Interactions Between the Physiological Environment and Titanium-Based Implant Materials: From Understanding to Control

Interactions between the physiological environment and titanium-based implant materials – from understanding to control

Sara Ferraris[a], Yolanda S. Hedberg[b,c], James J. Noël[c], Silvia Spriano[a]

[a]Department of Applied Science and Technology, Politecnico di Torino, Corso Duca degli Abruzzi 24, 10129, Torino, Italy
[b]KTH Royal Institute of Technology, Department of Chemistry, Division of Surface and Corrosion Science, Drottning Kristinas väg 51, SE-10044, Stockholm, Sweden
[c]The University of Western Ontario, Dept. of Chemistry, Surface Science Western, London, Ontario, Canada

Email addresses: sara.ferraris@polito.it (S. Ferraris), yhedberg@uwo.ca (Y. Hedberg), jjnoel@uwo.ca (J. Noël), silvia.spriano@polito.it (S. Spriano)

Abstract

Titanium and titanium alloys are widely used in different biomedical applications owing to their high biocompatibility, high corrosion resistance, good mechanical properties, and good osseointegration ability. Titanium and its alloys rapidly form a surface oxide layer in air and aqueous environments. This passive and thin (a few nanometers) surface oxide hinders active corrosion and ensures a low metal release, enhancing biocompatibility. Compared to that of other biomedical alloys, this surface oxide is exceptionally resistant to chemical attack by halides, primarily chlorides and fluorides, although the presence of fluorides can in some cases result in localized corrosion of titanium and its alloys. However, the combination of proteins, inflammatory conditions, and bacteria, which for instance generate hydrogen peroxide, can in a combined (electro-)chemical manner result in the reduction of the corrosion resistance of titanium-based materials. Titanium and its alloying elements, such as aluminium and vanadium, can then be released, which might trigger the immune system and reduce biocompatibility. Several surface modifications have been proposed in order to improve the bone bonding ability of titanium and its alloys, facilitate the healing process and enhance the success of the implant with a decreased risk of micromotions. Moreover, antimicrobial ions/nanoparticles can be added to the surface to reduce the infection risk. Surface modification of titanium (e.g. with artificially grown, micrometer - thick , titanium oxide layers) can significantly increase the corrosion resistance under critical conditions (e.g. inflammation and infection), however, the materials are not completely inert, and the effect of metal ion/nanoparticle presence should be carefully taken into account.
This chapter reviews and discusses the current strategies for modifying and controlling the surface of titanium-based implant materials, with particular focus on corrosion resistance, bone integration, inflammation and infection control, and interactions with the physiological environment.

Keywords: titanium, corrosion resistance, inflammation, bone integration, infection control

1. Introduction

Titanium (Ti) and Ti alloy implant materials can release metals into the physiological environment. These can be in an ionic form, aqueous complexes, bound to proteins, or metal (oxide) particles. Their form (chemical speciation) is decisive for any biological response and might be changed with time or upon a changed environment.

While direct immune response to Ti species has been debated for long time, newer research shows clear evidence that T-cell mediated hypersensitivity specific to Ti(IV) exists (Chan et al. 2011; Hamann 2018; Evrard et al. 2010; Hosoki et al. 2016). Hypersensitivity reactions to Ti have traditionally been overshadowed by those to other metals (Evrard et al. 2010; Hosoki et al. 2016) and are – due to chemical limitations – difficult to diagnose by patch testing (Hamann 2018). While Ti and its oxide,

such as Ti dioxide (TiO_2) have long been considered non-toxic and biocompatible, newer studies show that this is not always true (Jin and Berlin 2015). Small (< 4 µm) released Ti oxide particles can be taken up in cells (Kumazawa et al. 2002), be enriched in to the implant adjacent tissue or distal organs (Swiatkowska et al. 2018; Olmedo et al. 2008; Sarmiento-González et al. 2008), and cause different immunological responses (Thewes et al. 2001). Due to the low solubility of TiO_2, TiO_2 particles comprising 80% of the total detected Ti have been found in human post-mortem studies in different organs, such as spleen, liver, and kidney (Peters et al. 2020). TiO_2 nanoparticles are of relatively low toxicity as compared to other metal oxide or metal nanoparticles, however, it is now evident that they can cause the generation of oxygen species, inflammation, genotoxicity, metabolic changes, and potentially carcinogenesis (Grande and Tucci 2016; Shakeel et al. 2016).

The alloying elements in Ti alloys, such as aluminium (Al), niobium (Nb), tin (Sn), vanadium (V), nickel (Ni), or palladium (Pd) are often of greater short-term health concern than Ti (Chen and Thyssen 2018). Other common alloying elements of similar or lower health concern as compared to Ti are tantalum (Ta), zirconium (Zr), iron (Fe), and molybdenum (Mo). Chromium (Cr), which is a common metal allergen but in most cases not of concern due to its low bioavailability and solubility for implanted alloy materials, can also be an alloying element for titanium alloys (Hamann 2018). These, and other, alloying elements stabilize different phases of titanium resulting in different, or a mixture of, crystal structures with unique mechanical, machinability, and corrosion properties (Noël et al. 2018). Commercially pure (c.p.) Ti is used as coating material or for some dental applications (Gilbert 2017). For many biomedical applications, the use of Ti alloys is necessary, as pure Ti does not have sufficient mechanical properties. Ti containing 6 wt% Al and 4 wt% V (Ti6Al4V) is commonly used for parts of artificial joints (such as the stem of an artificial hip joint prosthesis) that require high corrosion resistance, high fatigue strength, but not necessarily high wear resistance (Gilbert 2017). Titanium and its alloys possess a comparably high osseointegration (tight integration of the implant with the bone), relatively low density (closer to that of natural bone), and relatively high biocompatibility compared with alternative alloys.

The interface between the titanium (alloy) surface and the physiological environment is dynamic and influenced by each other. For example, released metals can cause immunological reactions, which in turn can cause a more corrosive environment triggering more metal release. Infections, specific diseases, and other factors (such as implant design) can also cause aggressive environments causing corrosion and ultimately health effects or implant failure. This chapter will discuss these corrosion processes, how they are affected by the physiological environment, and how metal release, corrosion, and infections could be minimized by means of surface engineering. Particular attention will be given to the description of the complex physiological environment in which corrosion resistance, modulation of the inflammatory response, bioactivity and ability of infection control play interconnected roles. The recent strategies of surface modification of titanium in order to obtain a multifunctional action which takes into account all the above cited parameters are discussed.

2. Corrosion resistance of titanium and its alloy in the biological environment

2.1. Principles of corrosion of titanium and its alloys

A metal is a conductive material and as such, electrons can freely move within it. Corrosion of metals occurs via the oxidation of the metal and the reduction of an oxidant, most often oxygen, water, or protons. These two half-cell reactions are balanced. Due to the electron conductivity of the metal, the reduction half cell-reaction can occur on a very different location and over a differently sized surface area as compared to the oxidation half-cell reaction, which is critical for a number of localized corrosion types of titanium metal and its alloys.

Titanium metal is thermodynamically not stable in water or air. It is rapidly oxidized and reacts even with hydrogen, nitrogen, and many other elements. Its high affinity to oxygen is key for its ability to form a protective surface oxide that hinders further titanium metal oxidation and ensures titanium and its alloys to withstand the relatively corrosive physiological environment to a relatively large extent. In order to understand the corrosion of titanium and titanium alloys, we need to understand under which conditions the titanium surface oxide can form and reform.

At physiologically relevant pH values, titanium metal is oxidized to its most stable form of TiO_2 in several steps (McCafferty 2010; Schmets et al. 1974), with the following reactions showing the equilibrium states at standard conditions:

$$Ti^{2+} + 2e^- \leftrightarrow Ti \quad E^0 = -1.630\,V \tag{1}$$

$$Ti_2O_3 + 6H^+ + 2e^- \leftrightarrow 2Ti^{2+} + 3H_2O \quad E^0 = -0.478\,V - 0.1773pH \tag{2a}$$

or

$$Ti(OH)_3 + 3H^+ + e^- \leftrightarrow Ti^{2+} + 3H_2O \quad E^0 = -0.248\,V - 0.1773pH \tag{2b}$$

$$2TiO_2 + 2H^+ + 2e^- \leftrightarrow Ti_2O_3 + H_2O \quad E^0 = -0.556\,V - 0.0591pH \tag{3a}$$

or

$$TiO_2 + H_2O + H^+ + e^- \leftrightarrow Ti(OH)_3 \quad E^0 = -0.786\,V - 0.0591pH \tag{3b}$$

where E^0 denotes the standard electrode potential in V *vs*. the standard hydrogen electrode (SHE) and in standard conditions (25 °C, 1 M solute concentration, 1 atmosphere gas pressure). For other solute concentrations, the reader is referred to the equations given in (Schmets et al. 1974).
All of these reactions occur at potentials far more negative than the stability area of water, which means that the thermodynamic driving force for titanium oxidation to the Ti^{IV} valence state is very high, when compared with most other metals (Pourbaix 1974). This driving force ensures that a damaged surface oxide is rapidly repaired under benign conditions. This further ensures a very low corrosion rate, under so-called passive conditions, under which subsequent titanium oxidation is limited by a limited mass transport through the formed titanium surface oxide. Under worse, non-passive, conditions, this high thermodynamic driving force towards titanium oxidation can cause a high corrosion rate and large potential differences when coupled with other metals, phases, or intermetallic precipitates.

