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Research progress and clinical practice of TiO_2 nanotubes**☆

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Abstract

BACKGROUND: TiO_2 nanotube array prepared by anodic oxidation is a nanomaterial having a perfect promising application at present.

OBJECTIVE: To review the research progress of TiO_2 nanotube in clinic.

METHODS: The key words were TiO_2 nanotubes, anodization, and biomaterials. We retrieved PubMed Database for articles concerning the clinical application of TiO_2 nanotube published from January 2000 to June 2013. Repetitive and old studies were excluded, and 47 literatures were included for the review.

RESULTS AND CONCLUSION: The summarized results of the 47 literatures showed that TiO_2 nanotube promoted the adhesion and proliferation of osteoblasts and mesenchymal stem cells including human. *In vivo* experiments verified that TiO_2 nanotube could be used as a carrier to carry other drugs such as growth factor and antibiotics so as to promote the biocompatibility of the materials and to prevent bacterial adhesion. Results suggested that TiO_2 nanotube contributed to the osseointegration of the material *in vivo*, and had a good biocompatibility.

Subject headings: nanotubes; osseointegration; nanotechnology; biocompatible materials
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BACKGROUND

Skeletal disease and trauma have great impacts on human's health and quality of life. In particular, the skeletal disease impacted the quality of life and society greatly. In general, at least 10% medical cost was spent on the diseases related to bone every year (such as joint replacement and fracture fixation). With the social development, more and more biomaterials related to orthopedics have been used in clinic such as artificial joint, spinal fusion and bone clamp including internal fixation and external fixation. Every year, at least several millions of patients needed hip joint or knee replacement[1-2]. Although strict sterilization and aseptic procedures were performed, medical implant injection remains a main reason for failure[1-9].

Bacterial adhesion in implant mainly contained following pathways[10-17]: (1) pathogenic bacteria on the skin and pathogenic bacteria in surgical environment were adhered on the surface of the implant, inducing bacterial proliferation and infection. (2) Bacteria were extended on the surface of the implant through circulatory system and urinary system. Bacterial proliferation caused infection surrounding the implant. (3) Surrounding tissue infection resulted in bacterial invasion and implant-related infection. Implant-related infection is a severe complication after implantation in the Department of Orthopedics. Host infection has been defined as an unbalance of tissue and microorganism. Numerous studies demonstrated that the formation of bacterial biofilm on the surface of the metal is a direct inducement and basic characteristic of this kind of infection. Biofilm has a physical barrier can effectively prevent the killing effect of

immunocytes, antibodies and antibiotics against bacteria, finally leading to postoperative implant-related infection[10-17].

Surgical technology (aseptic technique and laminar flow operating room) in bone surgery and prosthetic design have a perfect improvement. Implant-related postoperative infection remains a giant challenge for doctors of the Department of Orthopedics. As for implant-related infection, bacterial adhesion is the first and important step. The procedure of bacterial adhesion is complicated, and bacterial adhesion was affected by environmental factor, bacterial property, the function, charge, hydrophobicity and roughness of material's surface[10-17]. At present, preventive method for implant-related infection contains systemic and local application of antibiotics. TiO_2 nanotube array prepared by anodic oxidation is the most attractive material at present.

This study sought to explore the clinical application of TiO_2 nanotube array, especially the problems related to implant in the Department of Orthopedics, and discussed the advantages of TiO_2 nanotube on decreasing inflammation and infection and elevating osseointegration. This study summarized the research progress of TiO_2 nanotube on inflammation and infection decrease and biocompatibility and osseointegration increase.

DATA AND METHODS

Retrieval strategy

Retrieval database: The first author retrieved PubMed Database using computer. The key words were TiO_2 nanotubes, anodization, and biomaterials. Search time was from January 2000 to June 2013.

Inclusion and exclusion criteria

Inclusion criteria: treatise and review addressing cytological experiments and animal experiments of TiO_2 nanotube biocompatibility.

Exclusion criteria: unrelated literatures of TiO_2 nanotube biocompatibility; old and repetitive literatures.

Data extraction

109 literatures were retrieved. A total of 62 literatures unrelated or weakly related to study objective were excluded, and 47 literatures were included. Four people independently got out the study content and discussed the problems. They focused on the information about the research progress of inflammation and infection decrease and osseointegration increase of TiO_2 nanotube.

