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Surface Biofunctionalization of Titanium Implants by Anodic Oxidation: Microstructure and Biological Properties

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Abstract
Titanium and its alloys are widely used for dental, orthopedic and spinal implants because of their favorable mechanical strength, corrosion resistance and biocompatibility. However, the native titanium surface is generally bioinert and cannot fully satisfy the clinical requirements for rapid osseointegration, antibacterial protection, angiogenesis and controlled local therapy. Anodic oxidation provides a simple and controllable route for constructing TiO_2 nanotube arrays on titanium substrates. The nanotubular oxide layer changes surface roughness, wettability, oxide crystallinity and ion-exchange behavior, thereby affecting protein adsorption, cell adhesion, osteogenic differentiation and bacterial colonization. This review briefly summarizes the formation mechanism of anodized TiO_2 nanotubes, the relationship between anodization parameters and surface physicochemical properties, and the major biological functions of anodized titanium surfaces. Particular attention is paid to osteogenesis, antibacterial activity, angiogenic regulation, immunomodulation and drug loading. Post-treatment strategies, including hydrothermal treatment, thermal annealing, bioactive element incorporation and nanotube-based drug delivery, are also discussed. Finally, current challenges such as long-term stability, multifunctional balance and clinical translation are summarized. This mini review aims to provide a concise theoretical reference for the design of biofunctional titanium implant surfaces by anodic oxidation.
Keywords: *titanium implant; anodic oxidation; TiO_2 nanotubes; surface modification; osseointegration; antibacterial activity; drug delivery*

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I. INTRODUCTION

Titanium and titanium alloys have become one of the most important metallic biomaterials for hard tissue repair. Compared with stainless steel and cobalt-chromium alloys, titanium possesses a relatively low elastic modulus, high specific strength, excellent corrosion resistance and good biocompatibility. These features make titanium-based materials suitable for artificial joints, dental implants, spinal fixation devices, bone plates and other long-term load-bearing implants [1–3]. In clinical applications, the success of a titanium implant depends not only on its bulk mechanical properties but also on the biological response occurring at the implant-tissue interface.

Although titanium is generally considered biocompatible, the naturally formed oxide film on its surface is relatively smooth and bioinert. Such a surface can protect the substrate from corrosion, but it does not actively promote early cell recruitment, osteogenic differentiation or vascularized bone formation. In addition, bacterial contamination during or after implantation may lead to biofilm formation and implant-associated infection, which remains a major cause of implant failure. Therefore, surface modification has become an essential strategy to endow titanium implants with improved biological functions while preserving their favorable mechanical performance [4–6].

Among various surface modification technologies, anodic oxidation has attracted extensive attention because it is simple, cost-effective, highly controllable and suitable for complex titanium substrates. Under appropriate electrochemical conditions, anodization can convert the titanium surface into ordered or semi-ordered TiO_2 nanotube arrays. Compared with conventional roughening or coating methods, TiO_2 nanotubes provide a nanoscale topography similar to the extracellular matrix and can also act as reservoirs for ions, drugs and bioactive molecules. Therefore, anodized titanium surfaces are considered promising platforms for achieving osteogenic, antibacterial, angiogenic and drug-delivery functions [7–10].

This review focuses on the biofunctionalization of titanium implants by anodic oxidation. From the perspective of surface structure-property-biological response relationships, the formation of TiO_2 nanotubes, the

regulation of surface physicochemical properties, the biological functions of anodized surfaces and the related challenges are summarized. The purpose is to provide a brief and practical reference for the design of titanium implant surfaces with multifunctional biological performance.

II. RESULT AND DISCUSSION

Anodic oxidation is an electrochemical process in which titanium serves as the anode and a counter electrode, usually platinum or graphite, serves as the cathode. When a certain voltage is applied in an electrolyte containing fluoride ions, titanium is oxidized to form a compact oxide film, while fluoride-assisted chemical dissolution simultaneously occurs at the oxide/electrolyte interface. The competition between field-assisted oxidation and localized dissolution gradually produces porous structures and finally develops into TiO_2 nanotube arrays [8–10].

The morphology of nanotubes is strongly dependent on anodization parameters. Voltage is generally the most important factor controlling nanotube diameter, while anodization time influences tube length and wall thickness. Electrolyte composition, water content, fluoride concentration, temperature and stirring conditions also affect the ordering degree and stability of the nanotube layer. In ethylene glycol- or glycerol-based electrolytes, relatively long and uniform nanotubes can usually be obtained because the dissolution rate is lower than that in aqueous electrolytes.

The biological performance of anodized titanium is closely associated with its surface morphology and physicochemical properties. TiO_2 nanotube arrays increase the effective surface area and provide nanoscale cues for protein adsorption and cell-material interaction. Nanotube diameter is particularly important. Small-diameter nanotubes are often favorable for initial cell adhesion, whereas larger nanotubes may influence cell elongation, cytoskeletal organization and differentiation behavior. Therefore, rational control of nanotube dimensions is necessary for different implant applications [11,12].

Freshly anodized TiO_2 nanotubes are usually amorphous. Thermal annealing can transform the amorphous oxide into anatase or anatase/rutile mixed phases, which generally improves surface stability and bioactivity. In addition, anodization can enhance hydrophilicity and increase surface roughness, both of which contribute to protein adsorption and early cell spreading. However, excessive roughness or unstable nanotube layers may induce particle detachment or inflammatory reaction. Thus, surface morphology, crystalline structure and mechanical adhesion of the oxide layer should be considered simultaneously.

