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Application of antimicrobial nanocoatings on biological implants

Jiarui Wang

Faculty of Applied Science, University of British Columbia, 3233 Wesbrook Mall, Vancouver, BC, Canada, V6S 0B4

elinawjr@student.ubc.ca

Abstract. Implant infections have become a major obstacle to implant failure. Although traditional antibiotic treatments have provided a solution to some extent, conventional antibiotic drug treatments fail to eradicate bacteria and even cause antibiotic resistance. Therefore, the development of biomedical implants employing antimicrobial coatings becomes the focus of more and more research. Nanomaterials, with their excellent biocompatibility and unique antimicrobial properties, have been widely used in biomedical devices. This paper focuses on the application of nanocoatings in biomedical implants and the introduction of potential surface functionalization materials for implants. This paper will analyze metals as well as their oxide nanoparticles and 2d-nanomaterial-based Nanocoatings with antimicrobial properties. It is also essential to highlight how these nanoparticles can deal with biofilm infections and achieve antimicrobial properties. In addition, the article describes different nanoparticle coating strategies that provide a variety of options for the design of antimicrobial coatings for implants. In conclusion, nanotechnology provides clues to solve the problem of biomedical implant infections, reduces the risk of infection, and generates more reliable and effective treatments for patients.

Keywords: Surface Functionalization, Antimicrobial Nanocoating, Implant.

1. Introduction

With the advancement of medical treatments, more and more artificial implants are being used in the clinic, such as artificial joints, artificial blood vessels, artificial heart valves, etc. Implant infections include lung infections, urinary tract infections, etc. Since patients need to be treated with anti-rejection drugs for a long time after surgical trauma, their body's mechanical defenses are reduced, which makes pathogens invade the organism more quickly, resulting in the risk of infection. During the surgery, tissues are detached and excised, whereby some bacteria in the organs contaminate the surgical site, leading to infections. Also, exogenous bacteria, wound contamination, blood accumulation, and ischemia can lead to wound infection. Titanium implants, one of the most widely used materials in clinical practice, still pose unpredictable risks because of their inherent biological inertness and susceptibility to oxidation, making them susceptible to thrombosis between the implant surface and surrounding tissues after implantation and leading to the release of toxic ions, compromise of physical and mechanical properties, or increased inflammatory reactions [1]. Transplantation surgery aims to alleviate the patient's pain, restore organ function, and improve the quality of life. However, if postoperative complications occur,

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the consequences can be "catastrophic," often implying costly secondary surgical repairs, resulting in patient suffering and socioeconomic burdens, and even life-threatening. The complications include rejection, infection, and organ failure of the transplanted organ, and this article focuses on the problem of implant infection. The surface of an infected implant already forms a biofilm made up of microbial aggregates, so dealing with this biofilm is very challenging. To avoid biomedical implants being contaminated by bacteria, the use of antibiotics is the most common option. However, prolonged use of antibiotics tends to cause the bacteria to develop antibodies to the antibiotics. It can lead to biofilm formation on the implant surface, ultimately leading to further bacterial resistance. Therefore, to address antibiotic resistance, nanomaterial biofilms or coatings have become one of the most effective means of eliminating hospital-acquired infections associated with implants, medical devices, etc [2]. This paper will introduce the role of nanomaterial coatings, potential surface functionalization materials for implants, and several techniques for coating nanoparticles on substrates to show the importance of nanomaterial coatings in the study of implants.

2. Importance of nanomaterials coatings in implants

Biofilms that form on the implant surfaces are the leading cause of clinical infections [3]. Therefore, the implant surfaces require the application of durable biomedical materials with antibacterial and antibiofilm surfaces [4]. Nanomaterials were used for various biomedical applications because of their distinctive physicochemical characteristics. Due to the thin thickness of the nanocoating, the nanoparticles have a high surface-to-volume ratio, which means that more active surfaces can be exposed to the exterior, significantly increasing their chemical reactivity and good biocompatibility [4].

These properties endow nanomaterials with antimicrobial properties. Antimicrobial nanomaterials can simultaneously act on multiple cellular targets to inhibit significant bacteria mutations and drug resistance. Moreover, the size of nanoparticles is very tiny; the diameter of a hair is about 60,000 nanometers. Therefore, microbial cell membranes and biofilms are more easily penetrated by nanoparticles, thus leading to viral cell damage and death [2].

