Antibacterial Coating on the Surface of Implantable Materials

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Abstract: The desire for life has never diminished since ancient times. In ancient times, there was alchemy for longevity, while in modern times, there is surgery for bone replacement. However, on the way to survival, microorganisms such as bacteria and fungi have become one of the biggest stumbling blocks for human beings. How to cross this tiny but very threatening stumbling block to human life and health has become a popular topic among scientists for many years. In this paper, it highlights the research done by scientists in recent years on antibacterial coating on the surface of implantable materials, including polymers such as antibacterial polypeptides, titanium dioxide nanotubes and their improved products, and antibacterial coating materials obtained by surface modification methods. In addition, some prospects are presented for this field based on the previous work.

1. Introduction

In today's society, the continuous improvement of human quality of life has made people pay more attention to their own health. At the same time, the level of technology and medical science has also developed rapidly, and materials and surgical procedures that can be implanted in the human body have also emerged. But even so, bacteria, fungi and other microorganisms infection of human life threat cannot be underestimated. In 1928, Fleming invented penicillin, which has been a major player in the history of antibacterial activity. But it is not easy to defeat these microorganisms, as people continue to use and even abuse antibiotics, bacteria with their flexible genetic material replication mechanism to quickly evolve drug-resistant “superbugs”. The emergence of multi-drug resistant “superbugs” has made the diagnosis of bacterial infections more difficult [1]. According to the statistics released by the World Health Organization (WHO) in 2019, no less than 700,000 people worldwide die each year due to the transmission of drug-resistant bacteria. If this momentum continues to grow, there is a definite possibility that this number will increase to 10 million per year by the end of three decades. [2]

In surgical procedures where artificial medical materials are implantable into the body to replace damaged organs or tissues, there is no way to avoid a small amount of bacteria and fungi entering the wound and causing infection, despite the fact that doctors and hospitals are trying to achieve a sterile environment. In the case of a common artificial joint replacement, for example, viral infection around the prosthesis after surgery is one of the most prominent clinical complications after a common artificial joint replacement. First of all, the infection rate is usually 1%-2% after the replacement joint surgery, but increases to 3%-5% after revision surgery, and it has been shown that 70% of viral infections are caused by Staphylococcus aureus and Staphylococcus epidermidis [3-4] Once an infection is present, revision surgery is required, and multiple surgeries pose a significant financial and psychological challenge to the patient as well as to the surgeon's energy. In order to save patients from physical and mental suffering and to give doctors more energy to deal with other patients who are suffering from diseases, material scientists have contributed to the research of antibacterial coating on the surface of implantable materials. As Lienkamp said, “We require knights and walls to effectively defend the castle”, not only “defense”, but also “attack”. “Defense” means that the surface of the material is as unfavorable as possible to the adhesion of bacteria to inhibit the growth of bacteria. “Attack” means that when the bacteria gradually approach and lift on

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the surface of the material, the antibacterial coating still has the ability to destroy the germs, which is divided into release killing and contact killing. In the past, scientists may have developed more "defensive" materials, which are more biologically inert and less prone to errors. As materials science continues to progress, most current materials scientists have adopted a combination of offensive and defensive ideas to develop antibacterial materials. In this paper, the introduction of polymers such as antibacterial polypeptide/polyamino acid, titania nanotube and introduce of other trace elements, and the properties and preparation of materials obtained by means of surface modification of materials are reviewed.

2. Antibacterial Polymer Material

It has been found that natural antibacterial peptides exist in nature. Cecropin, which was extracted from the pupae of Bombyx amurensis, is one of the first natural antimicrobial peptides (AMP) in the world. [5-6]. The structural study of natural antimicrobial peptides shows that although they have different secondary conformations, antibacterial peptides usually have hydrophobic amino acid segments and positively charged amino acid segment, thus forming an amphiphilic relationship structure [9-10]. It is generally believed that the antibacterial mechanism of antibacterial peptides is mainly due to the mutual electrostatic attraction and affinity between their positively charged fragments and negatively charged bacterial cell membranes, while the hydrophobic fragments also act on the cell membranes, causing the bacterial cell membranes to perturb, rupture, and eventually cause bacterial apoptosis [9]. Based on this principle, scientists have developed a series of antibacterial peptides and other antibacterial polymers by means of artificial chemical synthesis to stimulate antibacterial peptides and improve the toxicity of natural antibacterial peptides to eukaryotic cells and mammalian hemolysis.

