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Biological Response to Nanosurface Modification on Metallic Biomaterials

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Abstract

Purpose of review New biomaterials for biomedical applications have been developed over the past few years. This work summarizes the current cell lines investigations regarding nanosurface modifications to improve biocompatibility and osseointegration.

Recent findings Material surfaces presenting biomimetic morphology that provides nanoscale architectures have been shown to alter cell/biomaterial interactions. Topographical and biofunctional surface modifications present a positive effect between material and host response.

Summary Nanoscale surfaces on titanium have the potential to provide a successful interface for implantable biomedical devices. Future studies need to directly evaluate how the titanium nanoscale materials will perform in in vivo experiments. Biocompatibility should be determined to identify titanium nanoscale as an excellent option for implant procedures.

Keywords Nanomaterials · Biocompatible · Titanium · Implants · Bone

Introduction

Life expectancy has increased over the years due to advances in technology that enhance quality of life. Thus, the demand for orthopedic and dental implants has grown substantially, leading to improved research and development of biomaterials with better mechanical and biological properties [1]. As can be observed, the global orthopedic implants market is expected to reach USD 64.0 billion by 2026 [2]. Additionally, the global dental implants market is projected to achieve USD 13.01 billion by 2023 [3]. Adequate selection and design of materials according to the intended application [4] are essential to prolonging the biomaterial lifetime.

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However, the ideal metallic material must have a low modulus of elasticity close to bone, tensile strength, fatigue resistance, density, hardness, elongation wear, and corrosion resistance. For many years, dental and orthopedic fields have used stainless steel and cobalt-chrome alloys for their implants [5]. They have shown clinical success because these materials have excellent mechanical properties, high strength, good corrosion resistance, and compatibility with the human body. Nevertheless, titanium and its alloys have been increasingly applied because of similar but improved mechanical and biological properties. Titanium has high biocompatibility and is bioinert. However, the long-term success of the implant depends on the interaction between bone tissue and the implant. The implicit idea is that the implant should be inert to avoid an adverse inflammatory reaction in the body [6]. On the other hand, implants must stimulate osseointegration. In this way, the surface characteristics of an implant significantly influence its stability and lifetime depending on the biomaterial [7].

Nowadays, there are many approaches for performing surface modifications, such as topographical and biofunctional, to improve osseointegration. For example, techniques such as electrochemical etching [8–10], the sol–gel method [11], heat or alkaline treatment [12], ion implantation [13], plasma spray coating ([14, 15]), anodization ([16, 17]), and SBF coatings

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([8, 10, 18]) have all shown altered cellular response enhancement of the biocompatibility. The surface results at nanoscale present a positive effect between material and host response among all modification techniques [19].

Several studies have shown that cell cultures from the human body favorably interact with nanostructured surfaces and nanoscale materials [20], with some proteins more effective than conventional materials (Fig. 1). The nanosurface has unique properties such as a wide surface area, and it can be designed to have specific sizes and shapes. This characteristic enables the production of a surface with specific biological properties.

Why modify the Surface of the Material?

Many types of materials and surface modifications have been used in biomaterial fields to improve longevity and osseointegration.

Currently, most orthopedic and dental implants present titanium or titanium alloys in their composition [21]. The modulus of elasticity of Ti cp is 105 GPa and bone 17–25 GPa, which causes a phenomenon known as stress shielding, potentially leading to peri-implant bone resorption, implant loss, and bone fracture [5]. The addition of different metal elements, such as Ta [16], Mo [22], Nb [23], and Zr [24], can improve titanium alloy properties, including toughness, ductility, tensile strength, fatigue strength, elastic modulus, and surface hardness [25]. However, implants of titanium and its alloys often fail due to wear corrosion, fibrous encapsulation, inflammation, low fracture toughness, low fatigue strength, and mismatch in modulus of elasticity [26].

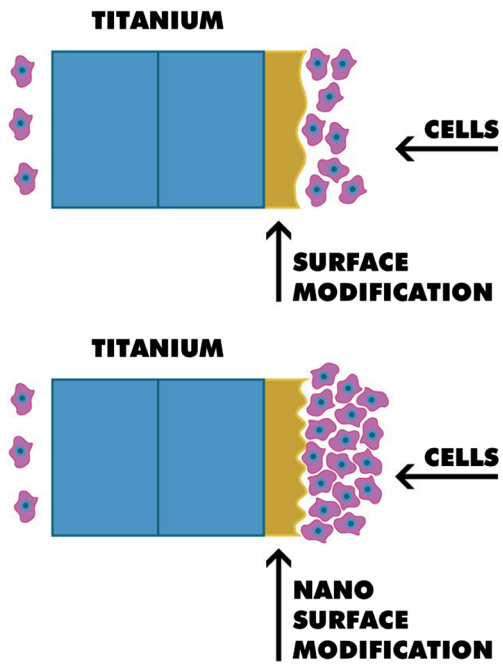

Fig. 1 Human cell cultures favorably interact with nanostructured surfaces showing higher cell growth on them

Thus, reaching excellent mechanical, chemical, physical, and biological properties to avoid implant failure remains challenging. Modifying titanium and titanium alloy implant surfaces is an excellent way to affect their long-term performance.