Therefore, utilizing the antimicrobial properties of nanocoatings for implant surface modification can effectively reduce implant infections. In addition, nanocoatings are also characterized by stability. For example, coating the surface of an implant material, such as titanium, with nanoparticles can improve implant and biological fixation as they can induce chemical bonding with bone and the growth of osteoblasts and blood vessels [5].

3. Potential surface functionalization materials for implant

3.1. Metal-Based Nanoparticle General Mechanisms

Numerous studies have been conducted on metal-based nanoparticles for various biomedical uses. It makes it challenging for bacteria to acquire resistance to metal-based nanoparticles because they do not bind to specific receptors on bacterial cells. Therefore, the most common inorganic nanoparticles are those made of metal, which are entirely different from conventional antibiotics, reducing resistance and still showing activity against bacteria that have developed resistance.

Metal or metal oxide nanoparticles are subjected to electrostatic interactions with bacteria. The principle of electrostatic interactions is based on mutual attraction and repulsion between charges. The surface of these nanoparticles may be positively or negatively charged, and the surface of the bacterial cell will also have a charge distribution. If the nanoparticles are positively charged, they will adsorb to the negatively charged areas of the bacterial surface and vice versa. This adsorption and binding allow the nanoparticles to be firmly attached to the bacterial surface, and the nanoparticles can be attracted to the bacterial cell surface. When the charged nanoparticles encounter the bacterial cell surface, they establish a strong bond that disrupts the bacterial membrane. This interaction increases their permeability or disrupts the integrity of the membrane while interfering with the metabolic and survival functions.

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3.1.1. Nano-Coatings of Silver and Silver derivatives. Silver has excellent electrical, thermal, ductility, antimicrobial, and chemical properties. Due to its unique physical and chemical properties, silver is valuable in many applications, including electronics, medical devices, packaging materials, medical supplies, textiles, and more. However, excessive use of silver may lead to the accumulation of silver ions in the environment, impacting the ecosystem or human homeostasis. Therefore, long-term exposure of humans to high silver ion concentrations may lead to health problems. At the same time, the antimicrobial effect should be reasonably balanced against potential environmental or health risks.

Silver nanoparticles (AgNPs) are more widely used in medicine than metallic silver. Silver nanoparticles release silver ions for a more extended period and, therefore, have a larger surface area to volume ratio, making them less likely to be chelated by other ions. Also, they are more antibacterial and biofilm-resistant [2].

AgNPs have two different cellular interaction mechanisms. The difference is that the smaller AgNPs penetrate the cell directly, while the larger nanoparticles cannot penetrate the cell and are retained outside the bacteria. The similarity is that AgNPs continuously release Ag^+ ions. The Ag^+ ions disrupt the cell membrane potential and lead to proton leakage. Notably, the instability of the cell wall increases the permeability of the bacteria, allowing the larger AgNPs to penetrate the cell sometimes [6]. When AgNPs and Ag^+ enter the cell, they interact with intracellular biomolecules, leading to cellular dysfunction. Ag^+ and AgNPs interact with the membrane's respiratory chain proteins and inactivate enzymes that play defensive roles in bacteria because of their strong affinity for phosphate, thiols, and carboxyl groups. Antioxidant enzymes catalase, superoxide dismutase, and glutathione (GSH) block ions from penetrating the bacterial cell membrane [7]. However, bacteria are still insufficient to resist the release of high concentrations of Ag^+.

3.1.2. Nano-coatings of Copper and Copper derivatives. Copper and copper-oxides can be synthesized via an environmentally friendly and economical method. Copper has excellent electrical conductivity and is often used in wire and cable manufacturing. It has excellent thermal conductivity, so it is often used as a material for heat exchangers. Copper is also resistant to corrosion; when exposed to air, the surface of copper will form copper acetate, a protective green oxide, which can prevent further deterioration. Copper also has good plasticity and ductility. Lastly, Copper and copper oxide nanoparticles are becoming increasingly popular due to their excellent biocompatibility and good antibacterial properties. They enable surface functionalization, which increases the initial antibacterial action. Concerning their desirable physical and chemical characteristics, copper is frequently employed in the energy, electronics, transportation, and medicine sectors [2].

