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The modulation of stem cell behaviors by functionalized nanoceramic coatings on Ti-based implants

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A B S T R A C T

Nanoceramic coating on the surface of Ti-based metallic implants is a clinical potential option in orthopedic surgery. Stem cells have been found to have osteogenic capabilities. It is necessary to study the influences of functionalized nanoceramic coatings on the differentiation and proliferation of stem cells *in vitro* or *in vivo*. In this paper, we summarized the recent advance on the modulation of stem cells behaviors through controlling the properties of nanoceramic coatings, including surface chemistry, surface roughness and microporosity. In addition, mechanotransduction pathways have also been discussed to reveal the interaction mechanisms between the stem cells and ceramic coatings on Ti-based metals. In the final part, the osteoinduction and osteoconduction of ceramic coating have been also presented when it was used as carrier of BMPs in new bone formation.

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1. Introduction

The proportion of orthopedic in surgery is growing with the development of orthomorphia and the increasing rate of fracture or joint degeneration which is the result of the aging population. New long-term implants are more strongly required nowadays. It is predicted that the amount of total hip implants will grow by 174%–572,000 procedures while the demand of total knee arthroplasties estimates to rise by 673% to 3.48 million by 2030 [1]. It has been reported that more than 500,000 bone graft surgeries happen in America and about 2.2 million throughout the world (these surgeries cost approximately 2.5 billion dollars each year) are performed to address bone fractures and other orthopedic-related injuries resulting from a variety of surgical [2,3], traumatic and degenerative causes [4]. Both the autoplastic transplantation and allograft from human living donors or cadavers are used in orthopedics transplantation. And xenograft bone from a non-human also can be an available graft in orthopedic operation. Currently, the best choice in bone graft treatment is autologous bone, harvested primarily from the patients' iliac crest or other parts like the proximal tibia, intramedullary canal, distal femur, and ribs [2,4–6]. Though the autograft bone is at an advantage of its immunocompatibility and fantabulous osteoconductive properties, it cannot be widely used for the sake of donor shortages. Metallic biomaterials are often used in orthopedic devices for the fixation and immobilization of bone fractures to meet the requirements of maintaining mechanical integrity and biocompatibility during the healing process. Due to their superior biocompatibility, relatively low modulus of elasticity, high mechanical strength and some other suitable mechanical properties [7], titanium and its alloys have been used extensively in biomedical fields for orthopedic applications under load-bearing conditions [8]. However, titanium and its alloys have been proven to be bioinert and they cannot have a direct chemical bonding to living bone tissues [9].

Researchers have done plenty of surface modifications to ameliorate the biological, chemical and mechanical properties of Ti and its alloys in the last decades. A series of surface engineering techniques, including plasma spraying, microarc oxidation, sol-gel, electrochemical deposition and laser cladding and etc. [10–14], were used to fabricate bioactive nanoceramic coatings on the surface of these metals. Nanoceramics have excellent performances, including high mechanical strength, superior tribological property, bioactivity and resorbability [2]. Nano calcium phosphate ceramics such as hydroxyapatite (HA), α-tricalcium phosphate (α-TCP), β-tricalcium phosphate (β-TCP) and tetracalcium phosphate [9,15,16] show good bone-bonding to natural bones. Macropores on or inside the ceramic can intensify the ingrowth of tissue and accelerate the degrading process of ceramic as well [15].

Table 1 enumerates the advantages and disadvantages of autogenous bone, allograft bone, heterogenous bone, Ti alloys and Ti alloys with nanoceramic coatings [7,9,13,14]. Among the ceramics mentioned above, HA coatings have the most similar ingredients to human bones. Once the biomaterials are transplanted into body to replace the defect sites, the implants inevitably attach with surrounding tissue and may react with them. Table 2 gives types of bioceramic-tissue attachments [17].

Tissue engineering applied concepts and methods which are from both engineering and life sciences to maintain existing tissue or to promote regeneration of new tissue [18]. Based on the understanding of tissue formation and regeneration, tissue engineering proposes to induce the formation of new functional tissues rather than to implant new spare parts compared to classical biomaterials methods [19]. The alleged triplets in tissue engineering comprehend three essential components: scaffolds, cells and signaling biomolecules (or growth factors). Among them, the cells, which are widely cognized as the parts of an engineered tissue or absorbed onto/inside the scaffolds, compose the "prototype" of the living tissue to generate and to synthesize matrices for repopulation. After the implants transplanted into human body, stem cells play vital roles in restoring new bones. According to the stage of development, stem cells can be divided into two types: embryonic stem cells (ESCs) and somatic stem cells. All kinds of stem cells such as ESCs, mesenchymal stem cells (MSCs, derive from bone marrow or umbilical cord blood), adipose tissue-derived stem cells (ADSCs), muscle-derived stem cells (MDSCs) and dental pulp stem cells (DPSCs) [20] are used in bone tissue engineering for osteogenic differentiation owing to their potential of differentiate into different lineages after suitable stimuli.

Therefore, in the following sections, we will firstly generalize these proper stimuli which come from the surface characters of nanoceramic coatings on Ti and its alloys, including the surface chemistry, surface roughness and microporosity, and their corresponding effects on the differentiation behaviors of stem cells will also be discussed as well.

2. Effects of surface chemistry

2.1. Protein adsorption

Protein adsorption in the differentiation and proliferation of stem cells is a complex process. Surface charge, ionic environment and solubility of substrates can play important roles in protein adsorption. Nanophase hydroxyapatite (HA) is a nano-scaled needle-like crystal with circa 5–20 nm in width and 60 nm in length,

Table 1
Comparisons of different implant materials [7,9,13,14].

Type of implants	Advantages	Disadvantages
Autograft bone	Immunecompatibility and fantabulous osteoconduction	Donor shortages
Allograft bone	Osteoconduction	Transfer of infection and antigenicity
Heterogenous bone	Sufficient source	Immunorejection
Ti alloys	Biocompatibility, relatively low modulus of elasticity, high mechanical strength	Indirect chemical bonding to living bone tissues
Ti alloys with nanoceramic coatings [9] [13] [14]	Good bone-bonding to natural bones	Adhesion strength needs to be improved