Alloying elements can either improve or impede the corrosion resistance when compared to commercially pure titanium metal.
The titanium-nickel alloy (commercial name “nitinol”), which is used for its shape memory effect in cardiovascular stents and orthodontic appliances, is an example of a titanium alloy with significantly lower corrosion resistance as compared to titanium metal (Ding et al. 2018; Noguchi et al. 2008), accompanied with some nickel release (Saylor et al. 2016; Sullivan et al. 2015), approximately in the same range, or lower, as compared with austenitic nickel-containing stainless steel (Hedberg and Odnevall Wallinder 2016; Eliades et al. 2004; Suárez et al. 2010). This nickel release can cause a number of clinical adverse effects (Faccioni et al. 2003; Mani et al. 2007; Gong et al. 2013).
Titanium alloys containing aluminium and either vanadium and niobium are widely used for different biomedical applications, especially in orthopedic artificial joint prostheses (Gilbert 2017; Milošev 2017). The titanium alloy containing 6 wt% aluminium and 4 wt% vanadium (Ti6Al4V) has been reported to have a slightly less protective passive layer as compared to commercially pure titanium (Shukla et al. 2005). In the same study (Shukla et al. 2005), a higher alloyed titanium alloy with 13.4 wt% aluminium and 29 wt% niobium (Ti13.4Al29Nb) showed improved corrosion resistance

compared with titanium metal over one week of exposure in Hank's solution, a simple physiological simulant containing a number of salts and glucose at a pH value of about 7.4. A detailed x-ray photoelectron spectroscopy study in Hank's solution revealed a spontaneous formation of primarily TiO_2 in the surface oxide of Ti6Al4V and small amounts of Al_2O_3 on its utmost surface at the interface to the solution (Milosev et al. 2000). A similar study on Ti6Al7Nb showed that the surface oxide on this alloy formed less sub-oxides of TiO and Ti_2O_3 as compared to Ti6Al4V, and possessed a higher corrosion resistance (Milošev et al. 2008).

The formation of the passive surface oxide on titanium and titanium alloys is required for high corrosion resistance. Its formation is however strongly dependent on environmental conditions, as discussed in the following.

2.2. Physiological environments from a corrosion perspective

The physiological environment is highly complex, locally different, and dynamic over time. Only recently, it has been acknowledged that simple salt-based solutions, such as 0.9% sodium chloride, Hank's solution, Ringer's solution, and phosphate-buffered saline, cannot simulate the physiological environment in a relevant and sufficient way for titanium alloys (Gilbert 2017; Zhang et al. 2018; Hedberg et al. 2019b).

Halides are important to many localized types of corrosion of passive metals. Titanium has been considered to have low susceptibility to chloride-induced corrosion, however, in the combination with fluorides and other factors, the chlorides contribute to the corrosion process in a synergistic manner (Li et al. 2007). Fluoride is actively used in the cleaning and protection of natural teeth; therefore, especially titanium-based dental implants and orthodontic nickel-titanium wires are regularly exposed to fluorides. The TiO_2-containing passive film of titanium and its alloys is susceptible to fluoride attack. It was found that fluorides increase the corrosion rates of titanium and its alloys under conditions of relevance for dental environments (Li et al. 2007; Mirjalili et al. 2013; Noguchi et al. 2008; Reclaru and Meyer 1998).

The physiological environment also contains a high number of complexing agents and proteins. The high ionic strength of the physiological environment ensures their rapid adsorption even on similarly charged surfaces (Fukuzaki et al. 1995; Hedberg et al. 2014; Claesson et al. 1995). Proteins and other complexing agents, such as peptides, amino acids, organic acids, or different anions, can form a complex either directly with titanium or with any of its alloying elements. This can occur either directly with the metal, with a metal ion in solution, or – most relevant for passive conditions – directly with the surface oxide. It has been suggested that this process plays an important role for the depletion of Al_2O_3 from the surface oxide of Ti6Al4V and that it is accelerated in the presence hydrogen peroxide (Hedberg et al. 2019b).

Inflammation and immunological reactions can result in a chemical attack and a very high redox potential in the in-vivo environment or locally on the implant surface. Most important, there is increasing evidence that the surface reactions and corrosion triggers the biological response, which in turn accelerates the corrosion rate (Hedberg 2018; Gilbert 2017; Milošev 2017). For example, immune and inflammatory cells can produce a range of highly oxidizing species, including hydrogen peroxide, hydroxide radical, and hypochlorous acid, resulting in an extremely oxidative environment (Gilbert and Kubacki 2016).

2.3. Pitting and crevice corrosion

Pitting and crevice corrosion are localized corrosion types that are important to most passive metals and alloys. For titanium alloys, most pitting or crevice corrosion cases have been found in conjunction with the crevice induced in modular tapered junctions (Gilbert 2017), schematically

illustrated in Figure 1. The difference between pitting and crevice corrosion is its initiation: pitting corrosion requires the damage of the surface oxide, which is often unlikely to occur for titanium alloys, while the crevice already provides the optimal conditions for an initiation of this localized corrosion process. Once initiated, the propagation and failure or repassivation steps of pitting and crevice corrosion are similar and involve a large passive area providing the necessary reaction surface area for the cathodic reaction, and a very small confined space for the anodic reaction (metal oxidation). If pitting corrosion occurs, it is often located in vicinity to a crevice (Gilbert 2017), as the local chemical environment there is far more anaerobic, acidic, and enriched in chlorides, fluorides, or other anions able to attack the titanium surface oxide. The anodic half-cell reactions inside the crevice or pit require cathodic half-cell reactions. These cathodic half-cell reactions can involve the reduction of oxygen on passive surfaces of the titanium metal or alloy – far away from the crevice or pit. Another even more important cathodic reaction is the reduction of protons resulting in the formation of hydrogen gas or absorbed hydrogen in the metal (Noël et al. 2018), which embrittles the metal and can cause cracking, Figure 1. Protons inside the confined space originate from hydrolyses of the released metal ions. These positively charged protons and metal ions also attract negatively charged counter-ions, such as chlorides, fluorides, or sulfates to maintain charge neutrality inside the crevice or pit. This results in an extremely concentrated and aggressive solution chemistry. Crevice and pitting corrosion are often combined with mechanically assisted corrosion types, which then can result in cracking or faster propagation. A change in the geometry, replenishing of the solution inside the confined space, and/or a shift in potential due to oxidants may result in repassivation of the surface. Although crevice and pitting corrosion are rarely observed directly from retrieved titanium alloy implant materials, it is suspected to be part of the overall corrosion mechanism (Hall et al. 2018; Gilbert 2017).

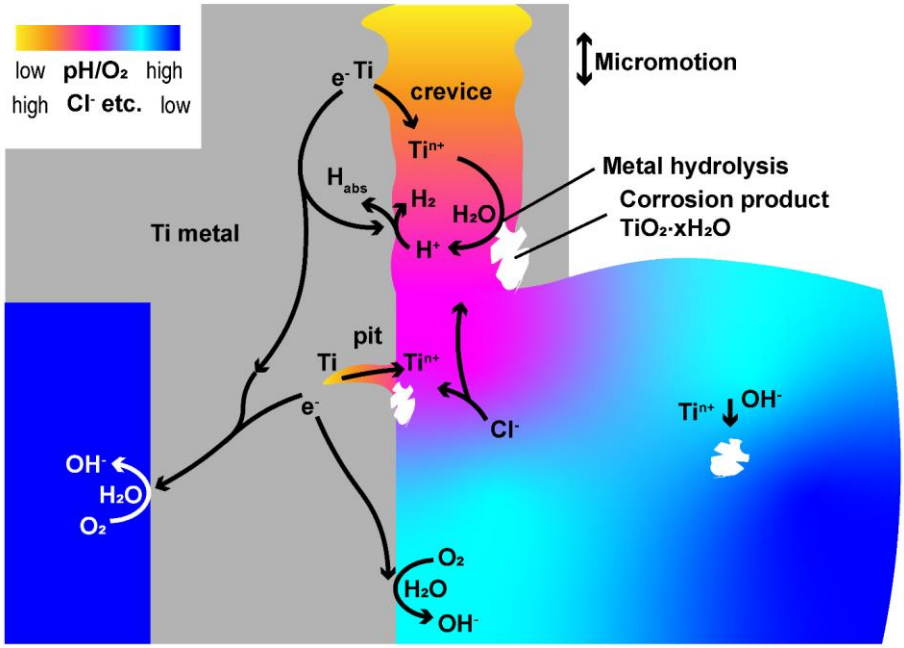

Figure 1*. Schematic illustration of the local chemical environment during pitting and crevice corrosion of titanium or its alloys. Inside the confined space of the crevice or pit, the solution chemistry is characterized by a very low pH, an anaerobic environment, and very high concentrations of ions. Charge neutrality is ensured by the free movement of electrons inside the metal and the migration of*

ions in and out of the confined spaces. The corrosion reactions result in the buildup of corrosion products on the surface of the confined spaces and as particles. Micromotion is often present for crevices of orthopedic and dental implants.

