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Metals and Medicine*1

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The research and development of metallic biomaterials and their future prospects are overviewed. Approximately 80% of implant devices and 95% of orthopedic devices are still made of metal, and metallic materials therefore continue to play an important role in medical treatment. Current research efforts in metallic biomaterials can be summarized into the following categories: the elucidation of interfacial reactions between metals and tissues (including evaluations of safety and corrosion resistance); the development of new surface treatment techniques (including the control of surface morphology); the development of new alloys; and the development of new manufacturing processes. Interfacial reactions between metals and living tissues are discussed from the viewpoints of biocompatibility and biofunction, corrosion resistance, and calcium phosphate formation on the surface oxide film. The transitions taking place in the surface treatments for osteogenesis, soft tissue adhesion, antibacterial property, and antithrombotic property are summarized, followed by a discussion of their future prospects. In addition, the concept of a dual-functional surface is explained. A review is done of zirconium alloys that decrease magnetic resonance imaging (MRI) artifacts, Ni-free austenitic stainless steel, high-pressure torsion and sliding processing, and additive manufacturing. Finally, the future of biomaterials research is considered. [doi:10.2320/matertrans.MT-M2020268]

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1. Introduction

Materials used for medical activities, such as diagnosis and treatment, and those used for biological research are collectively called "biomaterials". The major difference between research and development of biomaterials and other materials is that biological evaluations using cell culture and animal tests are necessary for biomaterials, and depending on their intended use, approval/certification by a national institution is required, for example, from the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan, and the Food and Drug Administration (FDA) in the USA. Therefore, for biomaterials, biological evaluation constitutes a large part of the research process. In contrast, in materials engineering, biological evaluation is kept to a minimum, since the tissue compatibility and biofunction of newly developed materials that need to be verified by means of cell culture and animal tests are a later part of the process. This highlights the important role played by materials research and development, reducing the number of such materials that proceed to the practical research stage. When studying metals for use as biomaterials, it is essential to first ensure their durability and safety, through analysis of their mechanical properties and corrosion resistance. This ensures that there are fewer cases where the biological evaluation stage is reached. In this regard, considerable progress has been made by metallic biomaterials researchers. This paper presents an investigation of the research and development of metallic biomaterials for medical applications, and explores their future prospects.

2. Metals as Biomaterials

As shown in Fig. 1, polymers form the basic constituent elements of humans and other organisms. Enzymes, sugar chains, lipids, nucleic acids, and the like, that control biological functions also consist of polymers. Therefore, if molecules that mimic the polymers existing in the human body can be synthesized, it is possible to design molecules with biological functions. The basic inorganic component of human hard tissues (such as bone, cartilage, and tooth) is hydroxyapatite (HA), which is a form of calcium phosphate (Ca–P). This has been studied extensively as the typical inorganic material that promotes osteogenesis and osseointegration. While there are metallic elements that function as essential biological elements in the human body that are developed by the body for carrying out biofunctions, there are no metallic materials. This reduces the expecting degree of metals as research target for biomaterials. Furthermore, pollution-related diseases, such as Minamata disease and Itai-itai disease, are caused by heavy metals, broadly indicating the harmfulness of metals. This has led to the misconception that metallic materials are not suitable candidates for biomaterials.

Consequently, the advances in ceramics, glass, and synthetic polymers have meant that these have been used to replace metallic medical devices. However, despite such changes, approximately 80% of implant devices and 95% of orthopedic devices are still made of metals, and metallic materials therefore continue to have importance in medical treatment. For dental esthetics, metallic luster is a critical flaw, and therefore the use of white or transparent ceramics and polymers is recommended for dental restoratives.

For more information on metallic biomaterials, refer to the books[1–4] and for medical Ti alloys a book and a review are also available for reference.[5–7]