2.1 Antibacterial Polypeptides/Polyamino Acids

In addition to genetic engineering, antimicrobial peptides and their mimetic products can be prepared by various chemical synthesis methods. At present, the most common method for the preparation of antibacterial peptides is the solid phase synthesis method (firstly, the C-Terminus of amino acids and insoluble resin are cured, then the peptide chain is elongated by condensation of amino acids on the resin, and finally the peptide chain is detached from the resin and purified), which was pioneered by Merrifield in 1936. This method is easy to operate, but has a series of problems such as short synthesis sequence, long preparation time, low efficiency and purity of synthesis and high cost [10].

The preparation of α-polypeptides/polyamino acids using the α-amino Acid Carboxy Anhydride (NCA) method has been favored by researchers because of its simplicity, low cost, high yield, and short synthesis period. Chan-park pointed out that antibacterial oligopeptides can be obtained using the NCA method. The researchers obtained random copolymerized peptides with good antibacterial activity, with the combination of E. coli, P. aeruginosa and S. aureus having a Minimum Inhibitory Content (MIC) of more than 31μg/mL [11]. Based on the NCA method, several scientists have improved a lot. Hammond used alkyne-azide click chemistry to graft primary, secondary, tertiary, and quaternary aminated side chains on pre-treated polyglutamic acid main chains made by the NCA method, and measured the results. It is proved that the cationic polypeptides obtained by this method had a broad spectrum of biological antibacterial activity against S. aureus and E. coli and a very low hemolytic activity against mammals. Cheng et al. designed and synthesized a pH-responsive antibacterial polypeptide, which utilizes the slight change of pH in the vicinity of bacterial infection to realize the transformation of the secondary structure of the antibacterial polypeptide, thereby achieving the goal of reducing the toxicity to mammals while maintaining high antibacterial activity. [14-16]. Yazici et al. designed a bifunctional antibacterial peptide that combines the formation of a robust surface coating with high antibacterial activity.

2.2 Natural Antibacterial Polymers and Their Derivatives

2.2.1 Chitosan Derivatives

In addition to natural antibacterial peptides, there are also some other biological substances that are naturally antibacterial in nature. For example, chitin exists in the shells of shrimps, crabs, shellfish and other hard-shelled plants and animals, and the chitosan obtained by eluting the deacetyl group through concentrated alkali solution is a straight-chain polysaccharide with positive charge, which is a kind of natural antibacterial macromolecule material commonly used. Chitosan can be protonated and positively charged at a low pH, resulting in excellent antibacterial effects, while it is unable to exert antibacterial effects due to its insufficient water solubility at neutral conditions. Therefore, chitosan derivatives with high antibacterial activity and good water solubility must be obtained through chemical modification [10].

Li and his team proposed antibacterial hydrogel materials based on decyl dimethylamine chitosan (highly quaternized) grafted poly (DMDC-Q-g-EM) and poly (ethylene diacrylate). The test results show that the hydrogel materials have strong biological antibacterial characteristics against E. coli, S. aureus and P. aeruginosa. The good biocompatibility and non-toxicity of the hydrogel coating in contact with the conjunctiva of rabbits is also confirmed in animal experiments [17].

El-Newehy prepared quaternary ammonium salt and quaternary phosphonium salt from chloroacetylated and bromoacetylated chitosan by chemical method. It is confirmed that the antibacterial activity of quaternary phosphonium salt modified chitosan was higher than that of quaternary ammonium salt modified chitosan under the same negative ionic conditions [18].

Niu guanidinylated chitosan by incorporating the hydrophilic functional fragment into the molecular structure of chitosan to prepare a bifunctional chitosan diffracter CS-G/mPEG. It has high efficiency and selectivity in killing Gram-positive bacteria, effectively controlling the propagation of S. aureus without causing hemolytic reactions [20].

2.2.2 Cellulose and Starch Derivatives

In addition to chitosan, cellulose and starch can also be used as raw materials for the preparation of derivatives with antibacterial effect. Cai's team has produced dietary cellulose/montmorillonite/cetylpyridine bromide composite membrane with good antibacterial properties [21-22]. Guo has made a variety of starch derivatives by a click chemical method, which have better antibacterial activity than native starch. [23-24].

2.3 Synthesis of Antibacterial Peptide Macromolecular Mimics

Compared with natural antimicrobial peptides, synthetic antibacterial peptides have the advantage of controllability, and the toxicity and hemolytic properties can be minimized by modifying and adjusting the ratio of positively charged fragments to hydrophobic fragments, with low cost and high yield.