2.4. Mechanically assisted corrosion types

Titanium and its alloys are usually not intended for wear-exposed parts of biomedical implants due to their relatively lower wear resistance as compared to cobalt-chromium alloys or ceramic materials. Nevertheless, mechanically induced corrosion types are still of high importance for biomedical titanium (alloys) and therefore an important target for surface engineering.

An important type of corrosion of titanium alloys as biomedical materials is the mechanically assisted crevice corrosion (MACC) (Hall et al. 2018; Gilbert 2017), which is the combination of fretting corrosion and crevice corrosion. Fretting corrosion requires micromotion between the titanium (alloy) surface and a hard countersurface able to damage the surface oxide (Swaminathan and Gilbert 2012). In implant materials, such as dental implants (screws) or modular taper junctions of joint prostheses, cyclic micromotions are common. The hard countersurface can for instance be an oxide-coated metal, a ceramic material, or particles deriving from the corrosion process (Figure 1) or wear. This oxide damage then initiates or accelerates localized corrosion, most often crevice corrosion.

Stress corrosion cracking can be a result of hydrogen embrittlement due to absorbed hydrogen (Figure 1) or be related to the stresses that occur during oxide growth ('oxide-induced stress corrosion cracking' - OISCC) (Gilbert 2017). MACC and OISCC can ultimately result in the buildup of a relatively thick (several hundreds of micrometers) titanium oxide layer, termed 'direct conversion to oxide' (Gilbert 2017; Gilbert et al. 2012). These thick titanium oxide layers have been found in-vivo (Gilbert et al. 2012), especially in modular taper junctions providing the optimal geometry of a crevice in combination with micromotions. The combination of OISCC and direct conversion to oxide can result in rapidly growing pits filled with oxide. As these oxides have a higher volume than the metal, the material is cracking and the pit can propagate further. This can result in millimeter-long oxide-filled pits and cracks (Gilbert et al. 2012), Figure 2.

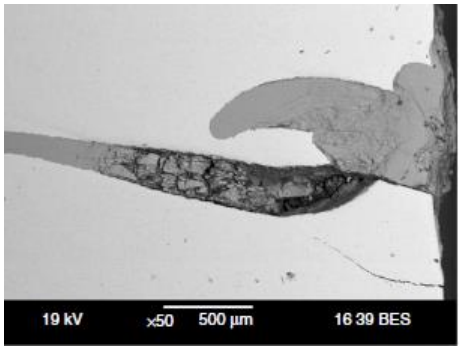

***Figure 2**. Permission required from: (Gilbert et al. 2012). On-going…*

2.5. Selective, galvanic, and intergranular corrosion

Ti6Al4V contains both alpha (hexagonal closed-packed structure) and beta (body-centered cubic structure) phases. It has been shown for retrieved implants that pits and directly converted oxide propagate along the beta phases and then convert the alpha phases into oxide (Gilbert et al. 2012). This selective corrosion is due to a lower corrosion resistance of the beta phase as compared to the alpha phase (Noël et al. 2018). It has been hypothesized that the combination of hydrogen peroxide

(from inflammatory reactions) and cathodic potentials, e.g. due to crevice corrosion, can provide conditions that selectively dissolve the beta phase of Ti6Al4V alloys (Gilbert et al. 2012).

Intergranular corrosion, for which the corrosion occurs preferentially along grain boundaries, is relatively rare for titanium and its alloys in biomedical applications, but has been observed as a consecutive corrosion mechanism following other corrosion types such as MACC (Gilbert 2017).

Due to the very negative standard potential of titanium and its alloys (see section 2.1), this metal can be susceptible to galvanic corrosion when coupled with other metals and when the oxide is damaged. Coupling to other metals is common in most orthopedic and dental implants (Cortada et al. 2000; Lucas et al. 1981). In dental implants, the couple can even include very noble metals such as gold alloys. This can theoretically increase the release of titanium ions and synergistically contribute to other corrosion types, but has not been found to be a dominating corrosion type for biomedical titanium alloys (Cortada et al. 2000; Lucas et al. 1981; Gilbert 2017). Any galvanic effects of incorporated noble metal nanoparticles in the oxide of titanium alloys have recently been studied and are discussed in section 4.3.

2.6. The role of cells, proteins, and reactive oxygen species

The titanium (alloy) material is not only influenced by the physiological environment but does also change the physiological environment by triggering different cell and immune responses, which in turn influence corrosion mechanisms. This two-way response is a relatively new paradigm within corrosion science and has been supported and proposed by a number of recent scientific studies and discussions (Gilbert 2017; Hedberg 2018; Hedberg et al. 2019a; Hedberg et al. 2019b; Gilbert and Kubacki 2016; Gilbert et al. 2015; Milošev 2017; Yu et al. 2015; Zhang et al. 2018).
There is a large arsenal of chemical species and cells in the response of the human body to the metal or alloy. Each of them alone is often not of greater concern, but combined with other factors, their action can be devastating to the corrosion process.

A recent study demonstrated a combined effect of mechanical stress and proteins on the corrosion resistance of, and metal release from, nitinol (Ni-Ti) alloys (Zhang et al. 2020).

Several studies have shown the combined action of proteins, such as serum albumin, and hydrogen peroxide, which is one of the chemical species produced under inflammatory conditions, on the corrosion resistance and metal release of Ti6Al4V (Yu et al. 2015; Zhang et al. 2018; Hedberg et al. 2020; Hedberg et al. 2019b). It has been hypothesized that hydrogen peroxide primarily forms a complex with TiO_2, weakening its bonds and chemical stability, while serum albumin primarily complexes aluminium from the surface oxide (Hedberg et al. 2019b). These complexation processes result first in the enrichment and then the depletion of aluminium in the surface oxide, and in the growth of a relatively thick oxide (Hedberg et al. 2019b), similar to those found in-vivo. These complexation and metal complex detachment processes take time and are not necessarily possible to detect in short-term accelerated corrosion tests (Zhang et al. 2018; Hedberg 2018).

It should be emphasized that proteins are not necessarily detrimental to the corrosion process, but can also be neutral or beneficial – this depends on the circumstances (Hedberg 2018). In addition to their complexation abilities, they can also have shielding effects reducing the access to an oxidant, and they can also act as biomarkers attracting certain cells (both beneficial and detrimental to the corrosion process).

As outlined in section 2.2., inflammatory and infection conditions can be considered a worst-case environment. Direct etching tracks related to immune cells have been observed on cobalt-chromium alloys (Hall et al. 2017), but would most probably result in a thicker oxide, instead of etching, in the case of titanium alloys. The immune system reacts also to protein aggregates, which can be induced

by metal ions or nanoparticles (Hedberg et al. 2019a), wear particles (Sundfeldt et al. 2006), and to relatively low amounts of released metal ions in the case of sensitization to one or several of the metals in the alloys (Chen and Thyssen 2018).

From an engineering perspective, it is hence interesting to target the avoidance of infections, the decrease of the release of metals, and the increase in wear resistance of biomedical titanium alloys.

3. Titanium surfaces and inflammatory reaction

3.1. Host response to titanium surfaces (Sara & Silvia)

The host response to an implanted biomaterial depends on materials characteristic (e.g. composition, surface texture, degradability, mechanical properties) and on host specific features (such as age, anatomic factors, co-morbidities, immune response). This response begins at implantation time and last for the whole permanence of the material in in the human body (Londono and Badylak 2015). It is of particular importance because it can affect implant properties (e.g. degradation, surface alteration) and its functional outcome (e.g. fibrous encapsulation vs physiological integration).

