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Construction of poly(lactic-*co*-glycolic acid)/ZnO nanorods/Ag nanoparticles hybrid coating on Ti implants for enhanced antibacterial activity and biocompatibility

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ABSTRACT

Poly(lactic-*co*-glycolic acid)/Ag/ZnO nanorods coating were successfully prepared on the surface of Ti metallic implants using a hydrothermal method and subsequent spin-coating of mixtures of poly(lactic-*co*-glycolic acid) and silver nanoparticles. The poly(lactic-*co*-glycolic acid)/Ag/ZnO nanorods coating exhibited excellent antibacterial efficacy of over 96% against both *Staphylococcus aureus* and *Escherichia coli* when the initial content of Ag nanoparticles was over 3 wt%. In addition, the release of both silver and zinc could last for over a hundred days due to the enwrapping of poly(lactic-*co*-glycolic acid). Proliferation of mouse calvarial cells exhibited minimal cytotoxicity on the poly(lactic-*co*-glycolic acid)/Ag/ZnO coating with an initial content of Ag nanoparticles of 1 wt% and 3 wt%, while it inhibited cell proliferation once this value was increased to 6 wt%. The results revealed that this poly(lactic-*co*-glycolic acid)/Ag/ZnO composite could provide a long-lasting antibacterial approach and good cytocompatibility, thus exhibiting considerable potential for biomedical application in orthopedic and dental implants with excellent self-antibacterial activity and good biocompatibility.

1. Introduction

Because of their excellent mechanical properties and good biocompatibility, titanium-based metals are widely used in hard-tissue repair, especially load-bearing orthopedic applications [1–3]. However, bacterial infection, which is mainly caused by *Staphylococcus aureus* (*S. aureus*) and *Escherichia coli* (*E. coli*) during and after surgery, often causes failure of the metallic implants. Thus, it is essential to endow metallic implants with a self-antibacterial ability [4–6], and recent studies have proven that surface modification is an effective strategy that can fulfill this mission [7–10].

Recently, nanostructured ZnO-based materials have been widely studied by biomaterial scientists because their unique characteristics endow these materials with novel biological functionalities [11–13]. For example, titanium implants with ZnO nanorods possess good antibacterial activity against antibiotic-resistant bacteria [12–14]. In addition, the zinc released from ZnO nanorods on titanium plays a significant role in the regulation of bone metabolism; in particular, it has a positive effect on bone formation and mineralization, as well as an inhibitory effect on bone resorption [15,16]. However, these functions of zinc are highly dependent on release behavior due to the excess release that can produce cytotoxicity [17,18]. In addition, the surface of ZnO nanorods on titanium shows a hydrophobic nature [19], which is not beneficial for cell proliferation and differentiation because the expressions of related proteins (i.e. vinculin) are suppressed [20,21]. With regard to these problems, poly(lactic-*co*-glycolic acid) (PLGA) copolymers, which possess excellent biocompatibility and biodegradability, were introduced to control the release of zinc and improve wettability [22–24]. However, the antibacterial activity of the surface is impaired by the covering of PLGA, which can also be solved through the doping of Ag nanoparticles (AgNPs).

In addition, the antibacterial activity of ZnO nanorods is higher toward Gram-positive bacterium (*S. aureus*) than Gram-negative bacterium (*E. coli*) [25,26]. Meanwhile, it has been reported that the incorporation of silver can significantly improve the antimicrobial efficacy [27–30].

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In this strategy, two inorganic antibacterial agents with strong performance (ZnO and AgNPs) can play this role effectively while avoiding potential cytotoxicity through using a PLGA covering to encapsulate ZnO and AgNPs. The PLGA/Ag/ZnO composite coating on titanium implants should therefore allow the release of dual antibacterial agents to improve surface antibacterial efficiency and improve the biocompatibility, as illustrated in Scheme 1.

2. Materials and methods

2.1. Materials

All the chemical reagents in this work were of analytic grade. Pure titanium plates (δ = 2 mm, φ = 6 mm) were mechanically polished with SiC water sandpaper of gradually finer grades, and used as substrates after cleaning with deionized water and ethanol.

