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LETTER

Nanoscale TiO_2 nanotubes as a basis for governing cell behaviors and application challenges

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Dear editor

TiO_2 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 al[3] published in the *International Journal of Nanomedicine* on investigating the effects and molecular mechanisms of TiO_2 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 al[4] 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 al[6] explored the cytocompatibility of TiO_2 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 al[7] 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 TiO_2 nanotubes. Oh et al[8] 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,

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inducing selective differentiation into osteoblast-like cells. This special phenomenon may be attributed to the fact that MSCs cultured on <50 nm TiO_2 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 TiO_2 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, TiO_2 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, TiO_2 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 TiO_2 nanotubes as compared to polymer implants. Another important concern is the potential nanotoxicity of TiO_2 nanotube-based implants, which could be caused by nanotube delamination or degradation after implantation and release of TiO_2 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 TiO_2 nanotube production, scalability and reliability before they start to be produced at industrial scale. Finally, current public opinion regarding the clinical application of TiO_2 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 al[3] 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 TiO_2 nanotubes on a number of different cell lines.

Disclosure

The authors report no conflicts of interest in this communication.

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