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Recent advances in anti-infection surfaces fabricated on biomedical implants by plasma-based technology

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ABSTRACT

Infection is one of the major post-surgery complications in orthopedics and dentistry and plasma-based technology is effective in mitigating infection by introducing antibacterial agents into the biomedical implants. By selecting the proper elements and operating parameters in the plasma-based processes, anti-infection and osseo-integration can be accomplished simultaneously. In this mini-review, recent advance in the design and construction of anti-infection surfaces by plasma-based techniques is discussed with emphasis on plasma immersion ion implantation and deposition (PIII&D) and magnetron sputtering. The underlying mechanisms are discussed and a better understanding enables the design and fabrication of better anti-microbial surfaces.

1. Introduction

Implant-related infection is one of the most intractable complications in orthopedics and dentistry [1]. It commences with adhesion and colonization of pathogenic bacteria on the implant surface followed by the formation of biofilms which are highly resistant to antibiotics and the host immune system [2–6]. After biofilms are formed, it is difficult to treat thereby resulting in chronic suffering and even requiring removal of the dysfunctional implants in serious cases [7]. Surface treatment or deposition of coatings that incorporate bactericides is a direct and effective means to inhibit initial adhesion and kill bacteria to prevent post-surgery infection [8]. Compared to organic antibiotics, inorganic antibacterial agents such as silver (Ag), copper (Cu), and zinc (Zn), especially those with a nanoscale structure, possess advantages including good stability, broad-spectrum antibacterial properties, and low risk of occurrence of resistance [9,10]. In the case of Ag, although the antibacterial mechanism is still not completely understood, release of silver ions (Ag^+) that induce inactivation of bacterial proteins, condensation of DNA, and degradation of bacterial cell membranes appears to play a major role [11]. Since the host cells can be similarly impacted by these mechanisms, loading of these bactericides should be optimized to ensure minimal adverse effects and even promotion of host tissue integration simultaneously.

Plasma-based techniques are widely used to improve the surface properties of biomaterials [12]. From the perspective of anti-infection, plasma immersion ion implantation and deposition (PIII&D) is attractive because of the non-line-of-sight nature which bodes well for biomedical implants with a complex shape and it is easy to control the dopant concentration and depth [13]. Magnetron sputtering is also effective in incorporating antibacterial agents into the materials. By selecting the optimal processing parameters, both the antibacterial ability and biocompatibility can be improved. This mini-review aims at highlighting recent major advances in fabricating anti-microbial surfaces suitable for orthopedic and dental applications by plasma-based techniques. Attention is paid to the newly proposed antibacterial mechanisms based on the micro-galvanic couple and Schottky barrier.

2. Plasma immersion ion implantation and deposition

PIII&D, a versatile technique that can introduce a myriad of elements into the host materials, enables doping or synthesis of embedded nanoparticles in the near-surface of the substrate [14]. For example, as shown in Fig. 1b–d, after Ag is implanted into titanium by Ag PIII at an acceleration voltage of 30 kV for 0.5 h, 1 h, and 1.5 h, metallic Ag nanoparticles are homogeneously distributed on the surface [15]. As the implantation time is increased, the particles become larger (comparing Fig. 1c and d with Fig. 1b) and the Ag concentration goes up (Fig. 1e). During Ag PIII, when the local concentration exceeds the solubility limit, the system relaxes by nucleation leading to growth of Ag nanoparticles (NPs). On account of surface sputtering [16], some Ag NPs in the near

