

Nanoscale TiO₂ nanotubes as a basis for governing cell behaviors and application challenges

Min Li¹
Ying Yang²

¹Department of Oncology, Changsha Central Hospital, Changsha, People's Republic of China; ²Department of Orthopaedic Surgery, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University, School of Medicine, Shanghai, People's Republic of China

Dear editor

TiO₂ nanotube arrays with well-ordered nanotubular structures and controllable dimensions have emerged as a favorable substrate for advanced cell culturing with regulable cell behavior and differentiation.^{1,2} Unfortunately, the biological effects of nanotubes with different surface features on various cell lines are still inconsistent and inconclusive. Therefore, we read with great interest the enlightening work from Tian et al³ published in the *International Journal of Nanomedicine* on investigating the effects and molecular mechanisms of TiO₂ nanotubes with various topographies and structures on the biological behavior of cultured cells.

This study demonstrated that the nanotube diameter, rather than the crystalline structure of the coatings, was a major factor determining the biological behavior of the cultured cells. Based on the results provided by this study, it was found that the optimal diameter of the coated nanotubes for cell adhesion, proliferation and migration was 20 nm, which was also the critical threshold that suppressed the cell apoptosis. Similarly, Park et al⁴ reported that the biological behaviors of cells on nanotube coatings indicated that nanotubes with a diameter of 15–30 nm served as ideal materials to promote cell adhesion, proliferation and differentiation.⁵ The topic of this study is of significance for future localized therapeutics of both cancer and bone-related disorders. We appreciate the methodology of the study; nevertheless, we believe that the observations performed by the authors and their conclusions deserve further comment.

Closer examination of the data raises some concerns regarding the paper as the major conclusions presented are not in agreement with several previous studies. Even though the cell lines used in those studies are different, diverse biological performances of the tested cells mediated by similar topographies and structures also need further discussion. Çalışkan et al⁶ explored the cytocompatibility of TiO₂ nanotubes with various diameters (~30 nm, 60 nm and 90 nm) using human osteosarcoma cell line (Saos-2). This study found that the initial cell adhesion and proliferation rate was the highest on the nanotubes with intermediate diameter (60 nm). In addition, Choi et al⁷ demonstrated that the surface crystallinity of carbon nanostructures should be regarded as an additional independent factor for the inhibition of cancer proliferation. They indicated that human glioma cells (U372MG) significantly exhibited apoptosis, necrosis and cytotoxicity on carbon nanostructures with high crystallinity. In addition to cancer cells, mesenchymal stem cells (MSCs) have also been extensively used to examine the biological effects of TiO₂ nanotubes. Oh et al⁸ observed that small (~30 nm diameter) nanotubes promoted MSC adhesion without noticeable differentiation, whereas larger (~70–100 nm diameter) nanotubes elicited a dramatic MSC elongation,

Correspondence: Ying Yang
Department of Orthopaedic Surgery,
Shanghai Ninth People's Hospital,
Shanghai Jiao Tong University School of
Medicine, 639 Zhizaoju Road, Shanghai
200011, People's Republic of China
Tel +86 212 327 1133
Fax +86 216 313 7020
Email leeny520@126.com

inducing selective differentiation into osteoblast-like cells. This special phenomenon may be attributed to the fact that MSCs cultured on <50 nm TiO₂ nanotubes can more easily attach to the relatively narrow surfaces deposited with high population of extracellular matrix (ECM) proteins, whereas MSCs cultured on 100 nm TiO₂ nanotubes would probably have to struggle to search for more wider areas to establish initial contact. Our attention was drawn to the inconsistent results obtained from those investigations, which were mainly focused on the different biological responses with regard to the diameter and crystallinity of nanotube coatings.

Moreover, TiO₂ nanotube arrays were shown to possess a unique set of properties for local drug delivery (LDD) applications, including controllable nanotube dimensions, high surface area, tunable geometries and surface chemistry, high and versatile drug-loading capacity, ability to modulate drug release kinetics and so forth. Based on those outstanding characteristics, TiO₂ nanotube arrays have been widely used for localized therapeutics in various medical fields, such as orthopedic implants and localized cancer therapy.^{9,10} Nevertheless, some technical challenges must be addressed and further explored before this technology becomes feasible and reliable for actual clinical applications. One challenge is the poor biodegradability of TiO₂ nanotubes as compared to polymer implants. Another important concern is the potential nanotoxicity of TiO₂ nanotube-based implants, which could be caused by nanotube delamination or degradation after implantation and release of TiO₂ debris into the host body; therefore, more in vivo preclinical studies are required in the future to translate this technology into clinical trial stage. Furthermore, it requires more fabrication advances in terms of improvement of TiO₂ nanotube production, scalability and reliability before they start to be produced at industrial scale. Finally, current public opinion regarding the clinical application of TiO₂ nanotubes is also an important challenge, as the public has serious reservations about the use of nanomaterials in medicine.

