Materials Science and Engineering C 70 (2017) 1057–1070

Contents lists available at ScienceDirect

Materials Science and Engineering C

journal homepage: www.elsevier.com/locate/msec

Bio-functionalization of biomedical metals

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ARTICLE INFO

Article history:
Received 26 January 2016
Received in revised form 18 April 2016
Accepted 22 June 2016
Available online 23 June 2016

Keywords:
Bio-function
Biomedical metal
Titanium
Magnesium

ABSTRACT

Bio-functionalization means to endow biomaterials with bio-functions so as to make the materials or devices more suitable for biomedical applications. Traditionally, because of the excellent mechanical properties, the biomedical metals have been widely used in clinic. However, the utilized functions are basically supporting or fixation especially for the implantable devices. Nowadays, some new functions, including bioactivity, anti-tumor, anti-microbial, and so on, are introduced to biomedical metals. To realize those bio-functions on the metallic biomedical materials, surface modification is the most commonly used method. Surface modification, including physical and chemical methods, is an effective way to alter the surface morphology and composition of biomaterials. It can endow the biomedical metals with new surface properties while still retain the good mechanical properties of the bulk material. Having analyzed the ways of realizing the bio-functionalization, this article briefly summarized the bio-functionalization concepts of six hot spots in this field. They are bioactivity, bony tissue inducing, anti-microbial, anti-tumor, anticoagulation, and drug loading functions.

1. Introduction

Owing to their excellent mechanical properties, including high strength-toughness, fatigue resistance, and so on, biomedical metals have been extensively used in clinic for hundreds of years [1–3]. From gold teeth to titanium cardiac pacemaker, intravascular stent to hard tissue replacement, no matter small or big, simple or complicated, each successful application of biomedical metal is surely an evangel to patients. In orthopedics, biomedical metals are made into artificial hip joints, dentures, bone screws, bone plates, etc. [4]. In cardiac and cardiovascular applications, protective cases in pacemaker, the intravascular stents, and occlusion coils are often made of biomedical metals [5,6]. Although the biomedical metals are used in many fields, only several metal materials that process good biocompatibility have been successfully used in clinic. There is a common feature if we discuss about their functions. All of those biomedical metal devices are designed for the supporting or fixation of the damaged hard tissue. However, supporting and fixation are the most basic functions for those biomedical devices. An illness usually damages and disrupts many aspects of our body. For example, the bone fracture not only damages the bone but also causes the inflammation and weakens the body immunity [7,8]. If the bone substitute has not only good biocompatibility but also excellent bioactivity and anti-inflammation properties, the synergy of those multifarious functions would make the remedy become simple and patients' agonies might be reduced substantially. From this perspective, developing new functions of the biomedical metals has a promising future.

With the advanced material science and technology, many metallic materials have been developed new biomedical functions. Starting from simple load bearing, lots of specific functions of biomedical metals have been developed, such as bioactivity, anti-microbial function, drug loading, and even anti-tumor function. For instance, the early intravascular stents are only designed to get the supporting function for enlarging the blood vessels. Gradually, it has been found that the unmodified stents will cause blood clotting and the formation of thrombus. On the other side, after a period of time, the epithelial cells will proliferate on the surface of the intravascular stent and result in tissue hyperplasia, leading the vascular restenosis [9]. In order to solve this problem, the intravascular stent is redesigned and modified to gain the function of anticoagulation and to prevent the unexpected hyperplasia. For another example, biomedical metals are still the mostly used material for bone repair and replacement because they are good structural materials. Large portions of the bone substitute are bioinert metals, and they nearly cause no irritation to the normal tissues and our immune system. Zhang etc. found that bioinert metals are just encapsulated by fibrous tissue after implantation, but with the enhanced bioactivity of biomedical metals, chemical bond can form between the material and the bony

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http://dx.doi.org/10.1016/j.msec.2016.06.067
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tissue [10,11]. Bioactivation makes bioinert metals show content osseobonding, thus reducing the healing time of the hard tissue replacement surgery.

As show in Table 1, the biomedical metal for implantation applications mainly covers the orthopedics, dental, and cardiac fields. Titanium (Ti) and its alloys, stainless steel, and Co-based alloys are the three mostly used biomedical metals. The basic functions they played in those biomedical devices are simple, just supporting, fixation, and protecting. That is because we only utilized the good mechanical properties of those biomedical metals. We all know that there are more than 70 kinds of pure metals and much more alloys. However, Table 1 shows that there are only a few metals and alloys can be made into implantable biomedical devices, and the functions of those metals played are fairly simple. It demonstrates that there are many things need to be done on functionalization of the biomedical metals. Many biomedical metals which have unique biological properties need to be developed.

Except for designing new biomedical metals to realize new bio-functions, surface modification is a kind of method that draws lots of attention. It is an effective way to modify metals without changing the bulk materials' properties, which means gaining new bio-functions while still retaining the good mechanical properties of biomedical metals. Meanwhile, compared with designing a new alloy, surface modification usually requires less effort and energy. There are basically two kinds of surface modification methods, the physical methods and the chemical methods. Physical methods, including grinding, polishing, and sand blasting, are used to obtain specific surface topographies and roughness and remove surface contamination. Other physical methods such as the thermal spraying, plasma spraying, physical vapor deposition, and ion implantation, which alter the composition and the properties of substrate surfaces, are commonly used in fabricating films or coatings on biomedical metals especially for Ti and its alloys [33]. For chemical methods, there are chemical treatment, electrochemical treatment, sol-gel, chemical vapor deposition, and biochemical modification [34]. Chemical surface modification usually involves chemical reactions which result in the formation of new substances on the substrate surface. By emerging new coatings, the surface properties of the biomedical metals are modified. With the help of those various surface modification methods, biomedical metals can possess new biomedical functions.