Upon implantation the biomaterial surface come in contact with physiological fluids and water, ions and proteins sequentially interact with in few seconds. The protein layer that covers the surface depends on the material surface properties and affect the cellular/bacterial adhesion to it (Kasemo 2002). The first cells to approach the protein covered surfaces are neutrophils, with the aim to remove bacteria and debris or damaged tissues in analogy to the conventional wound healing process in absence of implants (Ratner BD 2001, Londono and Badylak 2015). In one day macrophages reach the surface. If in wound healing without implant macrophages modulate inflammation (inevitably associated with wounds) to get tissue repair, in case of presence of a foreign material, the above cited materials and host characteristic affect the macrophage response (Ratner BD 2001, Londono and Badylak 2015). Typically macrophage can show a pro-inflammatory polarization (M1 state) related to rapid immune activation or an anti-inflammatory polarization (M2) related to wound healing and tissue remodelling. A proper balance between these two states can guarantee a physiological healing assuring the removal of damaged tissues without the development of chronic inflammation (Hotchkiss et al 2016). In presence of non degradable implants (e.g. metallic implants) macrophages individuate the implant as a possible foreign body and try to engulf and digest it a process often called “frustrated phagocytosis” which results in the fibrous encapsulation of the implant (Ratner BD 2001, Londono and Badylak 2015). Metal ions and nanoparticles significantly affect the host response to implants. In particular it has been observed that metal ions can bind host proteins and cause an immunological response resulting in hypersensitivity (Yao et al 2015). These phenomena are particularly evident for toxic metals such as Nickel, Cobalt and Chromium ions released from Co-Cr alloys or their micro-nano particles produced in metal on metal joint replacement (highly debated now). Hypersensitivity and excessive immune-response are rarely reported for titanium (Yao et al 2015). Moreover, in case of titanium implants (which do not release toxic substances), it has been supposed that the collagenous capsule can evolve in bone mineralization due to the presence of ions and bone stem cells at the implant site (Ratner BD 2001). Titanium bone bonding ability has been widely studied and several surface modifications have been proposed in order to improve it, such as nano/micro textures, bioactive surface layers (obtained by chemical or electrochemical treatments), bioactive coatings (e.g. bioactive glasses or hydroxyapatite) and also surface grafting of bioactive molecules (Souza JCM et al 2019, Oliver JN et al 2019, Spriano et al. 2018, Kokubo and Yamaguchi2016, Lugovskoy and Lugovskoy 2014, Chen at al 2013, Spriano et al 2010). The cited surface treatments can induce a significant improvement in the biological response to titanium in terms of osteoblast adhesion, proliferation and differentiation (*in vitro*) and of bone formation (*in vivo*). However it has been reported that in certain cases a too rapid and conspicuous bone apposition can be associated with an excessive inflammatory response which can even lead to late implant failure (**CITARE QUI ARTICOLO SWEDEN**). Considering these aspects the development of titanium surfaces able to improve bone bonding and healing in a physiological

Commentato [S1]: Silvia hai il riferimento del famodo articolo citato da S&M? Potresti inserirmi I riferimenti qui a commento?

manner with strict control of the inflammation host response is of great interest in the biomaterial field. The strategies currently under investigation for inflammation control from titanium surfaces are discussed in the following section.
Finally prosthetic infection are always coupled with strong inflammatory reactions which can exacerbate the situation and lead to implant failure. The strategies for the preparation of antibacterial surfaces are discussed in section 4.

3.2. Surface modifications for inflammation control (Sara & Silvia)

The evolution of the biocompatibility concept moved from the idea of an inert mechanical resistant implant to the one of a bioactive implant able to improve and fasten tissue integration (especially in the bone contact field) and actually is mainly focused on the modulation of the host response to the implant for a physiological healing which pass also from the modulation of the inflammatory response.
Differently from bioactivity, bone integration and even antibacterial activity (see section 4) the immunomodulation is still less explored and is actually highly debated in the scientific literature. Some strategies for the control of the inflammatory response and foreign body reaction have however been proposed, such as the tailoring of protein absorption, the modulation of macrophage polarization, the use of topographical patterns able to modulate macrophage response, the use of biomimetic coatings, the local delivery of anti-inflammatory drugs, the regulation of NO and the induction of macrophage apoptosis (Spriano et al 2018).
Some interesting strategies applied to titanium surfaces are briefly summarized below.
At first an effect of surface topography on the host immunoresponse has been widely documented in the literature. A reduced attachment of macrophages and the production of anti-inflammatory factors (M2 polarization) has been documented on sandblasted and acid etched surfaces (SLA type) plasma treated to be super-hydrphylic (Hotchkiss et al 2016) compared to standard tissue culture polystyrene. A combined effect of roughness and wettability has been noticed for these materials. Similarly it has been observed that nanotextured titanium oxide layer rich in OH groups (hydrphylic, even not super hydrophilic) can significantly reduce macrophage adhesion and production of anti-inflammatory mediators on the surface of microbeads titanium implants (Barthes et al. 2020). An anti-inflammatory response of macrophages, mediated by an enhancement of the endothelial cells response and by the reduction of monocytes adhesion, has been observed also on nano and sumicrometric rough Ti coatings, intended for cardiovascular applications (Lu and Webster 2015).
On the other hand M1 macrophage polarization has been observed on titania nanotubes with diameter around 100 nm (He et al 2020, Shen et al 2019). However, under oxidative stress, a shift to M2 polarization has been observed in co-colture with mesenchymal stem cells (Shen et al 2019), upon higher MSc recruitment followed by osteogenic differentiation. Moreover it has been observed that different nanotextures, produced on commercially pure titanium by anodization, able to give analogous osteogenic activity in vitro promote different osteointegration in vivo, which has been explained observing different macrophage polarization mediated by surface roughness.
Titanium surfaces have been enriched with various ions (e.g. copper, silver, zinc) in order to promote a multifunctional response (e.g. addition of antibacterial activity) to the implant. Cu ions have been introduced on MAO oxidized titanium by hydrothermal treatment (Huang et al 2019) or addition of Cu to the anodization electrolyte (Huang et al 2018), on Ti6Al4V alloy by selective laser melting of pure Cu (Xu et al 2018), on titanium by Plasma Immersion Ion Implantation (Chen et al 2021). The effect of copper on the inflammatory response is controversial. Cu addition onto MAO titanium surfaces (Huang et al 2018, Huang et al 2019) induced macrophage polarization to inflammatory M1 state, however a favorable microenvironment for osteogenesis has been reported due to the release of pro-osteogenic factor by macrophages cultured on these surfaces. Moreover an antibacterial activity mediated by macrophages has been observed on these materials. On the other hand an anti-inflammatory effect has been observed on Ti6Al4V alloy enriched with copper by selective laser melting (Xu et al 2018) and on PIII titanium (Chen et al 2021). The addition of magnesium to MAO titanium surfaces has been observed as able to promote M2 macrophage polarization (Li et al 2018).

An anti-inflammatory effect modulated by calcium ions can be cited considering the reduction of pro-inflammatory factors produced by macrophages onto acid etched titanium enriched with nanoscale calcium phosphates (Nanotite, Biomet 3i, Hamlet and Ivanovski 2011) and the particular hybrid M1-M2 polarization of macrophages observed on hydroxyapatite coated rough titanium surfaces (Zhang et al 2019). Finally ceria coatings on titanium substrates showed the ability to affect fibronectin orientation and macrophage polarization (M2 state) mediated by Ce valence state (Shao et al 2020).
At last the strategy of grafting of specific organic molecules can be reported. The effect of some coupling agents, often used for further grafting of biomolecules, on the inflammatory response has been tested. It has been observed that (3-glycodoxypropyl)trimethoxy silane (GPTMS) increase the absorption of complement proteins and the pro-inflammatory polarization (M1) of macrophages and reduce osteointegration of sandblasted-acid etched titanium in a dose dependent manner (Araujo-Gomes et al 2019). On the other hand Amino propyl triethoxy silane (APTES) induce M2 macrophage polarization on NaOH treated titanium (Zhang et al 2018). A reduction of the inflammatory response has been observed on titania nanotubes loaded with anti-inflammatory agents such as dexamethasone (Shank et al 2020) or IL4 (Yin et al 2019). Different peptides such as a mussel inspired peptide (Bai et al 2020) or the cationic peptide cecropin B (Xu et al 2013) have been coupled with titanium by coordination chemistry or polydopamine mediated grafting respectively. Both peptides allowed to obtain anti-inflammatory macrophage activity, improvement of osteoblast adhesion and activity and antibacterial action. A macrophage recruitment agent (SEW2871) intercalated in layer by layer chitosan-gelatin coating onto dual acid etched titanium (He et al 2020) promoted rapid macrophage recruitment, anti-inflammatory activity and osteogenesis in in vivo tests. Finally a multifunctional response (anti-inflammatory, anti-bacterial and pro-osteogenic) has been observed after surface grafting of two antibiotics: bacitracin (polydopamine mediated covalent grafting to Ti6Al4V, Ni et al 2016) or Minocycline (introduced in layer by layer chitosan/gelatin coating onto Ti substrates, Shen et al 2019).
All these strategies are extremely interesting and promising but often difficult to be implemented due to the complexity of the biological system to be controlled. In fact it should be remembered that inflammation should be controlled but not completely suppressed because it is necessary for tissue healing, proteins which act as pro-inflammatory agents can also act as tissue repairing agents, the in vivo protein absorption conditions and cross-talk among different cell type are different from the ones reproduced in conventional in vitro experiments. Moreover it should be taken into account the surface modifications which involve the use of active molecules can significantly increase the complexity of the regulatory processes of the medical devices.

3.3. *Inflammation and corrosion resistance*

As outlined in section 2., there is increasing evidence that inflammation, which results in high redox potentials and the presence of hydrogen peroxide, has a considerable role in the degradation of titanium (alloys) and the release of metal ions. This is also true for titanium alloys that were optimized for osseointegration, although their corrosion resistance is higher and their metal release is lower, as compared to titanium alloys with a thin, native, passive surface oxide (Hedberg et al. 2020).