Evaluation of literature quality

A total 47 literatures were included[1-47]. The effects of TiO_2 nanotube on reducing inflammation and infection and in elevating biocompatibility and osseointegration were summarized.

RESULTS

General conditions of included data

There were 24 literatures concerning implant-related infection[1-24], 23 literatures addressing mechanisms, biocompatibility and clinical application of TiO_2 nanotube[25-47]. There were 6 literatures about effect of TiO_2 nanotube on diminishing inflammation[26-28, 37, 45-46], 14 literatures on promoting effect of TiO_2 nanotube on biocompatibility and osseointegration[30-33, 36-44, 47].

Characterization of research results of included data

Implant-related infection and strategy

Two thirds of implant-related infection was staphylococcus aureus infection[1-5, 9]. Bacterial biofilm is a property of most bacterial infection, especially staphylococci. Gilbert *et al* [18] confirmed that to kill bacteria in the bacterial biofilm needed a large dose of antibiotics, about > 1 000 times of killing the same kind of bacteria in cell suspension.

Another property of bacterial biofilm is to induce drug resistance of bacteria in bacterial biofilm. When drug concentration was low, and did not reach the minimal inhibitory concentration, pathogen easily had drug resistance, and increased the difficulty of treatment[19-21]. Poelstra and colleagues[22] found that the first 6 hours after the implant was implanted in the body was a key period to prevent infection. Six hours later, bacterial biofilm on the surface of the implant formed. Although aseptic processing was strictly performed and laminar flow operating room was used, the incidence of postoperative implant infection in patients undergoing joint replacement was 2%−4%[3-7].

What is more serious is that the incidence of implant infection after open fracture was 50%[20-21]. Differing from clinical common infection, the implant-related infection cannot be cured by common systemic application of antibiotics. The steel plate or artificial joint should be taken out of and surrounding tissues should be debrided and the operation should be operated again, which always brought huge pains on the soul and body and heavy economic burden. The patents have to take many risks such as long length of stay, complicated rebuilding,

prosthesis failure, even death. High-concentration systemic application of antibiotics would cause adverse reactions all over the body, including low efficiency, prolonged duration, repeated hospitalization, drug overdose, lacks of selectivity and toxicity[16]. Moreover, the drug is hard to be transferred to the site of the infection[16]. Under an ideal condition, pharmacodynamic action should be added and adverse reactions all over the body should be reduced. At present, the curative effects of local application of antibiotics were better than that of systemic application of antibiotics[8, 22-23].

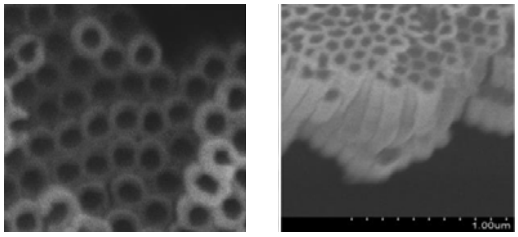
Local application of antibiotics could precisely control the dose of antibiotics in the implant, high effectively release antibiotics, avoid the adverse reactions of systemic application of antibiotics, and reduce the possibility of drug resistance of the bacteria. Administration of antibiotics all over the body had poor penetration ability for necrotic tissues, but elevation of drug dose would lead to toxic complications all over the body such as liver-kidney related toxicity[8, 22-23].

Local administration of antibiotics could increase local drug concentration and avoid adverse reactions of systemic medication, instead of systemic application of antibiotics. Local application of antibiotics in the prevention of infection has been selected in the clinic in the Department of Orthopedics, such as gentamicin bone cement. To overcome the defect of traditional strategy, local drug delivery has been a promising method. Local drug delivery system has been first used in antibiotics bone cement (PMMA) in 1980s by Buchholz *et al* [9].

The advantages of local drug delivery system comprised prevention of adverse reactions of systemic medication, and local high performance of antibiotics[24]. Nevertheless, the main shortcoming of antibiotic bone cement is that the implants have to been taken out twice. Antibiotic bone cement is not fit for cementless prosthesis (hip and knee joint prosthesis and implant steel plate). Another shortcoming of antibiotic bone cement is that when drug release concentration is low (lower than minimal inhibitory concentration), low-dose antibiotic release can lead to the production of drug-resistant bacteria. Kendall *et al* [19] found that bacteria could survive on the surface of antibiotic bone cement *in vitro* models. Anagnostakos *et al* [21] confirmed that pathogen was staphylococcus aureus and methicillin-resistant staphylococcus aureus in 18 patients suffering from antibiotic bone cement infection. Therefore, it should be careful whether antibiotic bone cement was extensively used in the prevention of prosthesis infection.