The results of the Kuroda’s study showed that it is possible to produce methacrylate copolymers using sulfhydryl groups as transfer agents. Tert-butoxycarbonylaminoethyl methacrylate, a highly hydrophilic monomer precursor with ammonium anion, can be copolymerized with highly hydrophobic binding monomers with different degrees of hydrophobicity, such as methyl methacrylate, butyl methacrylate and hexyl methacrylate, by free radical polymerization, and finally deprotected by trifluoroacetic acid and amphiphilic copolymer compounds are obtained. The newly synthesized polymeric mimics have important antibacterial functions against E. coli. In addition, the chemical structure and antibacterial functional properties of the antibacterial peptide macromolecules are studied, and the hemolytic properties shows that the increase in the concentration of water-repellent side chains would lead to an increase in both antibacterial activity and hemolytic activity. In addition, the chemical structure of microbial cell membranes is slightly different from that of mammalian cell membranes. Microbial cell membranes have strong negative electrical properties, while mammalian cell membranes have relatively weak negative electrical properties. Therefore, the positively charged copolymers without water-repelling side chains have a

stronger effect on microbial cell membrane, but at the same time have a weaker effect on mammalian cell membrane. Due to the increased concentration of the water-repelling side chain, the antibacterial activity and mammalian hemolysis are also enhanced. Therefore, it is necessary to find materials that exploit the hydrophobic side chain and cation to obtain more practical value [25].

Yang, in collaboration with Hedrick, made polycarbonate, an antibacterial substance with selective action on bacterial cell membranes, which initially induces cell membrane integration using electrostatic membrane association effect and causes imbalance in bacterial cell walls, and finally leads to their rupture and death. This compound has a selective effect on Gram-positive and Gram-negative bacteria, as well as fungal growth [26].

Divakara et al. concluded that hydrogen bonds play an important role in membrane interactions by isomeric substitution of esters in non-equivalent positions [27].

2.4 Photodynamic Antibacterial Polymers

Photodynamic Antibacterial Therapy (PDAT) is a method of killing bacteria by using photosensitizers interacting with visible light and ultraviolet light to form a phototoxic response to bacteria, fungi, and other microorganisms using oxidative damage [28].

Wang et al. made a complex consisting of an anionic water-soluble element polythiophene (PTP) and a cationic porphyrin (TPPN) generated under strong electrostatic force. The complex exhibits bactericidal properties under the irradiation of white light [29]. To enhance its selective identification, imaging and bactericidal ability, researchers made another class of multifunctional cationic diffractants with a polyethylene glycol side chain structure (PPV-1), which are able to selectively identify and bind pathogens and thus kill them by oxidative damage. However, one obvious drawback of the PDAT method is that it is difficult to get light into the organism, especially in deep tissues, and even a small amount of light irradiation cannot achieve stable irradiation for 24 hours a day, so it is necessary to obtain an “internal light source” to provide light that acts with the photosensitizer. Scholars have developed an electroluminescent sterilization system using electrochemiluminescence (ECL) technology. This method allows PDAT to be used in deep tissues without relying on an external light source, and such photodynamic antibacterial polymers can be used [30].

2.5 Inorganic Metal Salt/Polyacrylic Resin

Sun Hui et al. dissolved inorganic metal salts in water and added water-soluble acrylic resin in batches, then coated them on polyvinyl alcohol (PVA) substrate and left them to dry naturally to obtain inorganic metal salt/polyacrylic resin. After testing and research, silver nitrate/polyacrylic acid resin, cobalt acetate/polyacrylic acid resin, copper sulfate/polyacrylic acid resin and zinc sulfate/polyacrylic acid resin are found to have good antibacterial properties and could kill germs in a short period of time. By comparison, it is believed that zinc sulfate/polyacrylic acid resin process has stronger coating durability and better biocompatibility, and the lowest hemolysis rate is far below the medical material standard of 5% [31].

2.6 Quaternary Ammonium Salt Antibacterial Agent

Zhou Juntao et al. used a layer-by-layer self-assembly process, combined with “sulfhydryl-alkene” click chemistry, to graft quaternary ammonium salts or antibacterial drugs with sulfhydryl modifications at the end into the oxygen-containing norbornene tissue of the self-assembled coating, and obtained a coating with good antibacterial properties. They are non-toxic to cells, biocompatible and have a long-lasting bactericidal function [32].

3. Titanium Dioxide Nanotubes

Since Titanium Dioxide Nanotubes (TNT) largely increase the surface area of the prosthesis and make the biological cells fit more closely to the prosthesis. The length and diameter of the nanotubes can be controlled by the preparation parameters, which is a more ideal platform for drug delivery [33]. Therefore, titanium dioxide nanotubes have great potential for development and have

become one of the popular topics of research among material scientists.