4. Titanium surfaces for bone integration and infection control

4.1. Recent strategies to combine bioactivity and antibacterial activity (Sara & Silvia)

Prosthetic infections interests the 1-2% on hip and knee replacement and increases in case of revision surgery or fixation of open fractures (up to 30-40%) (Trampuz and Widmer 2006). Moreover prosthetic infections are among the most critical complications in orthopedic surgery because they are associated with both high morbidity and high hospital costs (Trampuz and Widmer 2006, Zimmerli et al 2004). Even if a strict antibiotic and antibacterial perioperative prophylaxis is currently applied and can significantly reduce the risk of infection both orthopedic and dental implant associated infections are mainly related to bacterial contamination of implanted surfaces by the

formation of a bacterial biofilm (Zimmerli et al 2004, Subramani et al 2009). The biofilm is a polysaccharidic structure in which bacteria can growth and hardly been reached by systemic antibiotics and antimicrobial treatments. In this context the development of antibacterial surfaces, able to limit bacterial adhesion and proliferation is particularly promising.
A first strategy can be the reduction of bacterial adhesion to titanium surfaces without the introduction of any active antibacterial agent. This solution has the advantage that it is not time limited (no consumption of antibacterial agent due to release), does not involve potentially toxic substances and does not require complex certification procedures associated with active agents. On the other hand it hardly fights infections in cases of severe bacterial contamination (e.g. septic situations). In this scenario nanotextures have been proposed as potential anti-adhesive titanium surfaces. Nanopatterns with a thickness of 10-100 nm, able to prevent the direct contact between the bacterial cell wall and the titanium substrate have been reported as able to reduce bacterial adhesion and to impart mechanical stresses to bacterial cell wall reducing also bacterial viability (Linklater et al 2020). The flexibility and the geometric features (e.g. sharp edges) of these nanotextures can further improve their effectiveness against bacteria. On the opposite mammalian cells, due to the higher deformability of their membrane, can better accommodate stresses, with consequent biocompatibility, and even cell stimulation ability (focal contact formation) for host cells. Similarly a reduced bacterial adhesion has been documented on bioactive nanotextured titanium oxide layers, even in the absence of any antibacterial agent (Ferraris et al 2019). Recently also the role of surface microstructure (induced by electron beam or thermal treatments) in reducing bacterial adhesion has been reported (Ferraris et al 2019b, Ferraris et al. 2020).
Several strategies have been proposed also for the realization of bactericidal titanium surfaces. The introduction of inorganic antibacterial agents (e.g. Ag, Cu and Zn) by means of surface doping (e.g. ion implantation, in situ reduction or alloys), growth and doping of TiO2 layers (e.g. anodization) or deposition of doped coatings (e.g. plasma spray, sputtering or sol-gel), grafting of antimicrobial polymers, antimicrobial peptides, biomolecules or antibiotics (by direct grafting, covalent grafting mediated by silanes, catechol or phosphates or entrapment into coatings) can be cited among the most popular ones (Ferraris and Spriano 2016, Chourifa et al 2019, Hickok and Shapiro 2012). Considering that bacterial compete with cells for surface colonization of implanted biomaterials, as reported in the well known “race for the surface” (Gristina 1987), implant surfaces able, at the same time, to reduce bacterial contamination and improve tissue adhesion (bioactive and antibacterial), can be of particular interest.
In this view, inorganic antibacterial agents as well as antibiotics have been coupled to bioactive titanium surfaces such as, calcium phosphates, hydroxyapatite or bioactive glass coatings, bioactive TiO2 layers (obtained in the form of thick coatings, chemically modified thin layers or nanotubes), porous coatings intended for bone ingrowth, or complex multi-layers coatings (Ferraris and Spriano 2016, Chourifa et al 2019, Spriano et al 2018, Raphel et al 2016).
The above cited solutions can simultaneously counteract bacterial infection and promote bone regeneration, however it has been pointed out that in some cases infections can activate macrophages (LPS stimulation) to recruit osteoclast and induce infection mediated osteolysis (Raphel et al 2016). In these cases the immunomodulation strategies discussed in section 3 can be of interest to overcome the problem.
All the solutions discussed above are generally tested on bulk plane titanium/titanium alloys samples or model implants. Actually additive manufacturing (AM) is gaining increasing interest for the realization of customized titanium implants and the transfer of the developed technologies for the obtainment of bioactive and antibacterial surfaces to AM implants is under investigation (Li et al 2020). Strategies able to modify both the inner and outer surfaces of pores are advantageous at this purpose.

4.2. Mechanical stability (Sara & Silvia)

In order to be suitable for clinical applications innovative antibacterial and bioactive surfaces should be able to sustain implantation loads and friction as well as mechanical stresses for the whole

implant life. Otherwise the effective surface exposed to the biological environment will not be the designed one (with antibacterial and bioactive functionalities) and the formation of wear debris can stimulate inflammatory reactions.
The adhesion and the mechanical stability has been pointed out as a critical point in the application of anti-adhesive polymers (Raphel et al 2016), however it is not always well described for innovative multifunctional surfaces.
Coating adhesion is one of the key factors for the applicability to implantable medical devices. It can be measured in vitro by means of tensile tests, as suggested by ISO standard 13779-4, indentation test, scratch, tape, pull-out or bending tests, as reported in the scientific literature for various antibacterial and bioactive coatings (Vernè et al 2008, Utku et al 2015, Onoki et al 2008, Ferraris et al 2020b, Stan et al 2013, Surmeneva et al 2017). Moreover the realization of customized implant simulation test in non vital animal bone has been reported as a successful strategy to test the resistance of new surfaces to implantation friction and loads (Ferraris et al 2015, Li T et al 2018).
The adhesion strength of coatings and modified surface layers is strongly affected by surface pre-treatment before coating deposition (e.g. realization of intermediate layers, chemical and electrochemical treatments aimed at improving coating substrate affinity and mechanical interlocking) as well as by process parameters (e.g. in the preparation of TiO2 nanotubes) or of post treatments such as thermal treatments or sterilization processes, and by coating thickness (Stan et al 2013, Onoki et al 2008, Utku et al 2015, Li T et al 2018, Surmeneva et al 2017). Recently it has been evidenced that the addition of graphene oxide to vancomycin loaded Sr-doped hydroxyapatite electrodeposited on titanium surfaces can significantly improve the coating mechanical properties such as hardness, elastic modulus and adhesion (Zhang et al 2020).Considering bioactive and antibacterial surfaces, another critical factor to be considered is their reactivity in physiological environment which can affect their mechanical and chemical stability (Ferraris et al 2020c).

4.3. Chemical stability and corrosion resistance

For surface oxides incorporated with antimicrobial metal nanoparticles, such as silver (Hedberg et al. 2020) and copper (Bernstein et al. 2017) nanoparticles, galvanic effects could occur under certain circumstances. While only a slight effect was found in a study on Ti6Al4V with an artificially grown oxide with embedded silver nanoparticles (Hedberg et al. 2020), a more pronounced galvanic effect was found for Ti6Al4V without such a thick oxide and coated with silver (Furko et al. 2016).

All in all, it is more likely that such surface engineering efforts would benefit the overall corrosion performance by reducing the extent of infection/inflammation, however, under certain circumstances this galvanic couple could be a triggering factor for other corrosion types.

4.4. Ion/nanoparticles release

Infection control requires a certain release of antibacterial metal ions, such as silver and copper (Spriano et al. 2018). Ideally, this release is limited to ions and does not include the metal nanoparticles themselves. However, some release of metal nanoparticles can be expected. Indeed, an increased release of particles was observed in-vitro for Ti6Al4V with embedded silver nanoparticles as compared to a silver-free counterpart, however, it was unclear if this was due to released silver nanoparticles or due to silver-ion induced protein aggregation (Hedberg et al. 2020).
The actual measurable and stable ion release is strongly influenced by the solution chemistry of the metal. Titanium ions are very unstable in most aqueous and physiologically relevant solutions, while the stability of aluminium, silver, and vanadium ions is strongly influenced by the presence of complexing agents such as proteins (Hedberg et al. 2020) and sometimes the redox potential, such as for chromium. This may result in the underestimation of titanium ion release, be a main explanation for the primarily TiO_2-rich oxide growth, and the frequently observed presence of TiO_2 particles in-vivo.

5. Conclusions

References

Bai J, Wang H, Chen H, Ge G, Wang M, Gao A, Tong L, Xu Y, Yang H, Pan G, Chu P. K., Geng D., Biomimetic osteogenic peptide with mussel adhesion and osteoimmunomodulatory functions to ameliorate interfacial osseointegration under chronic inflammation, Biomaterials 255 (2020) 120197

Barthes J, Cazzola M, Muller C, Dollinger C, Debry C, Ferraris S, Spriano S, Vrana NE, Controlling porous titanium/soft tissue interactions with an innovative surface chemical treatment: Responses of macrophages and fibroblasts, Materials Science & Engineering C 112 (2020) 110845

Bernstein A, Suedkamp N, Mayr HO, Gadow R, Burtscher S, Arhire I, Killinger A, Krieg P (2017) Chapter 5 - Thin Degradable Coatings for Optimization of Osseointegration Associated With Simultaneous Infection Prophylaxis. In: Ficai A, Grumezescu AM (eds) Nanostructures for Antimicrobial Therapy. Elsevier, pp 117-137. doi:https://doi.org/10.1016/B978-0-323-46152-8.00005-6

Chan E, Cadosch D, Gautschi OP, Sprengel K, Filgueira L (2011) Influence of Metal Ions on Human Lymphocytes and the Generation of Titanium-Specific T-Lymphocytes. Journal of Applied Biomaterials and Biomechanics 9 (2):137-143. doi:10.5301/jabb.2011.8567