Development background and formation mechanism of TiO_2

The development of nanotechnology provides a new drug delivery platform for local drug delivery in implant. The aperture and length of nanomaterial could be controlled. TiO_2 nanotubes could be made by anodic oxidation[25] (Figure 1).



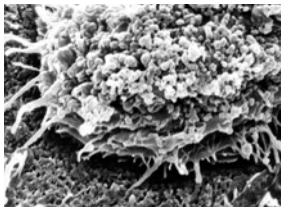
A: ×20 000 B: ×10 000

Diameter of nanotube was about 80 nm, and length of nanotube was about 2 μm.

Figure 1 TiO_2 nanotubes made by anodic oxidation under the scanning electron microscope

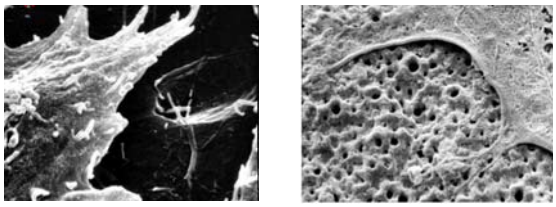
TiO_2 nanotubes are promising research subjects in the field of material at present. Drug can be delivered to the therapeutic region *via* nanomaterials effectively, which can overcome adverse distribution in the body, and avoid the defect of systemic medication (such as low efficiency, drug overdose, lack of choice and toxicity).

TiO_2 nanotubes not only elevated osseointegration of the metal, cell proliferation and differentiation, but also can be utilized as a drug carrier. TiO_2 nanotubes provided many cell attachment points to contribute to cell adhesion and proliferation by deposition of numerous proteins (Figures 2, 3).



Human osteoblasts adhered on the TiO_2 nanotubes for 2 hours. Osteoblasts extended a large number of pseudopodium towards TiO2 nanotubes. Scale bar: 1 μm.

Figure 2 Adhesion of human osteoblasts on TiO_2 nanotubes (Scanning electron microscope, ×5 000)



A: Osteoblasts implanted on the smooth surface of Ti for 6 h

B: Osteoblasts implatned on the TiO_2 nanotubes for 6 h

The adhesion of osteoblasts on nanotubes was better than that on the smooth surface of Ti.

Figure 3 Adhesion of human osteoblasts on TiO_2 nanotubes (Scanning electron microscope, ×10 000)

Totally new tissue culture scaffold can be obtained by changing materials' appearance. Biologically, interface modification can simplify the complicated biological problems, and can be used as an essential manner for controlling cell behavior. Ti and its alloy surface receive interface modification using anodic oxidation, and TiO_2 nanotubes coating can be prepared.

Studies demonstrated that this kind of nano-structured coating can induce a series of biological effects at cellular levels. During the research, that material would be first used in the study of cell adhesion, and gradually expanded on cell proliferation, migration and differentiation[26-35]. TiO_2 nanotube coating can be employed for precise control in the adhered structure of interaction between cells and materials at nanometer scale, and provide a valuable theoretic guidance for designing and developing intelligent cell culture scaffold[26-35]. Gong *et al* [25] first successfully prepared TiO_2 nanotube array in fluorhydric acid electrolyte system in 2001. Mean diameter, length and thickness of TiO_2 nanotube were controlled by parameters of anodic oxidation (oxidation time, voltage, and F-concentration)[25]. In the same electrolyte system, inner diameter of nanotubes increased with increased pressure of oxidation, and thickness of nanotube wall reduced. Nanotube length increased with prolonged oxidation time and elevated oxidation pressure. In different electrolyte systems, F-concentration and its corrosion rate on TiO_2 are important factors for nanotube length[25]. In the postprocessing of TiO_2 nanotube array, annealing temperature could affect the appearance and microstructure of TiO_2 nanotube coating. During annealing in the air, the coating has a thermal stability in a certain range. When annealing temperature was higher than 650 °C, the structure of nanotubes collapsed. Subsequently, numerous studies have focused on clinical application of TiO_2 nanotube[36-47]. TiO_2 nanotube contributed to biocompatibility[36-40, 42, 45-47]. Animal studies verified that TiO_2 nanotube promoted osseointegration of the implant in swine models[41, 43-44].

