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Nanostructured Titanium Biomaterials: Understanding and Applications

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Abstract. Nanostructured implant materials are considered as promising future biomaterials. Specifically, titanium based nanomaterial is the mostly used implant materials in orthopedic, dental and vascular surgeries. Due to the advantage of nanoscale features, treatment with nano porous and nano bump surface features have shown enhanced biocompatibilities, such as adhesion, proliferation and differentiation for bone and vascular cells. In addition, nanotoxicity issue with immune cells (macrophages) is currently paramount interest for determining subsequent tissue cellular response on implanted biomaterials. In this review, we demonstrated altered cellular interaction of bone, vascular cells on nanostructured titanium based alloys/materials through systematic controlling of nanoscale surface features, such as porosity and nanobumps. All this knowledge will be beneficial for both understanding and designing nanostructured biomaterials for increasing biocompatibility, thus, all these endeavors will lead increment of functionality of biomaterials and will eventually prolong the life time of implanted biomaterials.

Introduction

Traditionally, titanium-based materials have been considered as durable and biocompatible implant materials for both vascular and orthopedic applications [1-3]. The problem with current drug-eluting titanium stents lies in the fact that immunosuppressant drugs placed in a polymer coating on titanium stents also inhibits the proliferation of vascular endothelial cells (cells that naturally cover the interior of a healthy blood vessel) [4-5]. Although such inhibition caused by drug elution on vascular cells does not happen on bare titanium stents, sometimes bare titanium stents cause poor bonding with the endothelium or cause extensive inflammatory responses which further limit endothelialization [6]. For this reason, maximizing initial endothelial cellular adhesion and reducing inflammatory immune responses with titanium stent surfaces by altering intrinsic surface properties (such as topography, roughness and energy) are, thus, extremely important factors in the design of future vascular stents [5,7]. A similar situation has been reported for titanium used in orthopedic applications. It has been reported that almost 25% of all hip implant surgeries performed today require revisions to retrieve a failed titanium implant [8]. This is because the average functional lifetime of today's orthopedic titanium implants ranges only from 10 to 25 years; clearly additional orthopedic surgery (after 10-25 years) is a large burden for any patient [9]. One of the major causes of titanium implant failure involves incomplete osseointegration (or bonding of the implant to surrounding bone) and, thus, it is currently believed that early sufficient formation of new bone on a titanium orthopedic implant surface will quickly fix the implant into juxtaposed bone ensuring a longer functional lifetime [10-12]. In this respect, bio-inspired nano-materials (with surface structures less than 100nm) can be essential to resolving current problems associated with titanium-based vascular and orthopedic implant materials [7,13-14]. This is because desirable cellular responses on nano-structured titanium can lead to a stronger initial biointegration with surrounded tissue to increase both the lifetime and bonding between appropriate tissues and implant surfaces. Fig. 1 show that bone and vascular cell adhesion densities more increased on nano and submicron titanium compared to flat titanium (Fig. 1). This show clear evidence that nanoscale surface topography induced more protein adsorption (such as fibronectin and vitronectin), which eventually determined the subsequent initial cellular response.

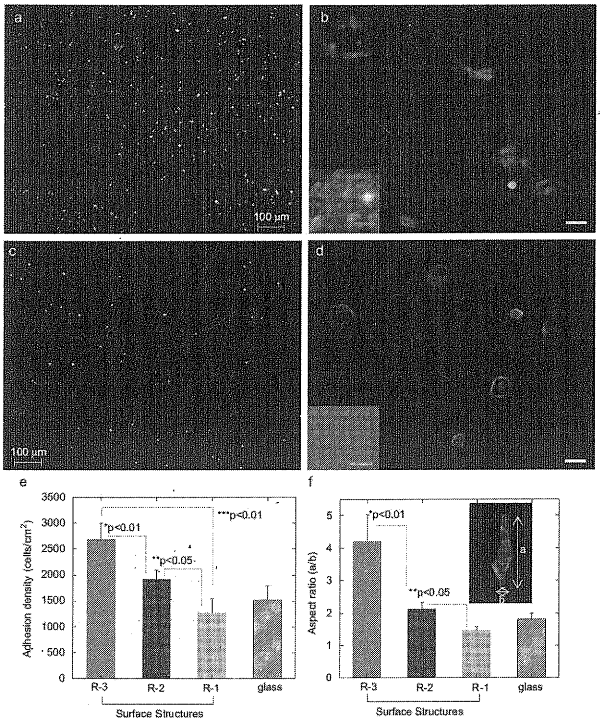
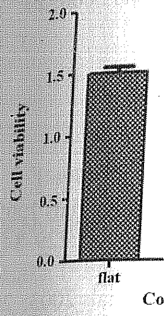