Copper ions released from the nanoparticles are positively charged. When they come into contact with negatively charged cell envelope components, they attract each other, interact electrostatically, and eventually rupture, leading to cell destruction and death. In addition, due to the permeability of bacterial cell membranes, copper ions can penetrate the cell membrane, disrupt the integrity of the internal biological structure, and cause cell death. Copper ions also disrupt the helical structure of DNA molecules in bacteria through cross-linking within and between nucleic acid chains, thereby destroying the internal system of bacteria and inhibiting bacterial reproduction [8].

3.1.3. Nano-coatings of Zinc and Zinc derivatives. The antibacterial and antiviral properties of zinc and its oxides make them widely used in medical treatment, food packaging, public facilities, textiles, water treatment, electronics, etc. Zinc ions are released from the coating. When ions come into contact with bacteria, they interact with the cell membrane, destroying the cell membrane and thus preventing bacterial growth.

The antimicrobial properties of ZnO nanoparticles have made them one of the most popular materials used for functionalized surfaces, which are intended to reduce the formation of biofilms on medical implants. Tejeda et al. supposed that Zn^{2+} ions released by ZnO particles generate ROS, which prevent cells from gathering on the surface thus preventing the formation of complex biofilm structures [9]. Schwartz et al. explained the antimicrobial activity of ZnO NPs coating on medical implants. The results

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showed that ZnO-coated implants had vigorous antimicrobial activity against Staphylococcus aureus, with an antimicrobial effect of approximately 37% higher than that of the uncoated implants with Zno coating. According to the findings of Memarzadeh et al., 100% ZnO composite coating displayed strong antibacterial activity against Staphylococcus aureus and contributed to the promotion of osteogenic development, cell adhesion, and proliferation establishing dependable connections with the host bone tissues for improved host tissue-implant integration [10]. Therefore, covering the implant surface with ZnO np can be effective in antimicrobial activity and reduce the formation of biofilm, thus reducing the problem of implant infection. Therefore, coating the implant surface with ZnO NPs can be effective in antimicrobial activity and reduce biofilm formation, thus reducing implant infection issues.

3.2. 2D-Nanomaterial-Based Nanocoating

Various 2D nanomaterials like Molybdenum-Disulfide-Based Coating, Black-Phosphorus-Based Coating, Boron-Nitride-Based Coatings, HA coatings, and many other 2D Materials are widely used in multiple antimicrobial coating agents. 2D nanomaterials, characterized by their single to few-atom thickness, have gained significant attention in biomedical applications and appeared attractive with unique physical, chemical, and mechanical properties.

It's challenging for metal and metal-oxide nanoparticles to ensure a uniform and stable coating on the implant surface. Therefore, there are concerns with regard to the longevity and stability of the coating. Also, potential cytotoxicity inflammatory responses of metal coatings are detrimental to the plant devices. 2D nanomaterials, a class of atomically thin materials extending in two dimensions, are introduced to address these issues with metal and metal oxide nanoparticles.

3.2.1. Graphene and Graphene-Oxide based nano-coatings. Graphene and its derivatives have excellent electrical conductivity, flexibility, and strength and hold great promise in the biomedical field. Studies have shown different mechanisms for graphene oxide's bactericidal or bacteriostatic effects. The first may be physical damage, where the sharp edges of the graphene oxide sheets can come into contact with the bacterial cell membrane and cause it to rupture, thus allowing the cell contents to leak out and ultimately leading to cell death. The second is oxidative stress, where graphene oxide can produce reactive oxygen species (ROS). These Reactive Oxygen Species, such as hydroxyl radicals, superoxide anion, and hydrogen peroxide, cause damage to the cell membrane, proteins, and nucleic acids of bacteria, which leads to bacterial death and inhibits bacterial reproduction. The bactericidal or bacteriostatic effect of graphene oxide may be affected by many factors. Therefore, safety and stability must be further studied and evaluated before widespread application [2].