Biocompatibility of TiO_2 nanotube

TiO_2 nanotubes promoted biocompatibility[36-40, 42, 45-47]. Biocompatibility of biomaterials is a core problem in the field of regenerative medicine and tissue engineering. The surface of the material is a ligament of implant inserted in the host. A totally new tissue culture scaffold was obtained by effectively changing materials' appearance and chemical component. The surface appearance of the biomaterial directly affected the physical and chemical behaviors of the biomaterials *in vivo* and *in vitro*. Surface appearance of the material is a hot problem in the field of regenerative medicine and tissue engineering. Nanomedicine has been considered as a new field with giant potential. A whole new function of biomaterials can be found by changing the surface appearance of present materials. Ti metal and its alloy have been extensively applied in clinical medicine for over 50 years due to its excellent biocompatibility. Recent studies suggested that the alteration of the surface appearance of Ti metal (such as TiO_2 nanotube) elevated its biocompatibility[36-40, 42, 45-47]. TiO_2 nanotube biomaterials not only elevated biocompatibility of the materials, but also increased its therapeutic function, such as anti-infection ability. Some studies demonstrated that TiO_2 nanotube surface is an effective platform of osteoblast growth and differentiation, and osteoblast viability was elevated by controlling nanotube appearance[40-45]. Cooper[30] pointed out that surface appearance of the implant influenced the osseointegration of the implant *in vivo*. The increase in surface appearance of the implant contributed to osteoblast viability and elevated osseointegration of the material[30]. The diameter of TiO_2 nanotube varied from several nanometers to hundreds of nanometers. Different diameters of nanotubes had different effects on the functions of osteocytes and bone marrow stem cells. The main dispute is the effect of big nanotube diameter (50 nm–100 nm) on cells.

Some scholarsdiscovered that the size of TiO_2 nanotube diameter affected osteoblastic adhesion, proliferation and differentiation[36-39]. Park *et al* [39] verified that 15 nm diameter facilitated integrin aggregation, and promoted cell adhesion and reduced apoptotic rate. When nanotube diameter was longer than 50 nm, osteoblastic adhesion and diffusion were suppressed, and cell viability was noticeably reduced, resulting in cell apoptosis[36-39]. However, numerous studies had an

opposite conclusion and indicated that large-diameter (80 nm−100 nm) could not cause cell apoptosis, but promote the proliferation and differentiation of bone marrow stem cells. Khang *et al* [32] investigated the effects of surface appearance (subnanometer, nanometer and submicron) of the implant on cells and confirmed that surface characterization of subnanometer, nanometer and submicron could selectively activate integrin receptor and induce the differentiation of bone marrow mesenchymal stem cells into osteoblasts, and surface roughness of nano-Ti contributed to osteoblast differentiation. At subnanometer and submicron scales, they studied stem cell reactions such as integrin activation, cyclin, key open gene of osteoblast differentiation and osteoblast phenotype gene-produced effects. Compared with subnanometer surface, pure nano-Ti surface has perfect activated integrin. Jayaraman *et al* [33] found that surface appearance of the implant influenced osteoblast proliferation, differentiation and extracellular matrix protein expression. Nanometer structure promoted fibronectin expression, and contributed to osseointegration of implant and bone tissue.

Some scholars pointed out that TiO_2 nanotubes accelerated osteoblastic adhesion and osseointegration[40-44]. The ability of accelerating osseointegration depends on the size of the diameter of TiO_2 nanotubes. Nanotubes of big diameter showed better ability on bone formation compared with nanotubes of small diameter. The nanotubes of small diameter (about 30 nm) contributed to osteoblastic adhesion, but nanotubes of big diameter (70−100 nm) induced cell differentiation and resulted in an elevated activation of alkaline phosphatase.