Chen C, S-M Zhang, I-S Lee, Immobilizing bioactive molecules onto titanium implants to improve osseointegration, Surface & Coatings Technology 228 (2013) S312–S317

Chen JK, Thyssen JP (eds) (2018) Metal allergy - from dermatitis to implant and device failure. 1 edn. Springer International Publishing, Cham, Switzerland. doi:10.1007/978-3-319-58503-1

Chouirfa H, Bouloussa H, Migonney V, Falentin-Daudré C, Review of titanium surface modification techniques and coatings for antibacterial applications, Acta Biomaterialia 83 (2019) 37–54

Claesson PM, Blomberg E, Fröberg JC, Nylander T, Arnebrant T (1995) Protein interactions at solid surfaces. Adv Colloid Interfac 57 (0):161-227

Cortada M, Giner L, Costa S, Gil FJ, Rodri´guez D, Planell JA (2000) Galvanic corrosion behavior of titanium implants coupled to dental alloys. J Mater Sci-Mater M 11 (5):287-293. doi:10.1023/a:1008905229522

Ding R, Shang J-X, Wang F-H, Chen Y (2018) Electrochemical Pourbaix diagrams of NiTi alloys from first-principles calculations and experimental aqueous states. Computational Materials Science 143:431-438. doi:https://doi.org/10.1016/j.commatsci.2017.11.033

Eliades T, Pratsinis H, Kletsas D, Eliades G, Makou M (2004) Characterization and cytotoxicity of ions released from stainless steel and nickel-titanium orthodontic alloys. Am J Orthod Dentofac 125 (1):24-29

Evrard L, Waroquier D, Parent D (2010) Allergies to dental metals. Titanium: a new allergen. Revue médicale de Bruxelles 31 (1):44

Faccioni F, Franceschetti P, Cerpelloni M, Fracasso ME (2003) In vivo study on metal release from fixed orthodontic appliances and DNA damage in oral mucosa cells. Am J Orthod Dentofac 124 (6):687-693

Ferraris S, Bobbio A, Miola M, Spriano S, Micro- and nano-textured, hydrophilic and bioactive titanium dental implants, Surface & Coatings Technology 276 (2015) 374–383

Ferraris S, Spriano S, Antibacterial titanium surfaces for medical implants, Materials Science and Engineering C 61 (2016) 965–978

Ferraris S, Cochis A, Cazzola M, Tortello M, Scalia A, Spriano S, Rimondini L, Cytocompatible and Anti-bacterial Adhesion Nanotextured Titanium Oxide Layer on Titanium Surfaces for Dental and Orthopedic Implants, Front. Bioeng. Biotechnol. 7:103. doi: 10.3389/fbioe.2019.00103

Ferraris S, Warchomicka F, Ramskogler C, Tortello M, Cochis A, Scalia A, Gautier di Confiengo G, Keckes J, Rimondini L, Spriano S, Surface structuring by Electron Beam for improved soft tissues adhesion and reduced bacterial contamination on Ti-grade 2, Journal of Materials Processing Tech. 266 (2019) 518–529

Ferraris S, Warchomicka F , Iranshahi F, Rimondini L, Cochis A, Spriano S, Electron Beam Structuring of Ti6Al4V: New Insights on the Metal Surface Properties Influencing the Bacterial Adhesion, Materials 2020, 13, 409; doi:10.3390/ma13020409
Ferraris S, Perero S, Costa P, Gautier di Confiengo G, Cochis A, Rimondini L, Renaux F, Vernè E, Ferraris M, Spriano S, Antibacterial inorganic coatings on metallic surfaces for temporary fixation devices, Applied Surface Science 508 (2020) 144707
Ferraris S, Yamaguchi S, Barbani N, Cristallini C, Gautier di Confiengo G, Barberi J, Cazzola M, Miola M, Vernè E, Spriano S, The mechanical and chemical stability of the interfaces in bioactive materials: The substrate-bioactive surface layer and hydroxyapatitebioactive surface layer interfaces, Materials Science & Engineering C 116 (2020) 111238
Fukuzaki S, Urano H, Nagata K (1995) Adsorption of protein onto stainless-steel surfaces. J Ferment Bioeng 80 (1):6-11. doi:http://dx.doi.org/10.1016/0922-338X(95)98168-K
Furko M, Lakatos-Varsányi M, Balázsi C (2016) Complex electrochemical studies on silver-coated metallic implants for orthopaedic application. J Solid State Electrochem 20 (1):263-271. doi:10.1007/s10008-015-3026-1
Gilbert J (2017) Corrosion in the human body: Metallic implants in the complex body environment. Corrosion 73 (12):1478-1495. doi:10.5006/2563
Gilbert JL, Kubacki GW (2016) Chapter Three - Oxidative Stress, Inflammation, and the Corrosion of Metallic Biomaterials: Corrosion Causes Biology and Biology Causes Corrosion A2 - Dziubla, Thomas. In: Butterfield DA (ed) Oxidative Stress and Biomaterials. Academic Press, pp 59-88. doi:https://doi.org/10.1016/B978-0-12-803269-5.00003-6
Gilbert JL, Mali S, Urban RM, Silverton CD, Jacobs JJ (2012) In vivo oxide-induced stress corrosion cracking of Ti-6Al-4V in a neck–stem modular taper: Emergent behavior in a new mechanism of in vivo corrosion. J Biomed Mater Res B 100 (2):584-594
Gilbert JL, Sivan S, Liu Y, Kocagöz SB, Arnholt CM, Kurtz SM (2015) Direct in vivo inflammatory cell-induced corrosion of CoCrMo alloy orthopedic implant surfaces. J Biomed Mater Res A 103 (1):211-223. doi:10.1002/jbm.a.35165
Gong Z, Li M, Guo X, Ma Z, Shi J (2013) Stent implantation in patients with metal allergy: a systemic review and meta-analysis. Coronary Artery Disease 24 (8):684-689
Grande F, Tucci P (2016) Titanium dioxide nanoparticles: a risk for human health? Mini reviews in medicinal chemistry 16 (9):762-769
Gristina AG, Biomaterial-centered infection: microbial adhesion versus tissue integration, Science 237 (1987) 1588-1595
Hall DJ, Pourzal R, Lundberg HJ, Mathew MT, Jacobs JJ, Urban RM (2017) Mechanical, chemical and biological damage modes within head-neck tapers of CoCrMo and Ti6Al4V contemporary hip replacements. J Biomed Mater Res B DOI 10.1002/jbm.b.33972
Hall DJ, Pourzal R, Lundberg HJ, Mathew MT, Jacobs JJ, Urban RM (2018) Mechanical, chemical and biological damage modes within head-neck tapers of CoCrMo and Ti6Al4V contemporary hip replacements. J Biomed Mater Res B 106 (5):1672-1685. doi:doi:10.1002/jbm.b.33972
Hamann C (2018) Metal Allergy: Titanium. In: Chen J, Thyssen JP (eds) Metal Allergy. Springer, Cham, Switzerland, pp 443-466
Hamlet S, Ivanovski S, Inflammatory cytokine response to titanium chemical composition and nanoscale calcium phosphate surface modification, Acta Biomaterialia 7 (2011) 2345–2353
He Y , Xu K , Li K, Yuan Z , Ding Y , Chen M , Lin C, Tao B , Li X , Zhang G , Liu P , Cai K, Improved osteointegration by SEW2871-encapsulated multilayers on micro-structured titanium via macrophages recruitment and immunomodulation, Applied Materials Today 20 (2020) 100673
Hedberg Y, Karlsson M-E, Blomberg E, Odnevall Wallinder I, Hedberg J (2014) Correlation between surface physicochemical properties and the release of iron from stainless steel AISI 304 in biological media. Colloid Surface B 122:216-222. doi:10.1016/j.colsurfb.2014.06.066
Hedberg YS (2018) Role of proteins in the degradation of relatively inert alloys in the human body. npj Materials Degradation 2:26. doi:10.1038/s41529-018-0049-y