3. Challenges of Metallic Biomaterials

Metallic biomaterials researchers have focused on several

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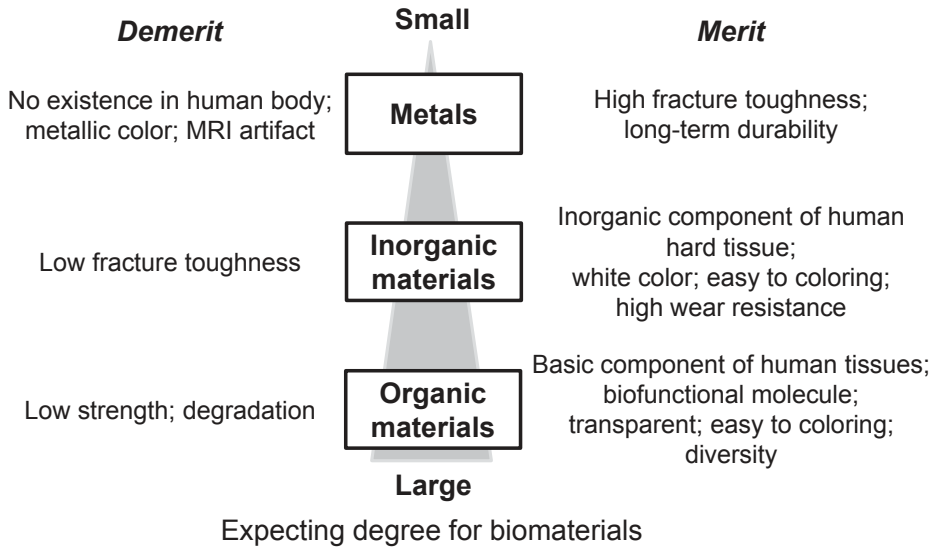

Fig. 1 Characteristics of each material and expected degree of use as a biomaterial.

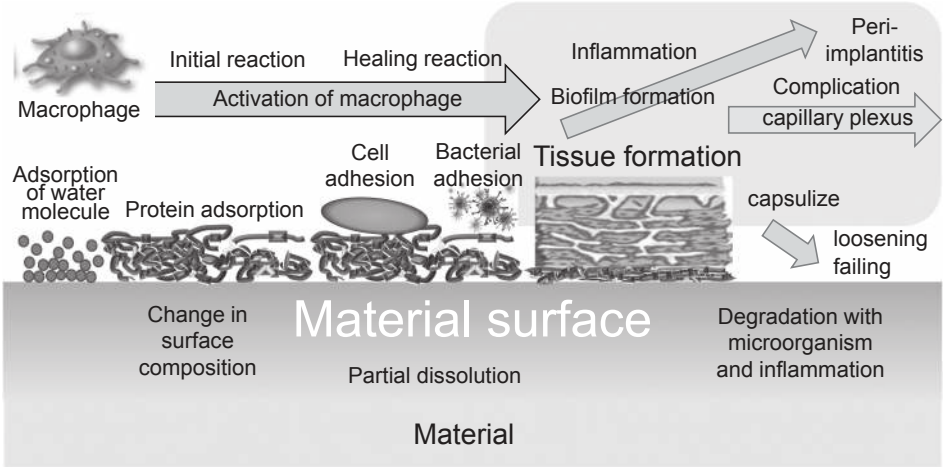

Fig. 2 Interfacial reactions between a material and the host body when the material is implanted into the human body (reproduced from a previous paper[6]).

major areas: the elucidation of reactions at the interface of metals and tissues; the development of surface treatment techniques; the development of new alloys; and the development of manufacturing processes. With the exception of biodegradable metals, such as Mg alloys, metallic materials for medical applications should maintain a fixed shape, so that: (1) they do not deform significantly during use; (2) they do not break during use; and (3) they are available for use in a solid form for a long duration. In other words, properties such as a high fracture toughness, high fatigue strength, and high corrosion resistance are required. However, it is impossible to impart a biofunction to a metal during its manufacturing process, that is, in the process of melting, casting, forging, and heat treatment. This is the greatest weakness of metals for use as biomaterials, and surface treatment and surface modification are therefore required to increase their biocompatibility and biofunction. Based on the above requirements, the current research efforts in metallic biomaterials can be summarized in the following categories:

- elucidation of interfacial reactions between metals and living tissues (including evaluations of safety and corrosion resistance).
- development of new surface treatment techniques (including control of surface morphology).
- development of new alloys
- development of new manufacturing processes.

4. Interfacial Reactions between Metals and Living Tissues

4.1 Biocompatibility and biofunction

When a metallic material comes into contact with living tissue, the adsorption of ions/molecules and cell adhesion by the material occur, the material surface changes, and the living tissue forms around the material (Fig. 2). The property of the material performing the intended function without disturbing this series of processes is known as “biocompatibility”. Biofunction can be defined as the “quality that promotes a biofunction.” Although there has been some basic