Popat *et al* [45] performed histological analysis at 4 weeks after implantation in Lewis rats and found that TiO_2 nanotubes promoted cell adhesion, cell viability, including alkaline phosphatase and calcium contents. Biocompatibility results demonstrated that TiO_2 nanotubes could not induce chronic inflammation or fibrosis. von Wilmowsky *et al* [43] implanted TiO_2 nanotubes into pig models for 3, 7, 14, 30 and 90 days, conducted histological examination, and found a significant high expression of type I collagen after implantation of TiO_2 nanotubes at 7 and 14 days. Nanotubes of 30 nm diameter enhanced osteoblast function and affected bone formation and development. The study showed that TiO_2 nanotubes contributed to cell adhesion and elevated cell viability and promoted osseointegration. Moreover, TiO_2 nanotubes exhibited a good and stable structure, and were not destroyed by shearing force. Bjursten *et al* [44] confirmed that nanotubes excessively promoted osseointegration *in vivo*. Study contained nanometer group (80 nm in diameter and 2 μm in length) and micrometer group (2 μm). Using rabbit models, study verified that nanotubes facilitated osseointegration. The contact rate of bone tissue and material was greater in the nanometer group than that in the non-nanometer group. The contact rates of bone tissue and material were (78.3±33.3)% and (21.7±24.7)% in the nanometer group and the micrometer group, respectively. Stretch forces were (10.8±3.1) N and (1.2±2.7) N in the nanometer group and micrometer group, respectively. Studies confirmed a large amount of new bone formation on the surface of nanotubes. Calcium and phosphorus contents were obviously increased on the surface of nanometer structure compared with the micrometer group. These characteristics benefited for the application of biotype implant in clinic, such as biotype artificial hip knee joint prosthesis and intravascular stent.

Application of TiO_2 nanotubes as drug carrier

At present, orthopedic implant only can be used for 10–15 years due to various reasons including infection and poor osseointegration. Recent study results demonstrated that TiO_2 nanotube smear layer not only promoted osseointegration in implants, but also can be utilized as drug carriers such as antibiotics and bone morphogenetic protein. TiO_2 nanotubes not only have good biocompatibility and contributed to ossification, but also can be used as a carrier to load other drugs such as growth factor and antibiotics. Peng *et al* [37] employed TiO_2 nanotubes to carry drugs (protein, rapamycin and paclitaxel). In this study, the size of TiO_2 nanotubes varied to elute albumin and common micromolecule drugs. Drugs on nanotubes eluted bioactivity and reduced cell proliferation *in vitro*. Nanotube height and diameter deeply affected dynamics of eluting. Small nanotube diameter and long nanotube height prolonged the time of drug release. Molecular weight of the drugs also affected the time of drug release. The release time of drugs with big molecules was longer than that of micromolecules. This study suggested that TiO_2 nanotubes are promising smear layer of implants. A previous study demonstrated that TiO_2 nanotubes are promising drug carrier of implants in the Department of Orthopedics[37]. Popat *et al* [45] loaded TiO_2 nanotubes with various doses of gentamicin. TiO_2 nanotubes were 80 nm in diameter and 400 nm in length, loaded with 200, 400 and 600 μg gentamicin. They studied release dynamics of these nanotubes and staphylococcus epidermidis adhering gentamicin. In addition, the study evaluated MC3T3-E1 effects on cell function by

observing cytological behavior of MC3T3-E1 on these nanotubes. Study results indicated that TiO_2 nanotubes carrying gentamicin not only contributed to osteocyte viability, but also significantly diminished the adhesion of staphylococcus epidermidis. Presently, TiO_2 nanotubes carrying dexamethasone, penicillin and streptomycin reduced infection and inflammation. George *et al* [44] verified that TiO_2 nanotubes carrying drugs (streptomycin, penicillin and dexamethasone) could promote osteoblast viability.

A recent study confirmed that TiO_2 nanotubes had apparent inhibitory effects on glial cells[34]. A study successfully prepared hydroxyapatite/TiO_2 nanotube complex smear layer by simulating body fluid soaking method[35], first investigated the biological behavior of glial cells on the surface of Ti nanotube array, and explored the effects of nanotubes of different diameters on survival rate and morphology of glial cells such as U87 cells and C6 cells. With increasing diameter of nanotubes, cell number and viability showed a decreased tendency on the surface of TiO_2 nanotubes smear layer. Cell apoptosis would appear if the nanotube diameter exceeded critical size (50 nm in this experiment).

