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Review article

A critical review of multifunctional titanium surfaces: New frontiers for improving osseointegration and host response, avoiding bacteria contamination

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ABSTRACT

Evolution of metal implants progressively shifted the focus from adequate mechanical strength to improved biocompatibility and absence of toxicity and, finally, to fast osseointegration. Recently, new frontiers and challenges of Ti implants have been addressed to improvement of bioactivity, fighting of bacterial infection and biofilm formation, as well as modulation of inflammation. This is closely related to the clinical demand of multifunctional implants able to simultaneously have a number of specific responses with respect to body fluids, cells (osteoblasts, fibroblasts, macrophages) and pathogenic agents (bacteria, viruses). This complex system of multiple biological stimuli and surface responses is a major arena of the current research on biomaterials and biosurfaces. This review covers the strategies explored to this purpose since 2010 in the case of Ti and Ti alloys, considering that the number of related papers doubled about in the last seven years and no review has comprehensively covered this engaging research area yet. The different approaches followed for producing multifunctional Ti-based surfaces involve the use of thick and thin inorganic coatings, chemical surface treatments, and functionalization strategies coupled with organic coatings.

Statement of Significance

According to the clinical demand of multifunctional implants able to simultaneously have a number of specific responses with respect to body fluids, cells and pathogenic agents, new frontiers of Ti implants have been addressed to improvement of bioactivity, fighting of bacterial infection and biofilm formation, as well as modulation of inflammation. Literature since 2010 is here reviewed. Several strategies for getting bioactive and antibacterial actions on Ti surfaces have been suggested, but they still need to be optimized with respect to several concerns. A further step will be to combine on the same surface a proven ability of modulation of inflammatory response. The achievement of multifunctional surfaces able to modulate inflammation and to promote osteogenesis is a grand challenge.

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1. Introduction

The demand of clinicians in dentistry and orthopedic medical fields was as first oriented to mechanical properties, durability and biocompatibility. Ti and Ti alloys largely fulfilled these requirements; surface mechanical properties (wear and friction resistance) are still an open issue in the case of artificial joints, but this specific topic will be not discussed in this review that is focused on tissue integration. In a further stage, surface chemical properties and surface-bone interface became the main topics with a clinical demand of faster osseointegration and a focus on the osteoblast response to the implant surface. Even if osseointegration of conventional Ti and Ti alloys is successful in many clinical cases of un-cemented implants, an osseoinductive behavior of the surface is demanded mainly when fast healing is required or quality and/or quantity of bone is poor. Several strategies were explored for this purpose and they can be divided up by those using bioactive approach (*in vivo* induced apatite precipitation) or those based on topographical stimulus of the osteoblasts through tailored roughness. Bioactive behavior can be obtained on Ti and Ti alloys by applying a coating of a foreign material (plasma spray coatings of apatite or bioactive glasses), using electrochemical processes (anodic oxidation or NTs) or chemical surface treatments (in acidic, basic or oxidative environments). A classification of the bioactive surfaces can be done according to the mechanism of bioactivity, which can be related to ion exchange with the body fluids [1] and/or to surface charge effects and micro- or nano-scale topography [2]. Some of these surface treatments are currently used in clinical applications [3,4].

More recently, the clinical demand moved to multifunctional surfaces able to simultaneously give a specific response to colonization by different cells (osteoblasts, fibroblasts, macrophages) and infection agents (bacteria, viruses). This complex system of multiple biological stimuli and surface responses is the main focus of the current research on biomaterials. Antibacterial surfaces able to avoid biofilm formation are highly challenging for bone contact implants. It has been reported that deep infections typically occur in 1–2% of patients with total hip arthroplasties [5] and dental peri-implant disease and infection have become a main focus in terms of prevention and treatment of oral implantology [6]. When deep infection occurs, removal and re-implantation of the implant is often necessary, with additional discomfort of the patients and costs for the health services. The main approaches, nowadays developed and under investigations, focused on simultaneous bioactive and antibacterial actions of Ti surfaces will be here resumed.

A focus of this review is on the inflammatory response elicited by Ti surfaces because it is strictly connected to physiological osseointegration and infections. Fewer macrophages and lower inflammation is reported on the Ti/Ti alloy surfaces than on stainless steel [7] or polyether ether ketone (PEEK) [8]. In general, Ti is well tolerated by the body as long as the implant is in bulk form, mechanically stable and non-infected. If the latter conditions are not met, the implants can be associated with an acute/chronic inflammatory reaction, osteolysis, loosening and failure. Human osteoclasts can corrode stainless steel, cobalt and Ti alloys leading to the production of metal ions responsible for inflammatory reactions. Traces of cellular activities on metal orthopedic explants have recently been reported as inflammatory cell-induced corrosion being the result of the cells sealing on the metal surfaces and releasing reactive oxygen species. The extent and clinical relevance of this phenomenon has yet to be completely understood [9]. A 19-year retrospective study of dental implant failure indicated that 47% of the early implant failures were caused by inflammation [10]. In the case of devices for stabilization of fractures, side effects related to the immune reaction of the body and excessive inflammation are often observed [11]. If we look at the soft tissue-implant interface, Ti showed higher inflammation reaction than ceramics, such as zirconia, even if lower than other metals, such as gold, as shown in the case of abutments [12,13].

This review, prepared by examining the relevant literature published since 2010 to present, aims at providing a picture of current knowledge and challenges concerning multifunctional Ti and Ti alloys surfaces, which can be useful to both experienced scientists and early-stage researchers working in the field.

2. Inflammation response and Foreign Body Reaction as open issues in bone implants: key strategies to control them

Healing reaction of Ti implants can occur through osseointegration (desired outcome) or fibrotic encapsulation through chronic inflammation (failure). The events related to inflammation response to an implant can be summarized in the following eight steps [14–16]: exudation, protein surface adsorption, development of a blood-based transient provisional matrix, recruitment of the cells of the innate immune system (leukocytes, platelets, complement and coagulation systems), migration of neutrophils, substitution by monocytes and differentiation into macrophages, Foreign Body Reaction (FBR), production of Reactive Oxygen Species (ROS), fusion of monocytes/macrophages to form Foreign Body Giant Cells (FBGCs) or apoptosis. The acute inflammation step usually resolves within less than 1 week: persistence of this state beyond 3 weeks is usually related to infection or failure. Osseointegration can be considered as a limited FBR without occurring of chronic inflammation. FBR can be histologically recognized because of a typical aspect with a thin layer of macrophages; type 2 inflammation is early activated and bone resorption is suppressed, suggesting a shift to a more pronounced bone forming environment (till after 4 weeks of implantation) [17]. Subjective host (patient) factors can interfere on this cascade of inflammation events such as age, nutritional status (malnutrition results in increased susceptibility to infections and in changes to the innate immune system), quality of the adjacent tissues, and comorbidities.

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