3.1 Preparation Method of Titanium Dioxide Nanotubes

3.1.1 Anodic Oxidation Method

Anodic oxidation is the most common method used in the production of titanium dioxide nanotubes. A thin metal plate of titanium or aluminum-magnesium alloy is used as the anode or a thin platinum plate as the cathode in a reactor with an aqueous solution of hydrofluoric acid or ammonium fluoride as the electrolyte solution [34].

3.1.2 Template Synthesis Method

The template synthesis method is to obtain titanium dioxide nanotubes with a specific structure by electrophoretic deposition based on a pre-made template. After the titanium dioxide nanotubes are synthesized, the template is removed. Therefore, the templates are usually made of materials that can be easily and completely removed, such as alumina film, zinc oxide, silicon dioxide, etc. [35, 36].

3.1.3 Hydrothermal Synthesis Method and Solvent Thermal Synthesis Method

The hydrothermal synthesis method is relatively simple, straightforward and efficient. The titanium dioxide precursor and the reaction solution are sealed together in a reactor. The reaction is completed under certain high temperature and pressure conditions, and the material is then cleaned with deionized water and a strong alkaline solution to remove surface contaminants. In this way, the titanium dioxide precursor can be completely converted into TNT.

3.2 Antibacterial Mode of Titanium Dioxide Nanotubes

3.2.1 Self-Antibacterial Property

Titanium dioxide nanotubes themselves also have antibacterial properties, which are related to their crystalline state, tube diameter, hydrophilicity ratio and their surface chemistry [37]. By adjusting the crystalline state and hydrophilicity of TNT, the adhesion of bacteria on the surface of the material can be adjusted. The difference in the shape of the tube diameter may also create a stress response to bacteria and lead to cell membrane rupture and bacterial lethality [38]. In addition, the sterilization method also affects the antibacterial effect. Irradiation of TNT with UV light produces a photocatalytic reaction, which enhances the antibacterial properties of TNT.

3.2.2 Tnt and Antibacterial Drugs

There are two methods to produce drug-loaded nanotubes, namely physical adsorption method and freeze-drying method. The physical adsorption method is to apply the drug evenly on the TNT and then dry it in vacuum or air at a certain temperature. The freeze-drying method is to dry in vacuum under very low temperature conditions. Either method has a high drug loading efficiency, which can reach more than 80%, and the drug loading efficiency increases with the increase of nanotube diameter [39-41]. Lin et al. showed that the larger the diameter of drug-loaded TNT, the stronger the antibacterial effect [42]. Caliskan's research results also confirmed that as the length of TNT increases, the drug loading and drug release time increases, and the continuous release of antibiotics may cause the occurrence of drug resistance of bacteria. Yang et al. concluded that although drug-loaded TNT is effective against bacteria, it does not prevent the emergence of drug-resistant bacteria or reduce infections. Also, TNT does not provide long-lasting protection against bacteria because the drug is rapidly excreted in a short period of time, and high concentrations of TNT may be toxic when used topically. Feng et al. coated the surface of TNT containing gentamicin with a mixture of gentamicin and chitosan to achieve a slow release of the drug [44]. Multi-drug combination loading is also a current research trend. Pawlik combined the antibiotic gentamicin with the anti-inflammatory ibuprofen and, depending on their solubility in water and organic synthesis media, increased the dosage by modifying the loading sequence [45]. TNT is loaded with a variety of drugs, and the realization of multi-stage drug release is an important

aspect of future research and development.

3.2.3 Tnt and Metal Particles

Silver nanoparticles also have the ability to sterilize by contact and release. Currently, it is common to use photoreduction method to load silver particles by UV irradiation of TNT soaked in silver nitrate solution [46]. The experimental results of Wei et al. concluded that TNT loaded with silver nanoparticles is mainly bactericidal by release of silver ions in large quantities within three days, mainly killing Gram-negative bacteria. After three days, silver ions are mainly bactericidal by contacting, mainly killing Gram-positive bacteria [46].

Zinc oxide has not only antibacterial properties but also possesses the ability to enhance osseointegration and has good biocompatibility [47-48]. Zinc is one of the major micronutrients in humans and also has great efficacy in synthesizing DNA and enhancing enzyme and nucleic acid metabolic activities [49-50]. Zinc is less toxic and produces very limited drug resistance. Therefore, ZnO can be used as an alternative to silver nanoparticles for loading into TNT.