DISCUSSION

Anti-infection of the implant is always a difficulty in medical field. With rapid development of tissue engineering, the theory of promoting osseointegration by anti-infection of TiO_2 nanotubes gradually formed. *In vitro* studies confirmed that TiO_2 nanotubes promoted biocompatibility (including accelerating adhesion and proliferation of human osteoblasts and human mesenchymal stem cells. Animal *in vivo* studies (pig model) verified that TiO_2 nanotubes facilitated osseointegration. TiO_2 nanotubes not only have good biocompatibility and promote osseointegration, but also can be used as biological carrier to load other drugs such as growth factor and antibiotics. TiO_2 nanotubes as biological carrier provides a new thinking and deserves further deep research. However, there is lack of the clinical application research of TiO_2 nanotubes. Present study mainly focused on biocompatibility of TiO_2 *in vitro*. No studies concerned drug-loaded TiO_2 nanotubes such as osseointegration, causticity resistance of *in vivo* materials and ion blood drug level, which requires further investigation and development. TiO_2 nanotubes are simple, have low cost, convenient establishment, and can be utilized as a drug carrier. TiO_2 nanotubes are promising medical implant smear layer. Nanotube appearance was in primary stage of the study, but we can predict that novel orthopedic nanomaterial would facilitate the development of the science of orthopedic material.

REFERENCES

[1] Darouiche RO. Treatment of infections associated with surgical implants. New Engl J Med. 2004;350(14): 1422-1429.

[2] Gulati K, Aw MS, Findlay D, et al. Local drug delivery to the bone by drug-releasing implants: perspectives of nano-engineered titania nanotube arrays. Ther Deliv. 2012; 3(7):857-873.

[3] Dale H, Hallan G, Hallan G, et al. Increasing risk of revision due to deep infection after hip arthroplasty. Acta Orthop. 2009;80(6):639-645.

[4] Lentino JR: Prosthetic joint infections: bane of orthopedists, challenge for infectious disease specialists. Clin Infect Dis. 2003;36(9):1157-1161.

[5] Kurtz SM, Lau E, Schmier J, et al. Infection burden for hip and knee arthroplasty in the United States. J Arthroplasty. 2008;23(7):984-991.

[6] Green SA. Complications of external skeletal fixation. Clin Orthop Relat Res. 1983;(180):109-116.

[7] Green SA, Ripley MS. Chronic osteomyelitis in pin tracks. J Bone Jt Surg. 1984;66(7):1092-1098.

[8] Diefenbeck M, Mückley T, Hofmann GO. Prophylaxis and treatment of implant-related infections by local application of antibiotics. Injury. 2006;37 Suppl 2:S95-104.

[9] Buchholz HW, Elson RA, Engelbrecht E, et al. Management of deep infection of total hip-replacement. J Bone Joint Surg Br. 1981;63(3):342-353.

[10] Donlan RM, Costerton JW. Biofilms: survival mechanisms of clinically relevant microorganisms. Clin Microbiol Rev. 2002;15(2):167-193.

[11] Hall-Stoodley L, Costerton JW, Stoodley P. Bacterial biofilms: from the natural environment to infectious diseases. Nat Rev Microbiol. 2004;2(2):95-108.

[12] Hetrick EM, Schoenfisch MH. Reducing implant-related infections: active release strategies. Chem Soc Rev. 2006;35(9):780-789.

[13] Ribeiro M, Monteiro FJ, Ferraz MP. Infection of orthopedic implants with emphasis on bacterial adhesion process and techniques used in studying bacterial-material interactions. Biomatter. 2012;2(4):176-194.

[14] Costerton JW, Stewart PS, Greenberg EP. Bacterial biofilms: a common cause of persistent infections. Science. 1999; 284:1318-1322.

[15] Mah TF, O'Toole GA. Mechanisms of biofilm resistance to antimicrobial agents. Trends Microbiol. 2001;9(1):34-39.

[16] Davies D. Understanding biofilm resistance to antibacterial agents. Nat Rev Drug Discov. 2003;2(2):114-122.

[17] Smith AW. Biofilms and antibiotic therapy: is there a role for combating bacterial resistance by the use of novel drug delivery systems? Adv Drug Deliv Rev. 2005;57(10): 1539-1550.