Fig. 1 RAEC adhesion on bulk substrates. (a) Fluorescence RAEC density on sub-micron structured surfaces. (b) Magnified fluorescence RAEC image of sub-micron surfaces showed high cell aspect ratios. Inset image shows SEM surface structures (bar is 100 nm). (c) Fluorescence RAEC density on flat surfaces. (d) Magnified fluorescence cell images of RAEC on flat surfaces show small cell aspect ratios (more round cellular shapes than on sub-micron surfaces. Bar is 100 nm). (e) Adhesion density showed that sub-micron structures led to the best adhesion density (seeding density was 3500 cells/cm^2). (f) Cell aspect ratios showed oriented cell morphology for flat, nanometer and sub-micron structures (increased right to left). Note that cell aspect ratios were calculated by the length of a single cell divided by its width (inset image of (f)). Image adopted from Ref. [15]

Titanium alloys also have been considered as an important material for hard tissue implant. This is due to their mechanical properties have shown both greater biocompatibility and enhanced osseointegration. Different elastic properties between the metal and bone, plays a very important role during fracture healing for many types of fixations. Thus, it must be considerated that the mechanical properties of the material that are the one of the most important factors. Ideally, the fixator should be matched with the natural rigidity of intact bone at the interface. Titanium-nickel alloys have exceptional mechanical properties including superelastic properties and shape memory effect. However, The low popularity of Ni–Ti is caused by high content of Ni, which is known to be carcinogenic and toxic [16]. Although this weakness, nitinol has been attractive due to the mechanical properties which is fit for bone fixators (bone clamps, plates, wires and pins), dental and laparoscopic devices. The biological properties of Nitinol can be improved by surface treatments[17-20]. For surface treatments, such as oxidation, nitriding, different types of coating (e.g. carbon, hydroxyapatite and polymers), chemical etching, polishing and electrochemical methods [18,21–26] have been proposed. Bioactivity can be altered by several different methods that change the topography, chemistry, wetting ability and surface energy. In this study, we studied the material and surface characterization of submicron porous Ni-Ti alloy and associated bone cell adhesion. Osteoblast (bone forming cell) adhesion experiments showed greater bone cell adhesion on greater porosed surfaces compared to small porosity and flat NiTi surfaces in identical chemistry. It is clear that osteoblast adhesion density is proportional to nano-submicron scale surface roughness (RMS) and surface porosity (Fig. 2). More consideration is required how surface porosity and nanoscale roughness induced more osteoblast adhesion. Future research will be focused on the proliferation and differentiation on various densities of porosity on NiTi surfaces.



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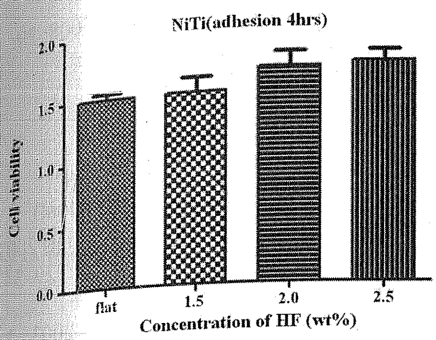

Fig. 2 MTT(Mitochondrial activity) : cell viability showed higher bone cell adhesion densities on greater porous Ni-Ti surfaces compared to small porosity and flat Ni-Ti surfaces in identical chemistry. This represent that bone cell adhesion is strongly depends on porosity.

Summary

Other studies demonstrated greater bone-forming cell (osteoblast) functions on various nano-materials, anodized titanium and nano-structured titanium surfaces as compared to conventional orthopedic implant materials. Efforts also have been focused on understanding the mechanisms of enhanced bone cell functions on these materials and these studies have provided clear evidence that altered amounts and bioactivity of adsorbed proteins (such as vitronectin, fibronectin and collagen) were responsible due to increased surface energy of nanostructured surfaces. In fact, it has been demonstrated that small changes in nanometer surface features can have larger consequences towards bone regeneration. Each of these studies provided clear evidence that bone cell behavior is strongly dependent upon the size and shape of surface features where nanometer and submicron sized surface features can substantially improve long term functions of bone and vascular cells.

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