs such as unstable structure and high synthesis cost. In recent years, studies have begun to explore host defense peptide mimetic polymers to combat drug-resistant microorganisms.

2.2 Release Bactericidal Agents Strategies

2.2.1 Passive Release Bactericidal Agents

Antibiotics are often loaded on the surface of implants to prevent implant infection, and various loading methods are used to develop antibiotic coatings. Studies have used silk fibroin (SF) and polydopamine (PD) as intermediates for titanium surface coatings to load amoxicillin (AMX), and found that both can be used for intermediate organic coatings. However, PD has better encapsulation efficiency and Ti-PD/AMX has the best suppression effect [40]. TNT can not only directly sterilize bacteria, but also be used as a drug carrier. TNT can not only directly sterilize bacteria, but also be used as a drug carrier; it can be used to load vancomycin and be used as implant biomaterials. Experiments done *in vivo* and *in vitro* have verified its excellent antibacterial properties and can be used to treat orthopedic implant-related infections [36].

Metal ion release for sterilization: Metal nanoparticle coating on dental implants is a promising surface modification strategy. Silver (Ag), copper (Cu), zinc (Zn), strontium (Sr), gold (Au) and metal nanoparticle coatings have been applied to titanium as functional modifications. The synergistic antibacterial effect of two or more metal ions can not only enhance the antibacterial effect but also reduce the drug resistance of bacteria, which is a commonly used modification method currently. A Sr/Ag double-coating strategy prepared on titanium samples by magnetron sputtering technique simultaneously enhanced osteogenic and antibacterial properties through Sr^{2+} release and slow Ag^{+} release [41].

2.2.2 Responsive Release Bactericidal Agents

2.2.2.1 pH Responsive Coating

Bacterial metabolism produces acid, which lowers the pH near the bacterial infection (pH 4.5-6.5). Based on this feature, the release of biocides can be controlled using acid-responsive polymers [42], thereby releasing biocides on demand and avoiding burst release. ZIF-8 is a zinc-ion-based metal-organic framework that decomposes at acidic pH, making it a smart carrier for pH-responsive antibiotic delivery. Using vancomycin (VAN) as a model antibiotic drug, *Han et al.*[43] prepared a zeolitic imidazole framework-8-functionalized bioglass (ZIF-8@VAN@BG) scaffold loaded with VAN with pH-responsive antibacterial effects. The study found that the scaffold has a three-dimensional porous structure and exhibits a faster release rate of VAN in a weak acidic solution. *In vitro* antibacterial experiments show that the ZIF-8@VAN@BG scaffold has a significant inhibitory effect on *Staphylococcus aureus*. At the same time, it promotes the proliferation of rat bone marrow mesenchymal stem cells (rBMSCs), stimulates the expression of related osteogenic genes, and shows high application potential and a promising strategy in the field of infected bone repair.

2.2.2.2 Enzyme Responsive Coating

The main purpose of developing bacteria-responsive coatings is to trigger the release of antimicrobial drugs enzymatically from the corresponding layer after bacterial infection, avoiding adverse reactions caused by a sudden release of drugs. Hyaluronic acid, a natural extracellular matrix component, is an ideal antimicrobial. Hyaluronidase is an endoglycosidase that cleaves the glycosidic bonds in the polysaccharide hyaluronic acid (HA) and breaks down HA into simple sugars. Zhang *et al*. developed a multifunctional TNT nanoarray from dopamine-modified hyaluronic acid (HA-c) and 3,4-dihydroxyhydrocinnamic acid-modified chitosan (Chi-c) on titanium substrates, and they used the TNT loaded with vancomycin; the release of vancomycin is triggered when bacterial infection produces hyaluronidase (HAase) [44].

2.2.2.3Photothermal/Photodynamically Responsive Coating

Photothermal therapy is to convert absorbed light energy into heat energy through photothermal agents, which can convert light energy into heat energy, and are often used in the treatment of bacterial infections and tumors. Lu *et al*. coated TiO2-Cu nanofilm on the surface of titanium, the copper ions in the nanofilm showed excellent antibacterial activity against *Streptococcus mutansin vitro*, combined with photothermal therapy to prevent peri-implantitis [45].

Antimicrobial photodynamic therapy, utilizes a photocatalytic coating loaded with antimicrobials and photosensitizer. Photocatalysis activates its antimicrobial properties when needed. Toluidine O (TBO) and methylene blue (MB) are the main photosensitizers used in the medical field. Park *et al*. evaluated the antibacterial effect of two photosensitizers on the biofilm of *Staphylococcus aureus* on the titanium surface; their results showed that TBO was superior to MB in dissipating biofilms [46]. By eliminating early colonized bacteria, photothermal and photodynamic can effectively prevent bacterial colonization around the implant to ensure the stability of the implant.

3. Targeted Biofilm Sterilization

Currently, bacterial biofilm-associated infection caused by bacterial drug resistance and antigenic escape is one of the most intractable problems for implantation. Once biofilm is formed, it is difficult for antibiotics to penetrate, leading to antibacterial failure and persistence of

infection. Su *et al.* proposed a bilayer metal-MOF-organic framework composed of MIL-100 and CuBTC to eliminate specific biofilms[47]. The CuBTC releases glucose oxidase (GOx) and photothermal agent 2,2'-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) sequentially under acidic conditions, and GOx can convert local glucose into H2O2 and gluconic acid [47]. Further acidification can accelerate the degradation of CuBTC and the release of GOx/ABTS, which is oxidized by hydrogen peroxide to oxABTS with photothermal effect under the catalysis of horseradish peroxidase MIL-100, resulting in a photothermal effect [47]. This biofilm-responsive strategy is expected to precisely eliminate refractory peri-implant biofilm infections and increase the success rate of implants.

Summary and Prospects

For implant infection, prevention is key; passive antifouling strategies of physical morphology and chemical modification are not bactericidal, but they can minimize the initial attachment of bacteria to the implant. Six hours after implantation is considered the "critical period" for antifouling, during which inhibition of bacterial adhesion is crucial for the success of the implant.

Antifouling strategies alone cannot satisfy the need of preventing implant-associated infection. Effective antimicrobial implants should include passive antimicrobial coatings to prevent initial bacterial attachment, and active antimicrobial coatings that release antimicrobial agents to kill bacteria on contact. We would rather expect high concentrations of antibiotics delivered locally at the time of infection, followed by effective long-term slow release. However, the uncontrolled release of antimicrobial agents is likely to cause problems such as waste of antimicrobial agents and drug resistance.

The ideal treatment for implant-associated infection is the local smart release of antimicrobial agents, i.e., the intelligent response of antimicrobial agents to pH, enzymes, photocatalysis to release antimicrobial agents, which represents a promising method that is intelligent, on-demand to achieve antimicrobial effects.

Implant-associated infection is rather a tricky problem and often leads to implant failure. It is already possible to address biofilm infections by targeted dissipation of biofilm. The biofilm response strategy is expected to accurately eliminate the infection of biofilm around the implants and improve the success rate of implants.

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