[18] Gilbert P, Collier PJ, Brown MR. Influence of growth rate on susceptibility to antimicrobial agents: biofilms, cell cycle, dormancy, and stringent response. Antimicrob Agents Chemother. 1990;34(10):1865-1868.
[19] Kendall RW, Duncan CP, Smith JA, et al. Persistence of bacteria on antibiotic loaded acrylic depots.A reason for caution. Clin Orthop Relat Res. 1996;(329):273-280.
[20] Tunney MM, Ramage G, Patrick S, et al. Antimicrobial susceptibility of bacteria isolated from orthopaedic implants following revision hip surgery. Antimicrob Agents Chemother. 1998;42(11):3002-3005.
[21] Anagnostakos K, Hitzler P, Pape D, et al. Persistence of bacterial growth on antibiotic-loaded beads: is it actually a problem? Acta Orthop. 2008;79(2):302-307.
[22] Poelstra KA, Barekzi NA, Rediske AM, et al. Prophylactic treatment of gram-positive and gram-negative abdominal implant infections using locally delivered polyclonal antibodies. J Biomed Mater Res. 2002;60(1):206-215.
[23] Wu P, Grainger DW. Drug/device combinations for local drug therapies and infection prophylaxis. Biomaterials. 2006;27(11):2450-2467.
[24] Zilberman M, Elsner JJ. Antibiotic-eluting medical devices for various applications. J Control Release. 2008;130(3): 202–215.
[25] Gong DW, Grimes CA, Varghese OK, et al. Titanium oxide nanotube arrays prepared by anodic oxidation. J Mater Res. 2001;16(12):3331-3334.
[26] Losic D, Simovic S. Self-ordered nanopore and nanotube platforms for drug delivery applications. Expert Opin Drug Deliv. 2009;6(12):1363-1381.
[27] Moseke C, Hage F, Vorndran E, et al. TiO_2 nanotube arrays deposited on Ti substrate by anodic oxidation and their potential as a long-term drug delivery system for antimicrobial agents. Applied Surface Science. 2012; 258(14):5399-5404.
[28] Song YY, Schmidt-Stein F, Bauer S, et al. Amphiphilic TiO_2 nanotube arrays: an actively controllable drug delivery system. J Am Chem Soc. 2009;131(12):4230-4232.
[29] Yang BC, Uchida M, Kim HM, et al. Preparation of bioactive titanium metal via anodic oxidation treatment. Biomaterials. 2004;25(6):1003-1010.
[30] Cooper LF. A role for surface topography in creating and maintaining bone at titanium endosseous implants. J Prosthet Dent. 2000;84(5):522-534.
[31] Webster TJ, Ejiofor JU. Increased osteoblast adhesion on nanophase metals: Ti, Ti_6Al_4V, and CoCrMo. Biomaterials. 2004;25(19):4731-4739.
[32] Khang D, Choi J, Im YM, et al. Role of subnano-, nano- and submicron-surface features on osteoblast differentiation of bone marrow mesenchymal stem cells. Biomaterials. 2012; 33(26):5997-6007.
[33] Jayaraman M, Meyer U, Bühner M, et al. Influence of titanium surfaces on attachment of osteoblast-like cells in vitro. Biomaterials. 2004;25(4):625-631.
[34] Yang H, Qin X, Tian A, et al. Nano Size Effects of TiO_2 Nanotube Array on the Glioma Cells Behavior. Int J Mol Sci. 2012;14(1):244-254.
[35] Zhang D, Tian A, Xue X, et al. The effect of temozolomide/ poly(lactide-co-glycolide) (PLGA)/nano-hydroxyapatite microspheres on glioma U87 cells behavior. Int J Mol Sci. 2012;13(1):1109-1125.
[36] Park J, Bauer S, Schmuki P, et al. Narrow window in nanoscale dependent activation of endothelial cell growth and differentiation on TiO_2 nanotube surfaces. Nano Lett. 2009;9(9):3157-3164.
[37] Peng L, Mendelsohn AD, Latempa TJ, et al. Long-term small molecule and protein elution from TiO(2) nanotubes. Nano Lett. 2009;9(5):1932-1936.
[38] Park J, Bauer S, Von Der Mark K, et al. Nanosize and vitality: TiO_2 nanotube diameter directs cell fate. Nano Lett. 2007;6:1686-1691.
[39] Park J, Bauer S, Schlegel KA, et al. TiO(2) nanotube surfaces: 15 nm-an optimal length scale of surface topography for cell adhesion and differentiation. Small. 2009; 5(6):666-671.
[40] Oh S, Brammer KS, Li YSJ, et al. Stem cell fate dictated solely by altered nanotube dimension. Proc Natl Acad Sci USA. 2009;106(7):2130-2135.
[41] Brammer KS, Seunghan O, Cobb CJ, et al. Improved bone-forming functionality on diameter-controlled TiO_2 nanotube surface. Acta Biomater. 2009;5(8):3215-3223.
[42] Popat KC, Leoni L, Grimes CA et al. Influence of engineered titanianantubular surfaces on bone cells. Biomaterials. 2007;28(21):3188-3197.
[43] von Wilmowsky C, Bauer S, Lutz R et al. In vivo evaluation of anodic TiO_2 nanotubes: an experimental study in the pig. J Biomed Mater Res B. 2009;89(1):165-171.
[44] Bjursten LM, Rasmusson L, Oh S, et al. Titanium dioxide nanotubes enhance bone bonding in vivo. J Biomed Mater Res. 2010;92(3):1218-1224..
[45] Popat KC, Eltgroth M, Latempa TJ, et al. Decreased Staphylococcus epidermis adhesion and increased osteoblast functionality on antibiotic-loaded titania nanotubes. Biomaterials. 2007;28(32):4880-4888.
[46] George EA, Chang Y, Thomas JW. Enhanced osteoblast adhesion to drug-coated anodized nanotular titanium safaces. Int J Nanomed. 2008;3(2):257-264.
[47] Park J, Bauer S, PittrofA et al. Synergistic control of mesenchymal stem cell differentiation by nanoscale surface geometry and immobilized growth factors on TiO_2 nanotubes. Small. 2012;8(1):98-107.

