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TiO_2 nanotubes as drug nanoreservoirs for the regulation of mobility and differentiation of mesenchymal stem cells

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ABSTRACT

The extracellular microenvironment plays a key role in the regulation of cellular behavior. To mimic the natural extracellular microenvironment, TiO_2 nanotube (TNT) arrays as drug nanoreservoirs for loading of bone morphogenetic protein 2 (BMP2) were constructed on titanium substrates and then covered with multilayered coatings of gelatin/chitosan (Gel/Chi) for controlled drug release. The multilayered coatings were constructed via a spin-assisted layer-by-layer assembly technique. The successful fabrication of this system was monitored by field emission scanning electron microscopy, atomic force microscopy, X-ray photoelectron spectroscopy and contact angle measurements. Multilayered coating with Gel/Chi retained the drug bioactivity and release properties, which were revealed by superoxide dismutase activity measurement. In addition, cytoskeleton observation and wound healing assay confirmed that BMP2-loaded and multilayer-coated TNT arrays were able to stimulate motogenic responses of mesenchymal stem cells (MSCs). More importantly, the system demonstrated that it was capable of promoting the osteoblastic differentiation of MSCs. This study may have potential impact on the development of bone implants for enhanced bone osseointegration.

1. Introduction

Extracellular microenvironments play a critical role in the regulation of a range of cell behavior, including cell adhesion, proliferation, migration and differentiation [1,2]. In order to develop novel functional implants it is essential to construct suitable interfacial microenvironments—which both direct cell fates and improve interactions between cells and implant materials—on the surfaces of materials [3]. With the advancement and convergence of materials science and biology, it is possible to construct biomimetic extracellular microenvironments on the surfaces of implants by combining functional drug-delivery systems with biomaterials [3,4]. Various strategies have been employed to construct extracellular microenvironments, such as functional proteins [5], fibrin hydrogels containing growth factor [6] and anti-inflammatory drug-eluting multilayers [7]. We have also developed gene-stimulating microenvironments on titanium and poly(D,L-lactic acid) substrates via a layer-by-layer (LbL) assembly technique which were able to regulate cell functions, including the differentiation of mesenchymal stem cells (MSCs) [8,9]. In addition, we have fabricated hybrid multilayers embedded with a nanoreservoir-type drug-delivery system onto titanium substrates, and demonstrated that this material has great potential for maintaining bone homeostasis [10]. Nevertheless, it is still necessary to develop a new strategy for the construction of biomimetic extracellular microenvironments with an efficient growth factor delivery system on implant surfaces for the regulation of cell behavior.

Herein, we report the fabrication of a novel Ti-implantable device, employing arrays of 110 nm diameter TiO_2 nanotubes (TNTs) on the surface of Ti films as growth factor (bone morphogenetic protein 2 (BMP2)) nanoreservoirs and using gelatin/chitosan (Gel/Chi) multilayers to control the release of the functional molecule and maintain its bioactivity. This device displayed great potential for retaining the bioactivity of the drug and regulating the motility and differentiation of MSCs. It is well known that commercial pure titanium (cpTi) and its alloys have been extensively used as orthopedic and dental replacements [11]. However, the poor osseointegration between Ti implant and the surrounding tissue has limited the clinical application of these materials [12]. To address this challenge, many efforts have been made to fabricate nanoscale features on Ti substrates to mimic the micro/nanostructures of natural bone [13–17]. Previous studies have confirmed that TNT arrays prepared on the surfaces of pure Ti substrate have great potential for biomedical applications owing to their unique nanoscale topography [14,15]. These prominent nanostructures would regulate the cellular behavior, such as proliferation and mobility [14,15]. Furthermore, Balasundaram et al. also demonstrated that biomacromolecule-functionalized TNT arrays could further improve adhesion and cell density of osteoblasts,

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