Although the concept of bio-functionalization has been existed for many years, summary on how to develop biomedical metals to realize bio-functions is still in need. This short article listed some typical bio-functionalization cases related to biomedical metals. By analyzing these cases, how to realize bio-function of biomedical metals was summarized. It might be of some help for designing and fabrication new biomaterials, especially novel biomedical metals with advanced functions.

2. Bioactivation of biomedical Ti metal

2.1. Bioactivity improved by surface modification

In recent years, stainless steel, cobalt alloy, Ti, and its alloy have been widely used for clinical applications, especially for the dental, orthopedics, and other hard tissue replacement. Due to their excellent biocompatibility, Ti and its alloys have now become one of the focuses of bioactive materials, and Ti-based biomaterials have been recommended as the ultimate choice for orthopedic implants [35]. Despite good mechanical properties, biomedical metals for hard tissue replacement should be of excellent anticorrosion property, biocompatibility, as well as good bioactivity [8,36–39]. However, Ti metals and it alloys are basically bioinert. Fibrous encapsulation will occur inevitably on the surface of the implants after implantation [40–43]. Thus, the implanted device is not directly bond to the host bone. The fiber tissue increases the risk of slip between implants and host bones, leading the loosening of the implants, which is the main reason why so many patients need another surgery years later after the initial hard tissue replacement surgery.

In order to solve the problem stated above and to enhance the bone bonding between the implant and the host bone, lots of efforts have been made to make the bioinert Ti and its alloys bioactive. Yavari et al. described that the acid alkali treatment improved the hydroxyapatite formation on the Ti metal [44]. Others proposed that the acid etching plus alkaline treatment influenced the surface morphology, wettability, roughness, and induced the changing of material's osteogenic property [45–49]. After acid treatment, surface of Ti metal form a three-dimensional network with the hole size of about 500 nm. The S_a and the *r* value of the surface is 1.18 μm and 1.56. It was rougher than the original surface [50,51]. This three-dimensional network with abundant Ti–OH would interact with the Ca^{2+} and PO_4^{3-} and resulted in the formation of hydroxyapatite *in vitro* and *in vivo* [52]. Anodic oxidation was invented for the Aluminum passivation traditionally. When put into the Ti surface modification, a TiO_2 layer can form on the Ti and its alloy substrate. It has been proved that this TiO_2 layer has two different crystal phases: anatase and rutile [53]. Yang et al. reported that TiO_2 layer with more rutile has better bioactivity and cell compatibility. That is because the rutile TiO_2 has better ability of inducing the formation of HA *in vitro* [54]. Anodization could alter the surface morphology and chemical composition of Ti metal to nano-crystalline TiO_2. Owing to this TiO_2 layer, the bioactivity was improved. As shown in Figs. 1 and 2, Fu et al. found that the Ti metal after anodization showed obvious bioactivity. New bone could form on the material surface in rabbit's muscle and femur after 90 days of implantation [55]. Alkali heat treatment was first introduced by Kim et al. to improve the bioactivity of Ti and its alloys. After alkali treatment, Ti metal surface was covered by an amorphous sodium titanate. The followed heat treatment provides environment for the crystallization of sodium titanate. The crystallized sodium titanate was more stable than the amorphous one and it still could provide abundant Ti–OH groups while the hydrolyzation process [56].

Lots of evidences indicated that inducing the formation of HA *in vivo* might be the key of enhancing bioactivity [57–59]. The nucleation of HA on biomedical metal surface is a typical heterogeneous nucleation process. Surface composition, —OH groups especially, would obviously influence the formation of HA on the material. Besides that, surface roughness is another important factor to influence bioactivity of biomaterials. Compared with smooth surface, HA crystal was easier to nucleate on rough surface. As shown in Fig. 3 [60], it is obvious that the surfaces of acid alkali, anodic oxidation, and alkali heat-treated Ti metals are all rougher than the untreated one. The large specific surface area also provided more nucleation sites which promoted the HA crystal formation and led to the enhancement of the bioactivity of biomedical metals [61].

Table 1
Commonly used biomedical metals in biomedical devices and their properties and basic functions.

Biomedical devices	Biomedical metals	Properties been used	Primary function	References
Dentures and related kits	Gold alloy, Co-based alloys, Ti-based alloys	High toughness, anticorrosion	Supporting	[12–15]
Internal fracture fixation	Stainless steel, Ti-based alloys	High toughness	Fixation	[16–20]
Artificial hip joint	Stainless steel, Ti-based alloys	High toughness	Supporting	[21–23]
Artificial cardiac valves	Co-based alloys, Ti-based alloys	Good wear resistance, anticorrosion	Separating	[24–27]
Intravascular stent	Ni–Ti alloy, Ti-based alloys, Mg-based alloys	Shape memory Biodegradable	Supporting	[28–31]
Cardiac pacemaker box	Stainless steel, Ti-based alloys	Anticorrosion	Protecting	[32]