Rapid and stable osseointegration is the primary biological requirement for titanium implants. TiO_2 nanotube surfaces can promote osteogenic responses through several mechanisms. First, the nanoscale topography enhances adsorption of serum proteins such as fibronectin and vitronectin, which facilitates integrin-mediated adhesion of osteoblasts and mesenchymal stem cells. Second, nanotube arrays can influence cytoskeletal tension and focal adhesion formation, thereby activating downstream signaling pathways related to osteogenic differentiation [11–13].

Many studies have shown that anodized titanium surfaces improve alkaline phosphatase activity, extracellular matrix mineralization and the expression of osteogenic markers such as *RUNX2, ALP, OCN* and *OPN*. The osteogenic effect can be further enhanced by incorporating bioactive elements, including calcium, phosphorus, strontium, magnesium and zinc. These ions can either directly participate in bone metabolism or regulate osteoblast differentiation. Therefore, anodic oxidation provides not only a structural modification method but also a platform for chemical functionalization of titanium implants.

Implant-associated infection is difficult to treat because bacteria can adhere to the implant surface and form biofilms that resist antibiotics and immune clearance. Anodized TiO_2 nanotubes can contribute to antibacterial performance in two ways. One is passive antibacterial regulation through surface topography, wettability and surface energy, which may reduce bacterial adhesion under certain conditions. The other is active antibacterial modification by loading or incorporating antibacterial agents such as silver, copper, zinc, antibiotics or antimicrobial peptides [14,15].

Among these strategies, silver-loaded TiO_2 nanotubes have been widely studied because Ag ions exhibit broad-spectrum antibacterial activity. However, excessive Ag release may cause cytotoxicity to mammalian cells. Copper and zinc can also provide antibacterial effects while participating in angiogenesis or osteogenesis at appropriate concentrations. Therefore, the key issue in antibacterial anodized surfaces is to balance bacterial inhibition and tissue compatibility. Controlled-release systems based on nanotubes are useful for achieving this balance.

Bone regeneration requires not only osteogenesis but also sufficient vascularization. A well-developed vascular network supplies oxygen, nutrients and osteogenic cells to the implant site. Anodized titanium surfaces can indirectly influence angiogenesis by regulating macrophage behavior, osteoblast activity and the release of pro-angiogenic factors. Surface nanotopography and incorporated ions may promote the expression of vascular endothelial growth factor and support endothelial cell adhesion and tube formation [16].

The immune response at the implant interface has recently become an important topic in biomaterial design. Macrophages can polarize toward pro-inflammatory *M1* or pro-healing *M2* phenotypes, and this polarization strongly affects subsequent bone formation. Properly designed TiO_2 nanotube surfaces may reduce excessive inflammatory responses and promote a regenerative immune microenvironment. Bioactive ions and anti-inflammatory drugs loaded into nanotubes can further regulate macrophage polarization and improve immune-mediated osseointegration.

The hollow structure of TiO_2 nanotubes enables them to serve as nanoscale reservoirs for local drug delivery. Antibiotics, anti-inflammatory drugs, growth factors, osteogenic molecules and anticancer agents can be loaded into nanotubes by physical adsorption, vacuum-assisted infiltration, polymer sealing or layer-by-layer assembly. Compared with systemic administration, local delivery from implant surfaces can increase drug concentration at the target site and reduce systemic side effects [17].

However, simple physical loading often results in burst release, which limits long-term therapeutic efficacy. To overcome this problem, researchers have introduced polymer coatings, hydrogel barriers, biodegradable caps and stimulus-responsive systems to regulate release kinetics. In the future, intelligent release systems responding to pH, enzymes, infection signals or inflammation may become important directions for anodized titanium implants.

Although anodic oxidation is promising, several challenges remain before wide clinical translation. First, the long-term mechanical stability of nanotube layers under cyclic loading and friction should be carefully evaluated. Second, multifunctional designs must avoid functional conflict. For example, strong antibacterial ion release may impair osteoblast viability, while high drug loading may weaken nanotube stability. Third, in vitro cell experiments cannot fully reproduce the complex *in vivo* environment, including immune response, mechanical stimulation, bacterial challenge and vascular remodeling.

Future studies should focus on the integrated design of structure, chemistry and biological function. Standardized evaluation systems, reliable in vivo models and long-term safety assessment are required. In addition, computational materials design, high-throughput surface screening and machine-learning-assisted optimization may accelerate the development of titanium surfaces with predictable biological performance.

III. CONCLUSION

In summary, anodic oxidation is an effective and practical method for constructing biofunctional surfaces on titanium implants. By forming TiO_2 nanotube arrays, anodization changes surface morphology, roughness, wettability, crystallinity and drug-loading capacity, thereby influencing protein adsorption, cell adhesion, osteogenic differentiation, bacterial colonization, angiogenesis and immune regulation. The biological performance of anodized titanium can be further improved through thermal treatment, hydrothermal modification, bioactive ion incorporation and controlled drug delivery. Nevertheless, the clinical application of anodized titanium surfaces still requires careful consideration of long-term stability, multifunctional balance, biosafety and standardized evaluation. A systematic understanding of the relationship among anodization parameters, nanotube structure, surface properties and biological responses will provide an important theoretical basis for the development of next-generation titanium implants with enhanced osseointegration and multifunctional therapeutic performance.

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