In conclusion, we wish to thank Tian et al³ for figuring out the critical threshold nanotube diameter (20 nm) that regulates the biological behaviors of the tested cells. However, it should be noted that certain other surface characteristics, such as nanotube length, roughness, surface energy and wettability, may also inevitably affect the biological behaviors of cells on the nanotubes, which deserve further investigation in future studies. In addition, it would be beneficial to compare the effects of TiO₂ nanotubes on a number of different cell lines.

Disclosure

The authors report no conflicts of interest in this communication.

References

1. Popat KC, Leoni L, Grimes CA, Desai TA. Influence of engineered titania nanotubular surfaces on bone cells. *Biomaterials*. 2007;28(21):3188–3197.
2. Gulati K, Ramakrishnan S, Aw MS, Atkins GJ, Findlay DM, Losic D. Biocompatible polymer coating of titania nanotube arrays for improved drug elution and osteoblast adhesion. *Acta Biomater*. 2012;8(1):449–456.
3. Tian A, Qin X, Wu A, et al. Nanoscale TiO nanotubes govern the biological behavior of human glioma and osteosarcoma cells. *Int J Nanomedicine*. 2015;10:2423–2439.
4. Park J, Bauer S, Schlegel KA, et al. TiO₂ nanotube surfaces: 15 nm-an optimal length scale of surface topography for cell adhesion and differentiation. *Small*. 2009;5:666–671.
5. Bauer S, Park J, Faltenbacher J, et al. Size selective behavior of mesenchymal stem cells on ZrO₂ and TiO₂ nanotube arrays. *Integr Biol (Camb)*. 2009;1:525–532.
6. Çalışkan N, Bayram C, Erdal E, Karahaliolu Z, Denkbaş EB. Titania nanotubes with adjustable dimensions for drug reservoir sites and enhanced cell adhesion. *Mater Sci Eng C Mater Biol Appl*. 2014;35:100–105.
7. Choi J, Lee S, Wang W, et al. Arresting cancer proliferation by controlling the surface crystallinity of carbon materials without generating reactive oxygen species. *Acta Biomater*. 2012;8(9):3457–3467.
8. Oh S, Brammer KS, Li YS, et al. Stem cell fate dictated solely by altered nanotube dimension. *Proc Natl Acad Sci U S A*. 2009;106:2130–2135.
9. Yang Y, Ao HY, Yang SB, et al. In vivo evaluation of the anti-infection potential of gentamicin-loaded nanotubes on titania implants. *Int J Nanomedicine*. 2016;11:2223–2234.
10. Kaur G, Willsmore T, Gulati K, et al. Titanium wire implants with nanotube arrays: a study model for localized cancer treatment. *Biomaterials*. 2016;101:176–188.

Dove Medical Press encourages responsible, free and frank academic debate. The content of the International Journal of Nanomedicine 'letters to the editor' section does not necessarily represent the views of Dove Medical Press, its officers, agents, employees, related entities or the International Journal of Nanomedicine editors. While all reasonable steps have been taken to confirm the content of each letter, Dove Medical Press accepts no liability in respect of the content of any letter, nor is it responsible for the content and accuracy of any letter to the editor.

International Journal of Nanomedicine

Publish your work in this journal

The International Journal of Nanomedicine is an international, peer-reviewed journal focusing on the application of nanotechnology in diagnostics, therapeutics, and drug delivery systems throughout the biomedical field. This journal is indexed on PubMed Central, MedLine, CAS, SciSearch®, Current Contents®/Clinical Medicine,

Submit your manuscript here: <http://www.dovepress.com/international-journal-of-nanomedicine-journal>

Dovepress

Journal Citation Reports/Science Edition, EMBASE, Scopus and the Elsevier Bibliographic databases. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.