Surface modifications include modifications to roughness, hydrophilicity, surface charge, surface energy, biocompatibility, and reactivity. These modifications are classified by mechanical, chemical, and physical methods depending on the formation of the surface layer [27]. The mechanical modifications are machining, grinding, polishing, and blasting; the chemical treatments include acidic, alkaline, and hydrogen peroxide treatment, sol–gel, anodic oxidation, CVD, and biochemical methods; and the physical methods are thermal spray, PVD, ion implantation and deposition, and glow discharge plasma treatment [28].

In addition, modifications in the surface morphology of a biomaterial that mimics the natural tissue architecture have been shown to improve cellular interactions and promote healthy tissue [29]. The surface of the anodized metal with tubular morphology presents a higher degree of oxidation and surface energy, and improves the biocompatibility [30]. Previous studies have shown that the use of titanium nanotubes, through anodizing of the same, for implants implanted in hard and soft tissues altered the cellular response, thus enhancing the biocompatibility [31–37].

Biological Response to Nanosurface Modification

In the osteogenesis processes, the synthesis of new bone is determined to start from the implant surface in the centrifugal direction. After the deposition of this first layer, strongly influenced by the implant surface, the production and combination of the collagen fibers and the bone matrix occur. The bone subsequently fully matures within 4 weeks. The following tissue reactions are influenced by both the physical–chemical properties of the material and the topographic features.

Several studies show the importance of the implant surface's characteristics for achieving a better result. Specifically, surface microscopical features have been shown to influence the behavior of the cells responsible for the final bone formation.

Nanosurface modification can affect the biomaterial's wettability in the water and protein content present in the implant site, making it possible to absorb bone morphogenetic proteins (BMP), osteogenetic proteins (OP), fibronectin, and osteopontin released at the implant site following surgery. It can also cause an increase in osteoblast proliferation and preosteoblastic cell differentiation, as well as migration to the implant site and an

Table 1 Effects of the nano-structured modification of surfaces and improvements on different cell lines

Reference	Year	Cell Line	Effect
[48]	2020	Mouse embryonic osteoblast cells (MC3T3-E1)	Enhanced cell proliferation
[49]	2020	Bone marrow mesenchymal stem cells (bMSCs)	Improved the osseointegration
[50]	2020	Osteoblasts (MG63), fibroblasts (L929), epithelial cells (SCC)	Improved the osseointegration and gingival epithelial sealing
[40]	2020	Primary human gingival fibroblasts cells (GFs)	Improved soft-tissue sealing
[41]	2020	Primary human gingival fibroblasts cells (GFs)	Improved the osseointegration and gingival epithelial sealing
[42]	2020	Mouse embryonic osteoblast (MC3T3-E1)	Enhanced cell proliferation and mineralization
[43]	2020	Human mesenchymal stromal cells (hMSCs)	Enhanced osteogenic differentiation
[44]	2020	Human osteoblast-like cells (MG-63)	Improved cell proliferation and mineralization
[45]	2020	Bone marrow mesenchymal stem cells (bMSCs)	Enhanced early adhesion, proliferation, and osteogenic differentiation
[46]	2020	Bone marrow mesenchymal stem cells (bMSCs)	Improved cell adhesion and proliferation
[51]	2020	Human osteoblast-like cells (MG-63)	Increased osteoconductive and osseointegrative
[52]	2020	Human osteoblast-like cells (MG-63)	Enhanced cell proliferation and differentiation
[38]	2020	Bone marrow mesenchymal stem cells (bMSCs)	Enhanced cell-nanotopography interactions and osseointegration
[53]	2019	Bone marrow mesenchymal stem cells (bMSCs)	Improved cell proliferation and differentiation
[54]	2019	Human osteoblast-like cells (MG-63)	Enhanced cell proliferation and differentiation
[55]	2019	Bone marrow mesenchymal stem cells (bMSCs)	Enhanced early adhesion, proliferation and osteogenic differentiation
[56]	2019	Epithelial HT29 cells	Improved cell proliferation and differentiation
[57]	2019	Bone marrow mesenchymal stem cells (bMSCs)	Enhanced early adhesion, proliferation, and osteogenic differentiation
[58]	2019	Mouse embryonic osteoblast (MC3T3-E1)	Enhanced cell proliferation and mineralization
[59]	2019	Adipose-derived stem cells (ADSC)	Enhanced cell proliferation and mineralization
[60]	2019	Mouse embryonic osteoblast (MC3T3-E1)	Enhanced cell proliferation and mineralization
[61]	2019	Mouse embryonic osteoblast (MC3T3-E1)	Enhanced cell proliferation and mineralization
[62]	2019	Primary human fermal fibroblasts adult (HDFa)	Improved cell adhesion and proliferation
[63]	2019	Human osteoblast-like cells (MG-63)	Enhanced cell proliferation and mineralization
[64]	2019	Bone marrow mesenchymal stem cells (bMSCs)	Enhanced early adhesion, proliferation and osteogenic differentiation
[39]	2019	Mouse embryonic osteoblast (MC3T3-E1)	Improved cell adhesion and proliferation
[65]	2018	Human osteoblast-like cells (MG-63)	Enhanced cell proliferation and mineralization
[66]	2018	Bone marrow mesenchymal stem cells (bMSCs)	Enhanced early adhesion, proliferation, and osteogenic differentiation
[67]	2018	Human osteoblast-like cells (MG-63)	Enhanced cell proliferation and mineralization