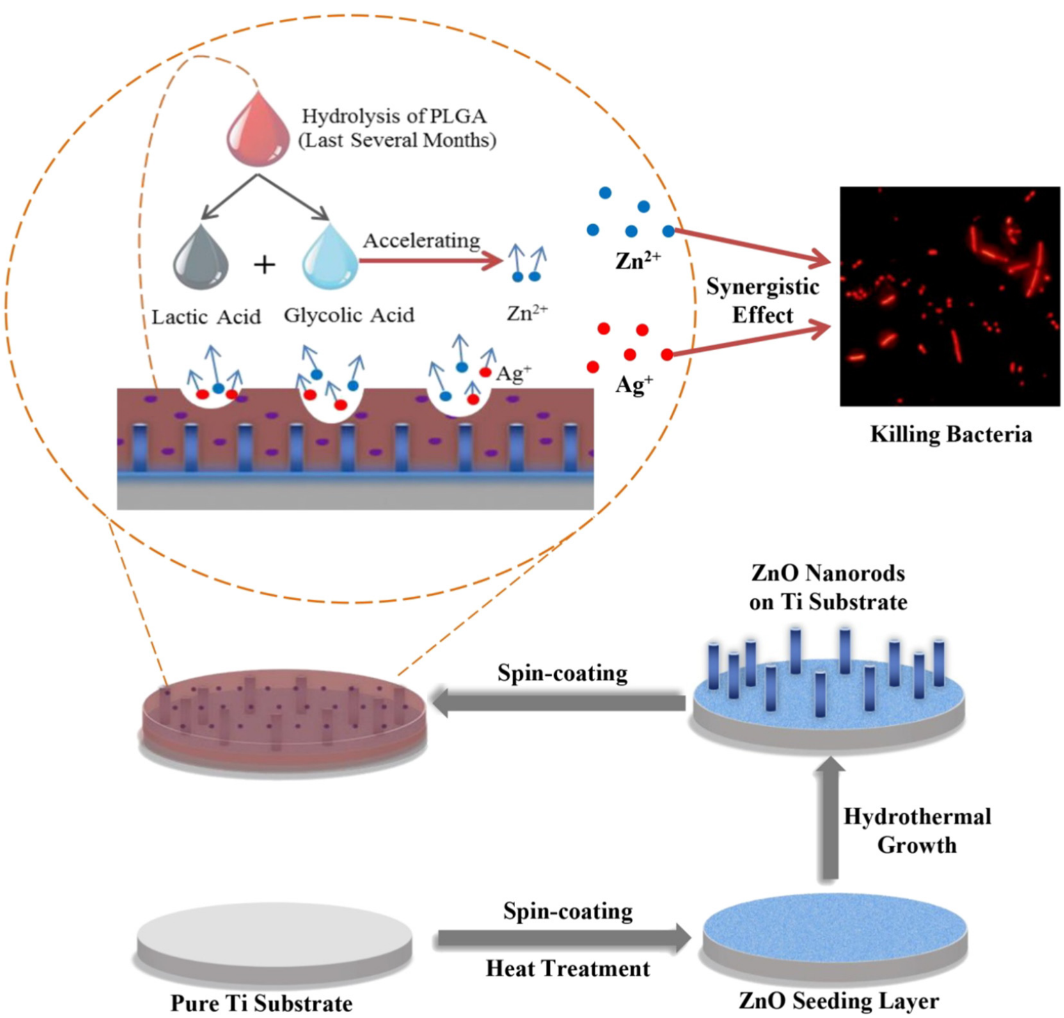
2.2. Hydrothermal growth of ZnO nanorods

To prepare ZnO seed layers, zinc acetate (0.75 M) and ethanolamine (0.75 M) were dissolved into ethanol at room temperature and stirred continuously for 4 h to use as a precursor solution. Then, 30 μL of the precursor solution was dropped onto the substrate and spin-coated at 600 rpm for 15 s and 5000 rpm for 30 s. The spin-coating process was repeated five times. The ZnO seed layers were then formed after firing at 500 °C for 60 min. The hydrothermal growth of ZnO nanorods was conducted as follows. Briefly, the hydrothermal growth of ZnO nanorods was carried out in a hydrothermal reactor (50 mL) containing 0.025 M zinc nitrate ($Zn(NO_3)_2$, AR) and 0.025 M methenamine ($C_6H_{12}N_4$, AR) aqueous solution. The ZnO seed layer coated titanium substrates were placed in this solution and heated at a constant temperature of 90 °C for 6 h. Finally, the substrates were removed from the solution, rinsed with deionized water and ethanol in sequence, followed by drying at 37 °C for 1 h.

2.3. Fabrication of PLGA/Ag/ZnO nanorods composite coating

AgNPs were carried out by mixing an ethanol solution of sodium oleate (0.0025 M) and silver nitrate (0.005 M) at 70 °C for 20 min, then the floc was washed with deionized water and acetone three times and dried for further use at room temperature.

A sol-gel method was used to prepare PLGA/Ag coatings on a titanium disk with ZnO nanorods. The PLGA/Ag solution was prepared by dissolving PLGA powder (average molecular weight MW = 120,000; *co*-polymer ratio = 75:25) and AgNPs in chloroform, and then stirred for 4 h using a magnetic stirrer. The PLGA concentration was 5% (wt/v) and the AgNPs' concentration was at different percentages (0%, 1%, 3% and 6% (wt/v)). The spin-coating process was conducted on the spin coater (KW-4A) at room temperature. Then, 30 μL of PLGA/Ag precursor solution was dropped onto the surface of the titanium disk with ZnO nanorods at a rotating speed for 15 s to make sure that the solution reached the edge of the sample. Afterward, spinning was conducted at



Scheme 1. Schematic illustration of fabrication process of PLGA/Ag/ZnO nanorods composite coating.