Hedberg YS, Dobryden I, Chaudhary H, Wei Z, Claesson P, Lendel C (2019a) Synergistic effects of metal-induced aggregation of human serum albumin. Colloid Surface B 173:751-758. doi:10.1016/j.colsurfb.2018.10.061
Hedberg YS, Gamna F, Padoan G, Ferraris S, Cazzola M, Herting G, Atapour M, Spriano S, Odenvall Wallinder I (2020) Surface modified Ti6Al4V for enhanced bone bonding ability - effects of silver and corrosivity at simulated physiological conditions from a corrosion and metal release perspective. Corros Sci 168:108566. doi:https://doi.org/10.1016/j.corsci.2020.108566
Hedberg YS, Odnevall Wallinder I (2016) Metal release from stainless steel in biological environments: A review. Biointerphases 11 (1):018901-018901 - 018901-018917. doi:10.1116/1.4934628
Hedberg YS, Žnidaršič M, Herting G, Milošev I, Odnevall Wallinder I (2019b) Mechanistic insight on the combined effect of albumin and hydrogen peroxide on surface oxide composition and extent of metal release from Ti6Al4V. J Biomed Mater Res B 107 (3):858-867. doi:10.1002/jbm.b.34182
Hickok NJ, Shapiro IM, Immobilized antibiotics to prevent orthopaedic implant infections, Advanced Drug Delivery Reviews 64 (2012) 1165–1176
Hosoki M, Nishigawa K, Miyamoto Y, Ohe G, Matsuka Y (2016) Allergic contact dermatitis caused by titanium screws and dental implants. Journal of prosthodontic research 60 (3):213-219
Hotchkiss K M., G B. Reddy, S L. Hyzy, Z Schwartz, B D. Boyan, R Olivares-Navarrete, Titanium surface characteristics, including topography and wettability, alter macrophage activation, Acta Biomaterialia 31 (2016) 425–434
Huang Q , Ouyang Z , Tan Y , Wu H , Liu Y., Activating macrophages for enhanced osteogenic and bactericidal performance by Cu ion release from micro/nano-topographical coating on a titanium substrate, Acta Biomaterialia 100 (2019) 415–426
Huang Q, Li X, Elkhooly TA, Liu X, Zhang R, Wu H, Feng Q, Liu Y., The Cu-containing TiO2 coatings with modulatory effects on macrophage polarization and bactericidal capacity prepared by micro-arc oxidation on titanium substrates, Colloids and Surfaces B: Biointerfaces 170 (2018) 242–250
Jin T, Berlin M (2015) Titanium. In: Nordberg GF, Fowler BA, Nordberg M (eds) Handbook on the Toxicology of Metals, vol 2. Fourth edn. Elsevier, Amsterdam, pp 1287-1296
Kasemo B. Biological Surface Science Surface Science 500 (2002) 656–677
Kokubo T, Yamaguchi S, Novel bioactive materials developed by simulated body fluid evaluation:
Surface-modified Ti metal and its alloys, Acta Biomaterialia 44 (2016) 16–30
Kumazawa R, Watari F, Takashi N, Tanimura Y, Uo M, Totsuka Y (2002) Effects of Ti ions and particles on neutrophil function and morphology. Biomaterials 23 (17):3757-3764
Chen L., Wang D, Qiu J, Zhang X, Liu X, Qiao Y, Liu X, Synergistic effects of immunoregulation and osteoinduction of ds-block elements on titanium surface, Bioactive Materials 6 (2021) 191–207
Li X, Wang J, Han E-h, Ke W (2007) Influence of fluoride and chloride on corrosion behavior of NiTi orthodontic wires. Acta Biomater 3 (5):807-815. doi:https://doi.org/10.1016/j.actbio.2007.02.002
Li X, Huang Q, Liu L, Zhu W, Elkhooly TA, Liu Y, Feng Q, Li Q, Zhou S, Liu Y, Wu H, Reduced inflammatory response by incorporating magnesium into porous TiO2 coating on titanium substrate, Colloids and Surfaces B: Biointerfaces 171 (2018) 276–284
Li J, Cui X, Hooper GJ, Lim KS, Woodfield TBF, Rational design, bio-functionalization and biological performance of hybrid additive manufactured titanium implants for orthopaedic applications: A review, journal of the mechanical behavior of biomedical materials 105 (2020) 103671
Li T, Gulati K, Wang N, Zhang Z, Ivanovski S, Understanding and augmenting the stability of therapeutic nanotubes on anodized titanium implants, Materials Science & Engineering C 88 (2018) 182–195

Linklater DP, Baulin VA, Juodkazis S, Crawford RJ, Stoodley P, Ivanova EP, Mechano- bactericidal actions of nanostructured surfaces, Nature Reviews Microbiology · August 2020
DOI: 10.1038/s41579-020-0414-z
Londono R. and Badylak SF Factors which affects the host response to biomaterials, in Badylak SF, Host response to biomaterials, Elsevier 2015
Lu J, Webster TJ, Reduced immune cell responses on nano and submicron rough titanium, Acta Biomaterialia 16 (2015) 223–231
Lucas LC, Buchanan RA, Lemons JE (1981) Investigations on the galvanic corrosion of multialloy total hip prostheses. J Biomed Mater Res 15 (5):731-747. doi:10.1002/jbm.820150509Lugovskoy A, Lugovskoy S., Production of hydroxyapatite layers on the plasma electrolytically oxidized surface of titanium alloys, Materials Science and Engineering C 43 (2014) 527–532
Ma Q-L, Zhao L-Z, Liu R-R, Jin B-Q, Song W, Wang Y, Zhang Y-S, Chen L-H, Zhang Y-M, Improved implant osseointegration of a nanostructured titaniumsurface via mediation of macrophage polarization, Biomaterials 35 (2014) 9853e9867
Mani G, Feldman MD, Patel D, Agrawal CM (2007) Coronary stents: a materials perspective. Biomaterials 28 (9):1689-1710
McCafferty E (2010) Thermodynamics of corrosion: Pourbaix diagrams. In: Introduction to Corrosion Science. Springer, New York, NY, pp 95-117. doi:10.1007/978-1-4419-0455-3_6
Milošev I (2017) From in vitro to retrieval studies of orthopedic implants. Corrosion 73 (12):1496-1509
Milošev I, Kosec T, Strehblow HH (2008) XPS and EIS study of the passive film formed on orthopaedic Ti–6Al–7Nb alloy in Hank's physiological solution. Electrochim Acta 53 (9):3547-3558. doi:https://doi.org/10.1016/j.electacta.2007.12.041
Milosev I, Metikos-Hukovic M, Strehblow HH (2000) Passive film on orthopaedic TiAlV alloy formed in physiological solution investigated by X-ray photoelectron spectroscopy. Biomaterials 21 (20):2103-2113
Mirjalili M, Momeni M, Ebrahimi N, Moayed MH (2013) Comparative study on corrosion behaviour of Nitinol and stainless steel orthodontic wires in simulated saliva solution in presence of fluoride ions. Mater Sci Eng C 33 (4):2084-2093. doi:https://doi.org/10.1016/j.msec.2013.01.026
Nie B, Ao H, Zhou J, Tang T, Yue B, Biofunctionalization of titanium with bacitracin immobilizationshows potential for anti-bacteria, osteogenesis and reduction ofmacrophage inflammation, Colloids and Surfaces B: Biointerfaces 145 (2016) 728–739
Noël J, Ebrahimi N, Shoesmith D (2018) Corrosion of titanium and titanium alloys. In: Wandelt K (ed) Encyclopedia of Interfacial Chemistry: Surface Science and Electrochemistry, vol 6. Elsevier, Amsterdam, pp 192-200
Noguchi T, Takemoto S, Hattori M, Yoshinari M, Kawada E, Oda Y (2008) Discoloration and dissolution of titanium and titanium alloys with immersion in peroxide-or fluoride-containing solutions. Dent Mater J 27 (1):117-123
Oliver J N., Y Su, X Lu, P-H Kuo, J Du, D Zhu, Bioactive glass coatings on metallic implants for biomedical applications, Bioactive Materials 4 (2019) 261–270
Olmedo DG, Tasat DR, Guglielmotti MB, Cabrini RL (2008) Biodistribution of titanium dioxide from biologic compartments. J Mater Sci-Mater M 19 (9):3049-3056. doi:10.1007/s10856-008-3438-x
Onoki T, Hosoi K, Hashida T, Tanabe Y, Watanabe T, Yasuda E, Yoshimura M, Effects of titanium surface modifications on bonding behavior of hydroxyapatite ceramics and titanium by hydrothermal hot-pressing, Mat Sci Eng C 28 (2008) 207–212.
Peters RJ, Oomen AG, van Bemmel G, van Vliet L, Undas AK, Munniks S, Bleys RL, Tromp PC, Brand W, van der Lee M (2020) Silicon dioxide and titanium dioxide particles found in human tissues. Nanotoxicology 14 (3):420-432