二氧化钛纳米管的理论研究进展及临床实践**☆

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文章亮点：

1 此问题的已知信息：二氧化钛纳米管显著的优越性能逐渐成为目前一个最有吸引力的生物材料，在医学内植物研究中有着良好的前景。

2 文章增加的新信息：目前学者们正通过各种方式对假体材料进行改进与修饰，以求降低材料的感染率，并增强其与骨组织的整合能力。

3 临床应用的意义：随着假体材料的不断推陈出新，二氧化钛纳米管若能在临床应用中取得突破性进展，定将会在人工关节置换领域得到广泛应用。

关键词：

生物材料；生物材料综述；组织工程骨材料；纳米管；骨整合；生物相容性；药物载体；抗菌；国家自然科学基金

主题词：

纳米管；骨整合；纳米技术；生物相容性材料

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摘要

背景：二氧化钛纳米管阵列电化学阳极氧化钛是目前应用前景较好的纳米材料之一。

目的：综述二氧化钛纳米管在临床应用方面的研究进展。

方法：以 TiO_2 nanotubes，Anodization，biomaterials 为检索词，检索 PubMed 数据库 2000 年 1 月至 2013 年 6 月中有关二氧化钛纳米管临床应用领域研究的文献。排除重复研究及陈旧研究，共保留 47 篇文献进行综述。

结果与结论：从检索到的 47 篇文献进行总结分析发现，二氧化钛纳米管能够促进包括人成骨细胞，间充质干细胞的黏附和增殖。体内实验证实，二氧化钛纳米管能够促进钛金属内植物在体内的骨整合。此外，二氧化钛纳米管还可作为载体负载其他药物如生长因子和抗生素以促进材料生物形容性及预防细菌黏附。结果说明，二氧化钛纳米管可促进材料的体内骨整合，具有良好的生物相容性。

作者贡献：第一作者和通讯作者构思并设计综述，并与第二、三、四、五、六作者共同分析文献资料，第一作者起草，通讯作者审校，第一作者及通讯作者对文章负责。

利益冲突：课题未涉及任何厂家及相关雇主或其他经济组织直接或间接的经济或利益的赞助。

伦理要求：没有与相关伦理道德冲突的内容。

学术术语：骨整合-在光学显微镜下，种植体与周围骨组织之间呈现的无纤维结缔组织界面层的直接接触，又称骨性结合。

作者声明：文章为原创作品，数据准确，内容不涉及泄密，无一稿两投，无抄袭，无内容剽窃，无作者署名争议，无与他人课题以及专利技术的争执，内容真实，文责自负。

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