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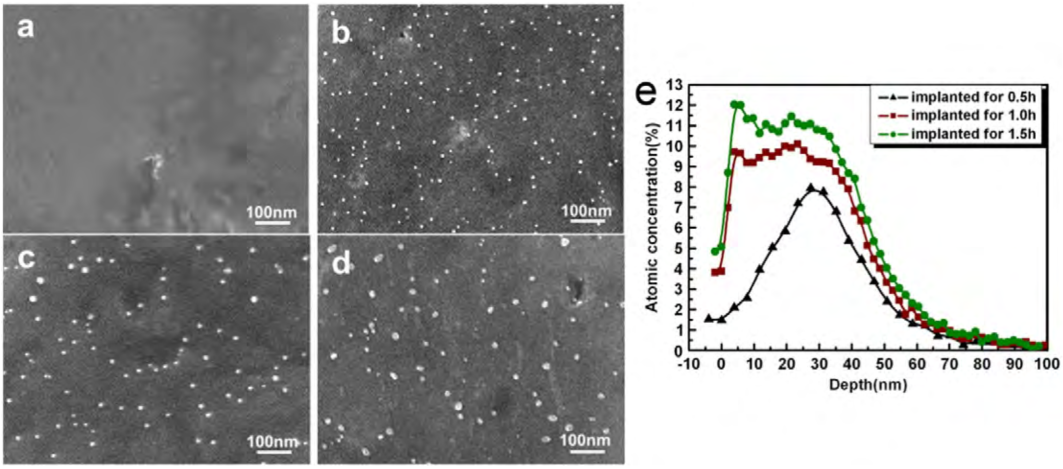

Fig. 1. SEM images of the titanium surfaces (a) before and (b–d) after Ag-PIII performed at the accelerating voltage of 30 kV for different durations: (b) 0.5 h; (c) 1.0 h; and (d) 1.5 h. The Ag NPs are dispersed on the surfaces and become larger when the implantation time is increased. (e) Silver depth profiles obtained from XPS after Ag-PIII for different durations [15].

surface are exposed. The Ag implanted surface has good antibacterial activity as it imposes bacteriostatic and bactericidal effects on both *Staphylococcus aureus* and *Escherichia coli* [17]. The anti-infection ability has also been verified *in vivo* by an implant-related infection model in rats [17,18].

The antibacterial mechanism of Ag NPs depends on the materials and environment. Besides the aforementioned release-killing ability, antibacterial mechanisms based on the micro-galvanic couple and Schottky barrier have recently been proposed when Ag is implanted into metallic and semiconductor substrates, respectively. By adjusting the ion implantation parameters, the ion concentration and depth distribution can be readily varied and consequently, the antibacterial ability can be controlled or optimized by careful manipulation of the implantation parameters.

2.1. Micro-galvanic couple

In corrosion science, a galvanic couple is established when two kinds of metals are in electrical contact with each other in a conducting corrosive environment. When Ag is implanted into a metallic substrate such as Ti to create Ag NPs, an antibacterial mechanism based on the galvanic couple is expected [15,17,18]. As shown in Fig. 2a, after the Ag implanted surface is immersed in a physiological liquid, a galvanic couple between each embedded metallic Ag NP and Ti matrix is triggered due to their different standard electrode potentials (−1.630 V for Ti and 0.7996 V for Ag). Owing to anodic protection rendered by the Ti matrix, only a small amount of Ag ions is released and hence, the direct antibacterial effects of Ag ions can be neglected. The Ti matrix serves as the anode and releases Ti ions (Ti^{n+}) by the anodic reaction $Ti \rightarrow Ti^{n+} + ne^{-}$. The generated electrons are transferred to the Ag NPs (red arrows) where they are captured by the electron acceptor according to the cathodic reduction reactions such as $2H^{+} + 2e^{-} \rightarrow H_2$. Therefore, the protons (H^{+}) adjacent to the Ag NPs are continuously consumed and a proton depleted region is formed eventually. When bacteria approach the surface, the proton gradient in their intermembrane space will be disrupted. Since the proton gradient is requisite to maintaining the energy-dependent reactions in bacteria, its disruption eventually causes death of the bacteria. Hence, the antibacterial ability of the Ag PIII&D surface can be ascribed to the galvanic couple built between the embedded Ag NPs and metallic substrate.