increase in the production of alkaline phosphatase, transforming growth factor (TGF) beta, and prostaglandin 2 (PGE2).

The surface treated with strontium loading on nanosurface Ti–6Al–4V implants enhanced the early bone-bonding ability by improving the surface characteristics in vitro and in vivo [38]. A titanium dioxide nanotubular surface with platelet-derived growth factor-BB covalent modification exhibited negligible cytotoxicity and satisfactory bioactivity for host cells. It significantly enhanced the attachment and osteogenesis-related functions (early-stage proliferation, extracellular matrix synthesis, and mineralization) of human bone marrow mesenchymal stem cells [27]. Titanium dioxide nanotubes could provide novel designs for dental implants to achieve excellent gingival epithelial healing and osseointegration, facilitating the clinical application of dental implants [39].

Anodized anisotropic titanium surfaces improved soft-tissue sealing around dental abutment surfaces, with implications toward reducing implant failure/peri-implantitis and

achieving long-term success, especially in compromised patients [40]. The oxidized titanium nano-foveolae (TiNF) surface performed better for human gingival fibroblast biological activities compared to traditional smooth surfaces [41]. Tantalum coated on titanium dioxide nanotubes presented good adhesion, differentiation, mineralization, and osteogenesis-related gene (BMP-2, ALP, OCN, and OPN) expression in vitro. These results suggest that the Ta/TiO_2 nanotube composite coatings can provide a favorable application for dental implants to enhance cytocompatibility [42].

Optimized micro-/nanotopography on Ti–6Al–4V alloys stimulated the osteogenic differentiation capacity of hMSCs and confirmed the potential application of anodization to improve osteo-integrative surfaces in orthopedic implants [43]. The surface modification of orthopedic implants by optimized fluorine-substituted hydroxyapatite coating enhanced the growth of human osteoblast-like cells (MG-63) [44]. The fabrication of strontium-incorporated protein supramolecular nanofilm on titanium substrates had significant capability of new bone formation in vivo after implantation for 4 weeks [45]. Hybrid composites based on β-alloy Ti–xNb and oxide nanotubes improved cell adhesion and proliferation, which is vital for successful application in regenerative medicine [46].

The advantages of these surfaces are not only attributed to the roughness due to the pores, which can be similar to other types of surfaces, but mainly because of the chemical influence of the anodized layer. The anodized nanoporous surface offers excellent mechanical retention, and the pores are limited in size to allow efficient transport of factors and proteins essential for the osseointegration process [47]. Titanium nanotubes improved cellular interactions and reduced stimulation of the immune response compared to non-nanotube substrates.

The trend in metallic biomaterials is to improve the nanotopography in order to improve the cell interaction, consequently increasing the longevity of the implant. Table 1 shows the cell lines used to investigate cell behavior. We observed that independent of the cell line type, most of the studies are in agreement and show that the nano-structured modification of surfaces promoted cell proliferation.

Conclusion

This study shows that titanium implant devices could present an improvement in biocompatibility when their surfaces were modified to the nanoscale. This nanotechnology gives significant results when working on surfaces able to attract cells favoring the healing and integration process in the human body. Developing different techniques to alter the titanium surfaces, we can enable interactions between cells and the nanoscale surface and suitable biological responses. These new modified surfaces can be considered intelligent or a selective-microbial surface. The biomaterial used in the place of the bone graft should have clinical features similar to autologous bone, as per consistency and quantity. In particular, the excellent biological properties of nanoscale titanium allow its use as an implantable biomedical device. Thus, in the field of orthopedics or oral implant surgery, it is widely considered an incredible advantage.

However, nanoscale titanium should be tested in animal models to compare the results to cell cultures in vitro. It is critical to ensure that these nanoscale materials will have excellent mechanical, physical, chemical, and biological properties in in vivo situations. Additionally, the animal model will contribute to determining any limitations of the nanoscale titanium. In this way, the next step could be to perform clinical trials in human.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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