4. Trace Elements

The important contribution of silver nanoparticles and zinc in antibacterial coating is mentioned above. In addition to silver and zinc, there are other elements that can be used in antibacterial coating.

4.1 Copper Antibacterial Coating

Copper has some biological activity and is relatively inexpensive. Proper addition of copper does not show toxicity to cells and has some antibacterial properties. The copper ions released by the antibacterial coating cause the termination of bacterial respiration and the breakdown of DNA through direct or indirect action and the formation of superoxide [51]. The main problem in the use of copper is its tendency to be rapidly oxidized in air.

Li Muqin et al. obtained that copper plating at 50°C for up to three minutes would produce a relatively good copper concentration and good bonding of the plating, and the antibacterial properties of the plating could exceed 98.3% [57].

4.2 Fluorine and Fluoride Antibacterial Coating

It has been established that fluorine affects the increase of osteoblast viability and the inhibition of osteoclast function, and fluoride also possesses some antibacterial properties [52]. Yoshinari et al. introduced fluoride ions into pure titanium surfaces by ion implantation, and the coating shows excellent antibacterial activity against porphyromonas gingivalis and actinobacillus.

5. Antibacterial Surface by Changing the Roughness

The change of material surface roughness also plays an important role in the degree of adhesion between proteins and bacteria. Material surface roughening mainly includes macroscopic surface roughening and microscopic surface roughening. Macroscopic surface roughening is usually on the undulations of micrometer size, such as threads, while microscopic surface roughening is usually on the undulations of changes in mid-micrometer, submicrometer or nanometer size [53].

At the micron level, SLA uses sandblasting technique to make irregular undulations of 20-40 μm on the surface layer of the material, and then acid etching technique is applied to produce micropores of about 2 μm in diameter on the surface layer. Such a special configuration of the undulations combined with the microporous structure facilitates the attachment of proteins to the surface layer of the material [54].

At the nanoscale level, the nanoscale undulation of the material surface layer facilitates bone fusion, thus reducing the micro-motion at the initial stage of implantation. Singh et al. used a technique related to supersonic deposition to precisely control the thickness of the nanostructure of the material surface layer. The experimental results showed that after the nanostructure of the

material surface layer is greater than 20 nm, the degree of protein uptake increased correspondingly due to the increased roughness of the material surface layer, while the adsorption level of bacterial and biofilm is also reduced [55]. The results of Cao et al. showed that the nanoscale “pocket” structure on the surface of the material has the property of killing the monomeric bacterial and delaying the formation of bacterial biofilm [56].

6. Conclusion and Outlook

In the field of antibacterial coating on the surface of implantable materials, many researches have been made by previous scientists and remarkable results have been achieved. By simulating and modifying the natural antibacterial substances found, and by constructing antibacterial substances from different thinking and perspectives such as drug delivery and modification of the material surface, a series of surface coating with good antibacterial properties and low toxicity have been obtained. However, it is undeniable that most of the newly developed antibacterial coating are still in the research stage and have not been applied in clinical practice. It is a long process from the development to the commercial application of biomaterials, and there are some problems such as high cost, long preparation cycle, biocompatibility, hemolytic properties, drug resistance, etc., besides the need for caution in human use. In the developed antibacterial materials, there is still a large part of the antibacterial mechanism has not been clearly studied, which is also a major problem in the future research.

This paper believes that if these existing antibacterial coating can solve some of their own problems and get the optimal solution in the continuous exploration, they can be universally applied to the clinic in the future. The combination of multiple antibacterial methods, complementing each other's strengths, and multiple lines of progress will become the trend of future research in this area. For example, it is known that the topological structure of the material surface causes a certain stress on the growth of cells, which in turn changes their growth pattern. So can we design a topological structure that can make bacteria and other microorganisms grow on the surface of this kind of surface and crack them due to their own stress, so as to kill the bacteria without destroying the mammalian cells, by studying the morphological changes of bacteria, fungi and other microorganisms in the process of growth and the subtle differences of mammalian cells. In addition, titanium dioxide nanotubes have nanoscale bumps, so it is possible to design the topology of nanotubes to be bactericidal, or to design some special shaped nanoscale pores on the basis of nanotubes to achieve the purpose of bactericidal. Nanotubes can also be loaded with drugs and covered with polymeric membranes for slow release of drugs, thus achieving both release and contact bactericidal effects. In addition, enhancing the specificity and controllability of antibacterial activity will be a major trend in the future development, which can be used to adjust the opening and closing of polymeric membranes with subtle differences in the pH value of bacterial growth environment to achieve precise sterilization and minimize the toxicity and hemolysis of drugs on mammalian cells.

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