Besides Ag, Zn [19] and Mg [20] have been implanted into Ti by PIII&D to take advantage of their antibacterial ability [9,21] as well as their capability to stimulate bone formation, since they are essential elements involved in many metabolic and cellular signaling pathways [22–24]. Although both *in vitro* and *in vivo* tests demonstrate the superior osteogenic activity, the bacteriostatic effects of individual Zn PIII or Mg PIII are not sufficient to prevent infection [19,20,25]. Therefore, dual-element PIII of Ag and Zn (Ag/Zn PIII) [26] or Ag and Mg (Ag/Mg PIII) [20,27] has been performed to enhance the antibacterial ability. In these situations, owing to the more negative standard electrode potentials, Zn and Mg replace the Ti matrix to be the anode forming the galvanic couples with the Ag NPs (Fig. 2b). Zn^{2+} and Mg^{2+} are then released because of galvanic corrosion after exposure to the physiological medium. As bacteria transport ions by energy-consuming processes, the presence of these ions in the microenvironment makes the living conditions of the bacteria harsher. Moreover, the Ag NPs serve as the cathode

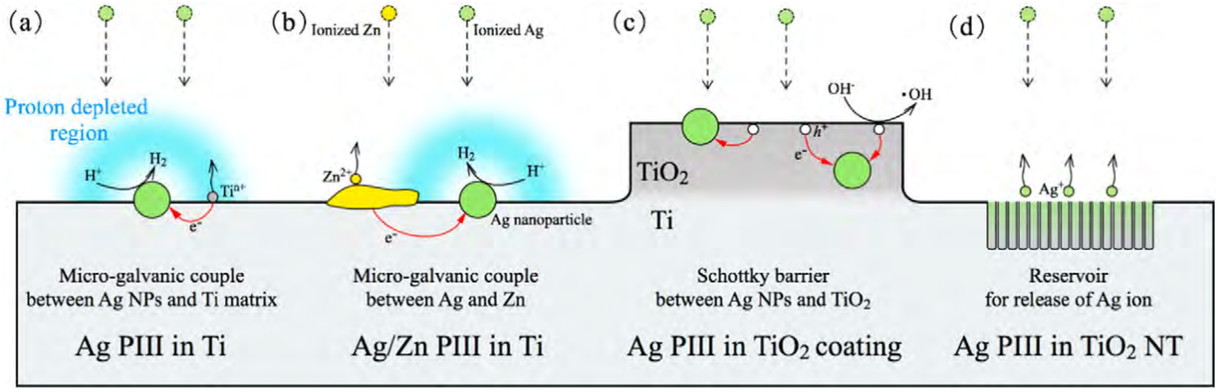

Fig. 2. Schematic illustration of the common strategies to prepare antibacterial surfaces suitable for orthopedic and dental applications by PIII&D.

to facilitate the formation of the proto-depleted regions. Ultimately, bacteria are killed due to the synergistic effects rendered by the released ions and disrupted proton electrochemical gradient around them [26]. At the same time, uptake of the released nutrient ions (Zn^{2+} or Mg^{2+}) by the host tissues facilitates bone healing and bone growth [20,26]. Therefore, the osteogenic activity and antibacterial ability are accomplished simultaneously by this dual-element ion implantation process.

Because the enhanced biological behavior results from the micro-galvanic couples, three different types of couples have been fabricated by implanting Ag and Zn into Ti simultaneously (denoted as Ag/Zn-PIII) and sequentially (Ag PIII followed by Zn PIII donated as Ag-Zn-PIII and the reverse being Zn-Ag-PIII) to investigate the effects of galvanic corrosion [28]. The corrosion rate of these surfaces is found to increase in the following order: Ag-Zn-PIII < Zn-Ag-PIII < Zn/Ag-PIII. *In vivo* tests performed in rabbit disclose differences in the anti-infection ability. Fig. 3 shows the micro-CT scans obtained from tibia of the rabbits 6 weeks after implantation of the rods in the animals. Osteolysis and resorption of cortical bone around the implant are observed from the untreated Ti (control) and Ag-Zn-PIII. Moreover, necrotic bone sequestra, which is characterized by a bone fragment (red arrow) within the area showing osteolysis, can be found from the Ti implant, indicating severe bacterial infection and inflammation. On the contrary, no sign of infection but rather new bone formation is observed from Zn/Ag-PIII. Therefore, Zn/Ag-PIII shows the best osseo-integration as well as anti-infection ability *in vivo*. These results confirm the positively correlated relationship between the galvanic corrosion rate and anti-infection ability demonstrating that the biological performance of the implanted surfaces can be manipulated by the designed micro-galvanic couples.