Pourbaix M (1974) Atlas of electrochemical equilibria in aqueous solution. NACE, Houston, Texas, USA
Raphel J, Holodniy M, Goodman SB, Heilshorn SC, Multifunctional coatings to simultaneously promote osseointegration and prevent infection of orthopaedic implants, Biomaterials 84 (2016) 301e314
Ratner BD, Replacing and Renewing: Synthetic Materials, Biomimetics, and Tissue Engineering in Implant Dentistry, Journal of Dental Education 65 (2001) 1340-1347
Reclaru L, Meyer JM (1998) Effects of fluorides on titanium and other dental alloys in dentistry. Biomaterials 19 (1):85-92. doi:https://doi.org/10.1016/S0142-9612(97)00179-8
Sarmiento-González A, Encinar JR, Marchante-Gayón JM, Sanz-Medel A (2008) Titanium levels in the organs and blood of rats with a titanium implant, in the absence of wear, as determined by double-focusing ICP-MS. Anal Bioanal Chem 393 (1):335. doi:10.1007/s00216-008-2449-2
Saylor DM, Adidharma L, Fisher JW, Brown RP (2016) A biokinetic model for nickel released from cardiovascular devices. Regul Toxicol Pharm 80:1-8. doi:https://doi.org/10.1016/j.yrtph.2016.05.019
Schmets J, van Muylder J, Pourbaix M (1974) Titanium. In: Pourbaix M (ed) Atlas of electrochemical equilibria in - Aqueous solutions. NACE, Houston, Texas, USA, pp 213-222
Shakeel M, Jabeen F, Shabbir S, Asghar MS, Khan MS, Chaudhry AS (2016) Toxicity of Nano-Titanium Dioxide (TiO2-NP) Through Various Routes of Exposure: a Review. Biol Trace Elem Res 172 (1):1-36. doi:10.1007/s12011-015-0550-x
Shao D, Li K, You M, Liu S, Hu T, Huang L, Xie Y, Zheng X., Macrophage polarization by plasma sprayed ceria coatings on titaniumbased implants: Cerium valence state matters, Applied Surface Science 504 (2020) 144070
Shen X, Yu Y, Ma P, Luo Z, Hu Y, Li M, He Y, Zhang Y, Peng Z, Song G, Cai K, Titania nanotubes promote osteogenesis via mediating crosstalk between macrophages and MSCs under oxidative stress, Colloids and Surfaces B: Biointerfaces 180 (2019) 39–48
Shen K, Tang Q, Fang X, Zhang C, Zhu Z, Hou Y, Lai M, The sustained release of dexamethasone from TiO2 nanotubes reinforced by chitosan to enhance osteoblast function and anti-inflammation activity, Materials Science & Engineering C 116 (2020) 111241
Shen X, Gu H, Ma P, Luo Z, Li M, Hu Y, Cai K, Minocycline-incorporated multilayers on titanium substrates for simultaneous regulation of MSCs and macrophages, Materials Science & Engineering C 102 (2019) 696–707
Shukla AK, Balasubramaniam R, Bhargava S (2005) Properties of passive film formed on CP titanium, Ti–6Al–4V and Ti–13.4Al–29Nb alloys in simulated human body conditions. Intermetallics 13 (6):631-637. doi:https://doi.org/10.1016/j.intermet.2004.10.001Souza J C.M.,, M B. Sordi, M Kanazawa, S Ravindran, B Henriques, F S. Silva, C Aparicio , L. F. Cooper, Nano-scale modification of titanium implant surfaces to enhance Osseointegration, Acta Biomaterialia 94 (2019) 112–131
Spriano S, Ferraris S, Bianchi CL, Cassinelli C, Torricelli P, Fini M, Rimondini L, Giardino R. Bioactive titanium surfaces. In: Sanchez PN, editor. Titanium alloys: preparation, properties and applications. New York: Nova Science Publishers, Inc.; 2010. ISBN: 978-1-60876-151-7.
Spriano S, Yamaguchi S, Baino F, Ferraris S (2018) A critical review of multifunctional titanium surfaces: New frontiers for improving osseointegration and host response, avoiding bacteria contamination. Acta Biomater 79:1-22
Stan GE, Popa AC, Galca A.C., Aldica G., Ferreira, J.M.F., Strong bonding between sputtered bioglass–ceramic films and Ti-substrate implants induced by atomic inter-diffusion post-deposition heat-treatments, Applied Surface Science 280 (2013) 530– 538
Suárez C, Vilar T, Gil J, Sevilla P (2010) In vitro evaluation of surface topographic changes and nickel release of lingual orthodontic archwires. J Mater Sci-Mater M 21 (2):675-683. doi:10.1007/s10856-009-3898-7
Subramani K, Jung RE, Molenberg A, Hämmerle C H. F, Biofilm on Dental Implants: A Review of the Literature, International Journal of Oral & Maxillofacial Implants . 2009, Vol. 24 Issue 4, p616-

626.Sullivan SJL, Dreher ML, Zheng J, Chen L, Madamba D, Miyashiro K, Trépanier C, Nagaraja S (2015) Effects of Oxide Layer Composition and Radial Compression on Nickel Release in Nitinol Stents. Shape Memory and Superelasticity 1 (3):319-327. doi:10.1007/s40830-015-0028-x

Sundfeldt M, V Carlsson L, B Johansson C, Thomsen P, Gretzer C (2006) Aseptic loosening, not only a question of wear: a review of different theories. Acta Orthop 77 (2):177-197

Surmeneva MA, Sharonova AA, Chernousova S, Prymak O, Loza K, Tkachev MS, Shulepov IA, Epple M, Surmenev RA, Incorporation of silver nanoparticles into magnetron-sputteredcalcium phosphate layers on titanium as an antibacterial coating, Colloids and Surfaces B: Biointerfaces 156 (2017) 104–113

Swaminathan V, Gilbert JL (2012) Fretting corrosion of CoCrMo and Ti6Al4V interfaces. Biomaterials 33 (22):5487-5503

Swiatkowska I, Mosselmans JFW, Geraki T, Wyles CC, Maleszewski JJ, Henckel J, Sampson B, Potter DB, Osman I, Trousdale RT, Hart AJ (2018) Synchrotron analysis of human organ tissue exposed to implant material. J Trace Elem Med Bio 46:128-137. doi:https://doi.org/10.1016/j.jtemb.2017.12.007

Thewes M, Kretschmer R, Gfesser M, Rakoski J, Nerlich M, Borelli S, Ring J (2001) Immunohistochemical characterization of the perivascular infiltrate cells in tissues adjacent to stainless steel implants compared with titanium implants. Archives of orthopaedic and trauma surgery 121 (4):223-226Trampuz A, Widmer AS, Infections associated with orthopedic implants, Curr Opin Infect Dis 19:349–356. 2006

Utku F.S., Seckin E, Goller G, Tamerler C, Urgen M, Electrochemically designed interfaces: Hydroxyapatite coatedmacro-mesoporous titania surfaces, Applied Surface Science 350 (2015) 62–68

Verne´ E, Ferraris S, Miola M, Fucale G, Maina G, Robotti P., Bianchi G, Martinasso G, Canuto RA, Vitale-Brovarone C, Synthesis and characterisation of bioactive and antibacterial glass-ceramic Part 2 – plasma spray coatings on metallic substrates, Adv. Appl. Ceram. 107 (2008) 245–253.

Xu Z, Lu Y, Li S, Guo S, He M, Luo K, Lin J, Copper-modified Ti6Al4V alloy fabricated by selective laser melting with pro-angiogenic and anti-inflammatory properties for potential guided bone regeneration applications, Materials Science & Engineering C 90 (2018) 198–210

Xu D, Yang W, Hu Y, Luo Z, Li J, Hou Y, Liu Y, Cai K, Surface functionalization of titanium substrates with cecropin B toimprove their cytocompatibility and reduce inflammation responses, Colloids and Surfaces B: Biointerfaces 110 (2013) 225– 235

Yao Z, Lin TH, Pajarinen J, Sato T, Goodman S, Host response to orthopedic implants (Metals and Plastics), in Badylak SF, Host response to biomaterials, Elsevier 2015

Yin X, Li Y, Yang C, Weng J, Wang J, Zhou J, Feng B, Alginate/chitosan multilayer films coated on IL-4-loaded TiO2 nanotubes for modulation of macrophage phenotype, International Journal of Biological Macromolecules 133 (2019) 503–513

Yu F, Addison O, Davenport AJ (2015) A synergistic effect of albumin and H2O2 accelerates corrosion of Ti6Al4V. Acta Biomater 26:355-365

Zhang C, He L, Chen Y, Dai D, Su Y, Shao L (2020) Corrosion Behavior and In Vitro Cytotoxicity of Ni–Ti and Stainless Steel Arch Wires Exposed to Lysozyme, Ovalbumin, and Bovine Serum Albumin. ACS Omega. doi:10.1021/acsomega.0c02312

Zhang Y, Addison O, Yu F, Troconis BCR, Scully JR, Davenport AJ (2018) Time-dependent enhanced corrosion of Ti6Al4V in the presence of H2O2 and albumin. Sci Rep-UK 8 (1):3185

Zhang H, Wu X, Wang G, Liu P, Qin S, Xu K, Tong D, Ding H, Tang H, Ji F, Macrophage polarization, inflammatory signaling, and NF-Bactivation in response to chemically modified titanium surfaces, Colloids and Surfaces B: Biointerfaces 166 (2018) 269–276

Zhang Y, Cheng X, Jansen JA, Yang F, van den Beucken JJJP, Titanium surfaces characteristics modulate macrophage polarization, Materials Science & Engineering C 95 (2019) 143–151

Zhang X, Song G, Qiao H, Lan J, Wang B, Yang H, Ma L, Wang S, Wang Z, Lin H, Han S, Kang S, Chang X, Huang Y, Novel ternary vancomycin/strontium doped hydroxyapatite/graphene oxide bioactive composite coatings electrodeposited on titanium substrate for orthopedic applications, Colloids and Surfaces A 603 (2020) 125223

Zhou L., Lin Z, Ding J, Huang W, Chen J, Wu D., Inflammatory and biocompatibility evaluation of antimicrobial peptide GL13K immobilized onto titanium by silanization, Colloids and Surfaces B: Biointerfaces 160 (2017) 581–588

Zimmerli W., j Trampuz A., Ochsner PE, Prosthetic-Joint Infections, n engl j med 351;16 www.nejm.org october 14, 2004