3.2.2. MXenes nanocoatings. MXenes are a group of 2D transition metal carbides and carbon-nitrides with excellent antimicrobial activity, biocompatibility, conductivity, flexibility, and stability. The main mechanisms by which MXenes coatings act as bactericidal or bacteriostatic are as follows. First, similar to other 2D materials, MXenes can catalyze the production of reactive oxygen species (ROS) under light conditions, which cause damage to the internal structure of microbial cells and thus inhibit the presence of bacteria. In addition, the ultra-thin and sharp layered structure of MXenes can cause physical damage to microbial cells. When MXenes come into contact with bacterial cell membranes, the cell membranes will rupture and cause cytoplasmic leakage, ultimately resulting in the bacteria's death and achieving antibacterial effects [2].

3.2.3. Layered silicates nanocoatings. Layered silicates, including clays and related minerals, such as montmorillonite and kaolinite, have a structure of Layered Silicates. Due to its unique structure, it has enhanced thermal stability, biocompatibility, and mechanical properties. Coated on implant surfaces helps achieve anti-inflammation responses, reduces infection risk, and promotes osseointegration [2].

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4. Various methods for coating nanoparticles on substrates.

4.1. Electrostatic Spray Deposition (ESD)

The coating protects the underlying material from corrosion and infections. The spray gun will create an electrical charge on powder particles while the substrate is grounded. Then the charged particles are directed towards the substrate. A thin layer will form when the charged particles are attached to the substrate. A voltage is applied between the nozzle and the substrate. The powder particle becomes charged when it exits the powder gun and comes into contact with the electrostatic field produced by the tip electrode. The charged particles migrate toward the substrate along the electric field lines and deposit a thin coating. The sample is then rinsed with deionized water and allowed to air dry after the solvent has evaporated [11]. Various factors, such as the resident time, can influence the thickness of coatings deposited using Electrostatic Spray Deposition (ESD). Longer residence times expose the charged particles to environmental conditions for an extended duration, which results in particles' aggregation or coagulation. The particles' properties may be slightly altered, finally affecting deposition behavior or film thickness.

4.2. Dip coating

Dip coating provides one of the easiest and cheapest methods when there are low standard qualifications for the packaging density of the film deposited on the substrate. The impregnation coating process has three stages: immersion, deposition and drainage, and solvent evaporation. Before dipping, the substrate is required to be cleaned to remove any contaminants on the surface for better adhesion of the film. Then, the cleaned substrate is immersed in the NPs solution to complete wet the surface. A computer can control the immersion for automated dipping and a consistent dipping rate. The immersion time can vary depending on the application. After draining the solvent, the surplus solvent on the substrate surface is air dried, forming a solid thin coating [12].

4.3. Suspension plasma spraying (SPS)

Suspension Plasma Spraying (SPS) is an advanced variant spray technique using a liquid feedstock rather than a solid powder feedstock to deposit NPs coatings. This method has extensive applications in coating complicated and irregular surfaces. Fine powder particles are dispersed in a liquid medium in suspension plasma spraying. This suspension is then injected into a plasma jet and propelled onto the substrate, where they flatten, cure, and form a coating.

5. Conclusion

This paper summarizes the key role of nanotechnology in dealing with the problem of infection of bio-implants. First, nanoparticles destroy bacterial cells and kill bacteria through a variety of mechanisms. Thus, nanocoating disrupts the bacterial biofilm and inhibits bacterial growth, which can form an effective, microscopic protective barrier on the implant surface, thereby significantly reducing the risk of infection. Certain nanomaterials, such as metal nanoparticles, metal oxide nanoparticles, and two-dimensional nanoparticles, have been shown to have outstanding performance in resisting bacterial attack by virtue of their unique surface properties and interaction mechanisms. However, a combination of coating strategies, coating material selection, and implantation objectives must be incorporated to achieve optimal antimicrobial efficacy and long-term stability. With time, nanocoatings may be affected by the surrounding tissue environment, which may affect their effectiveness and stability. Antimicrobial properties should not be pursued at the expense of other critical properties, such as biocompatibility. Although nanotechnology improves the safety and efficacy of biomedical implants, the performance of implants in complex physiological environments should continue to be researched, tested, and optimized. More stable and reliable implant coatings still need to be developed in interdisciplinary collaboration to reduce the risk of complications.

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