2.2. Schottky barrier

As shown in Fig. 2c, when metallic Ag NPs are embedded in a semiconductor such as TiO_2 by PIII&D, a Schottky barrier is formed as a result of the Fermi level alignment at the interface, thus endowing the Ag NPs with electron trapping capability [29–31]. In this way, electrons released by the adherent bacteria are collected by the embedded Ag NPs resulting in accumulation of valence-band holes (h^+) on the TiO_2 side. These highly oxidative holes can induce cytosolic content leakage and bacterial lysis either directly by reacting with the bacterial membrane, or indirectly by generating active oxygen species such as hydroxyl radicals •OH.

Since the antibacterial ability of this heterogeneous structure depends on the electron storage capability of the Ag NPs, the particle size and inter-particle distance are crucial. For example, the Ag NPs are larger when Ag PIII is performed at an accelerating voltage of 30 kV for 0.5 h or 1.5 h than 14 kV for 1 h. Because large Ag NPs are better in reserving electrons than small ones, the former Ag implanted surfaces deliver better antibacterial performance than the latter one [29]. As shown in Fig. 4, more serious cytosolic content leakage caused by cell lysis is indicated in Fig. 4c and d compared to Fig.4b. In addition, when Ag is implanted into a TiO_2 coating at 14 kV for 0.5 h and 1 h, the embedded Ag NPs have a similar size but different spacing distances. With increasing implantation time, the distance between NPs becomes smaller. The antimicrobial efficacy of the surface implanted for 0.5 h is superior to that for 1.0 h, since a relatively large inter-particle distance is more effective in collecting electrons without electron leakage [30]. In other words, better antibacterial efficacy can be achieved by fewer Ag NPs by optimizing the implantation parameters.

According to this mechanism, iron (Fe), an essential element without antibacterial activity, has been implanted into TiO_2 coatings which then possess the antibacterial ability against *S. aureus* in the absence of light [32]. This can again be attributed to the Schottky barriers formed between the surface iron oxide NPs, subsurface metallic iron NPs, and TiO_2 substrate. However, there is a lack of biocide effects against *E. coli* and it is believed to be due to the absence of electron transfer between *E. coli* and the coating.

2.3. Controlled ion release

The nano-morphology of the implant surface can be tailored to serve as cues to mimic the extracellular matrix (ECM) and enhance osseointegration [33,34]. Owing to the large surface area, they are also good reservoirs for antibacterial agents that can subsequently be released controllably. Ag NPs have been incorporated into TiO_2 nanotubes (NTs) for antibacterial purposes, but cytotoxicity is observed on account of burst release of Ag ions [35]. Fortunately, controllable release of Ag ions can be accomplished by Ag PIII. For instance, Mei et al. [36] have shown that by using the optimal processing parameters, TiO_2 NTs can be doped with Ag by PIII throughout the entire length of the nanotubes while the nanotubular structure is preserved (Fig. 2d). Ag ions released from the nanotubes in a sustained and controlled manner are effective in sterilizing pathogens without compromising the good biological functions of the nanotubular topography.

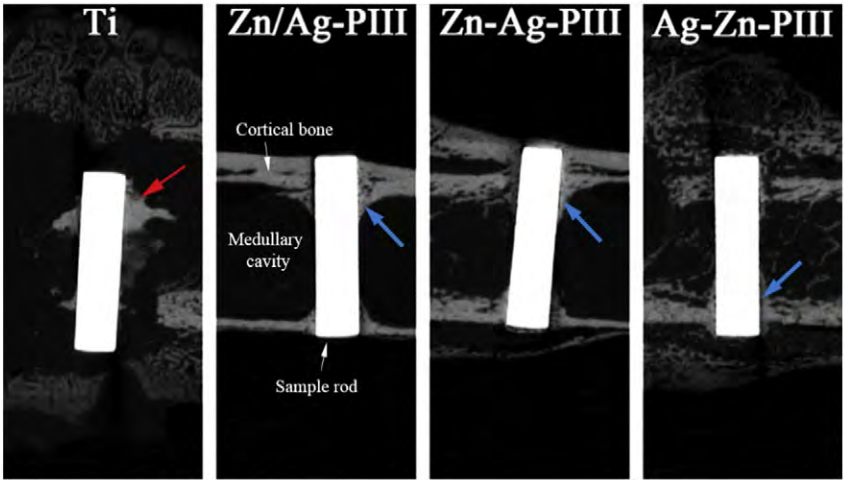

Fig. 3. Micro-CT results obtained from the rabbit tibia 6 weeks after implantation of the rods together with injection of bacterial suspension into the medullary cavity. The rods are implanted into the drilled holes which are perpendicular to the centerline of the tibia. The cortical bone cannot be seen and the density is smaller around the Ti and Ag-Zn-PIII samples indicating osteolysis and resorption of cortical bone. A piece of bone (red arrow) observed from the area of osteolysis is characterized as necrotic bone sequestra. New bone formation (blue arrows) is observed near the Zn/Ag-PIII, Zn-Ag-PIII and Ag-Zn-PIII samples. (Zn/Ag-PIII: Zn and Ag implantation into Ti simultaneously by PIII; Zn-Ag PIII: Zn and Ag implantation into Ti sequentially; Ag-Zn PIII: Ag and Zn implantation into Ti sequentially) [28].

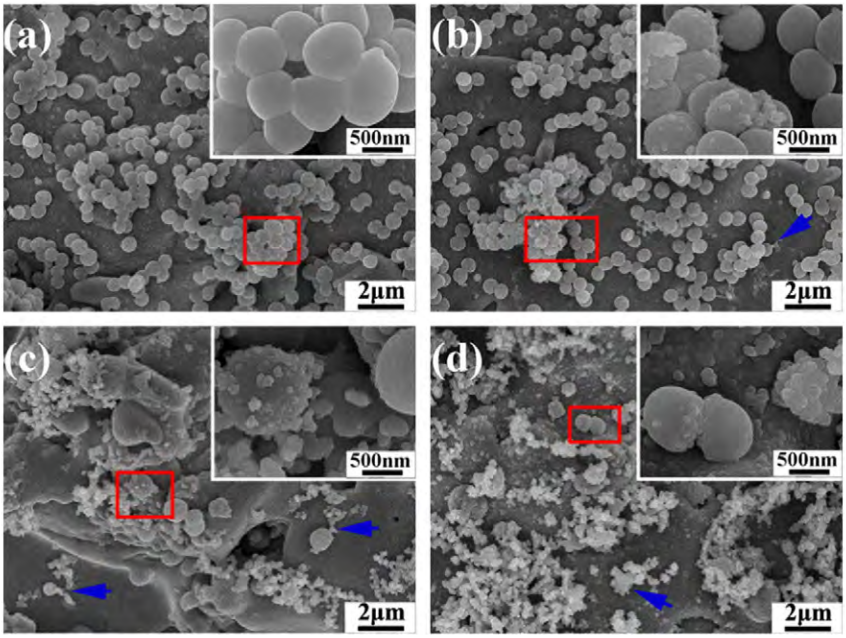

Fig. 4. SEM micrographs of *S. aureus* cultured for 24 h in darkness on (a) TiO_2 coating (control) and (b-d) Ag implanted TiO_2 coatings at different accelerating voltages and durations: (b) 14 kV for 1.0 h, (c) 30 kV for 0.5 h, and (d) 30 kV for 1.5 h. The insets show the corresponding high-magnification images of the areas demarcated by the red squares or rectangles. The cell membrane of the bacteria on the TiO_2 coating (a) is smooth and intact, whereas cytosolic content leakage (blue arrows) caused by cell lysis can be observed from the Ag-implanted TiO_2 coatings (b–d) and is more severe on (c) and (d) [29].

3. Magnetron sputtering

To obtain antibacterial ability, magnetron sputtering is an effective technique to incorporate inorganic bactericides into the biomaterials. Bai et al. [37] have fabricated nanostructured Ti-Ag coatings with different Ag concentrations (1.2 to 21.6 at.%) by co-sputtering Ti and Ag targets. The composite coating shows long-lasting antibacterial ability as a result of Ag^+ release. Furthermore, Ag affects the grain growth behavior of the composite coatings finally creating a nanostructured surface morphology which can serve as ECM cues to enhance the osteogenic capability.

In coatings containing Ag, only the surface Ag contributes to the antibacterial activity. In order to take better advantage of the Ag in the composite coatings, a post-treatment such as micro-arc oxidation

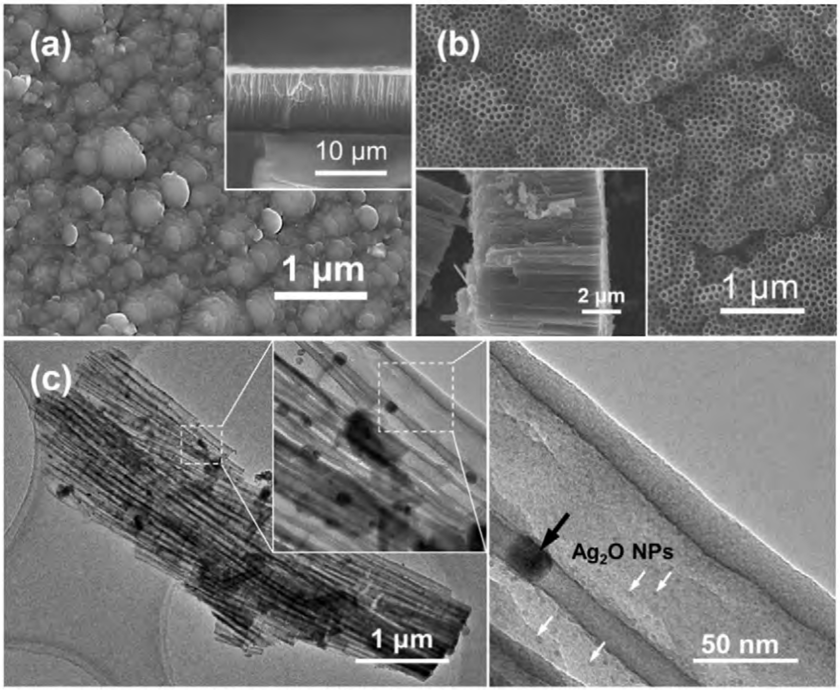

Fig. 5. SEM images of the top and cross-sectional view of (a) Ti-Ag composite coating deposited by magnetron sputtering and (b) Nanotube arrays fabricated by anodization of the Ti-Ag composite coating shown in (a). The insets show the respective cross-sections. (c) TEM images of the nanotubes shown in (b) and the corresponding high-magnification images acquired from the area enclosed by the dashed squares [39].

(MAO) [38] and anodization [39] has been performed to enhance the antibacterial activity. For example, after Ti-Ag composite coatings have been deposited by magnetron sputtering (Fig. 5a), they are anodized in the F-containing electrolyte to construct nanotube arrays [39]. Anodization is a common technique to fabricate TiO_2 NT arrays on Ti and its alloys [40]. As shown in Fig. 5b, after anodization, a highly-ordered nanotube array with a diameter of about 80 nm is produced. In conjunction with the formation of NT arrays, Ag in the composite coating is oxidized simultaneously to form Ag_2O NPs. The TEM micrograph in Fig. 5c shows that these Ag_2O NPs are embedded in the tubular wall. Owing to the large surface area of the nanotube arrays, the previously buried Ag are now exposed and more Ag is available for release. Their potent antibacterial ability is verified by that 97% of the antibacterial capability is retained after 28 days. More importantly, burst release of Ag ions from the NPs is suppressed by the barrier effect of the surrounding TiO_2 and so deleterious effects on osteoblast functions can be mitigated.

4. Conclusion

Plasma-based techniques are effective and versatile in introducing inorganic bactericides to biomedical implants to mitigate post-surgery infection. In this mini-review, recent progress in the design and fabrication of anti-microbial surfaces by PIII&D and magnetron sputtering are summarized and the associated mechanisms are discussed. Generally, Ag is the most frequently used antibacterial agent. It can be embedded by PIII and the bacteria inactivation mechanisms, including micro-galvanic couples, Schottky barriers, and release of Ag ions, vary depending on the materials and environment. The biological performance can be manipulated by adjusting the ion implantation parameters. In addition, magnetron sputtering is a desirable technique to deposit Ag-containing composite coatings. Additional surface treatment after deposition such as anodization can enhance the anti-infection capability of the films while preserving the biological benefits.

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