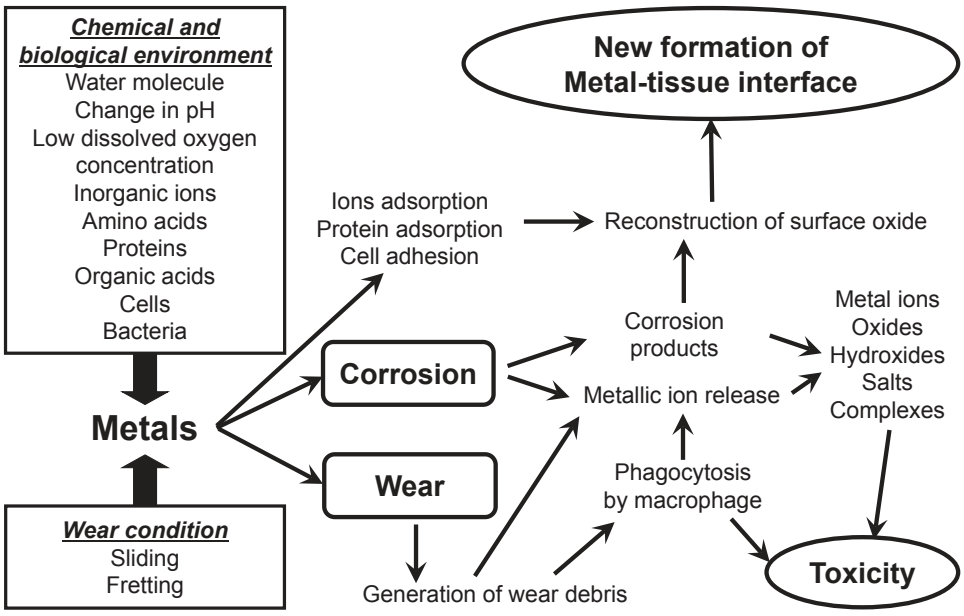

Fig. 3 Surface reactions on metals in the human body and their influences on the toxicity.

research aimed at elucidating the mechanism of biocompatibility, this has recently decreased, owing to difficulties arising from the complexity of living systems, and the transition to the development of surface treatment techniques aimed at promoting the formation of tissues on materials, which is desirable for their immediate use in clinical applications. Therefore, there is limited scientific understanding of the interfacial reaction between the material surface and living tissue.

4.2 Corrosion resistance

When metal ions are released from metals in the human body and combine with biomolecules or cells, they inhibit biofunctions, which can result in toxic effects (Fig. 3). Metallic biomaterials therefore require high corrosion resistance, and as such precious metals and passive alloys are used. In addition, wear debris generated by friction wear can be toxic. The fatigue of metals in a corrosion environment are considered to be a cause of fracture in the human body. Therefore, the corrosion resistance and other mechanical properties of metals are critical factors directly related to their toxicity and fracture.

When 316L-type stainless steel sternal wire has been implanted in the body for 10 to 30 years, corrosion pits appear on the surface, which are oriented in the direction of the wire drawing, and increase in depth and size with the duration of implantation.[8] In addition, 316L-type stainless steel spinal fixation rods retrieved from a patient were observed to have crevice corrosion where they made contact with the hook.[9] Thus, corrosion can occur in devices made of stainless steel.

There are very few reports on the corrosion damage of Co–Cr alloys and Ti alloys implanted in the human body. However, Ti is often detected in the tissue surrounding the implants. When a material is implanted in the human body, inflammation always occurs, causing macrophages to accumulate on the surface of the material. The activation of these macrophages generates active oxygen that corrodes Ti.[10] According to an evaluation based on electrochemical measurements under a cell culture, there is a decrease in the corrosion potential with Ti, but the presence of the cells themselves has little effect.[11–13] However, for stainless steel, the cells were found to release biomolecules as an extracellular matrix, causing corrosion to occur because the cells themselves act as barriers to the diffusion of dissolved oxygen. The presence of protein promotes the repassivation of Ti.[14] On the other hand, considerable quantities of metal elements are released in the form of fine debris and metal ions, even from a simple surgical operation involving implantation or retrieval of an implant.[15]

4.3 Surface oxide film and calcium phosphate formation

Since the above reactions occur on the surface of the metallic material, the surface state of the metallic material governs the reaction. Therefore, precise analyses have been conducted on the air-formed surface oxide films on commercially pure Ti (CP Ti),[16] alloys of Ti–Ni,[17] Ti–Zr,[18] Ti–Nb–Ta–Zr,[19] Co–Cr–Mo,[20] and Co–Ni–Cr,[21] and 316L-type stainless steel.[22]

The physicochemical Ca–P formation that occurs in body fluids is a critical factor that governs hard tissue compatibility. When Ti and its alloys are immersed in Hanks' solution, Ca–P precipitates,[23,24] and in a cell culture, sulfite or sulfide is formed in addition to Ca–P.[25] The formation of Ca–P also occurs with Co–Cr–Mo alloys[20,21] and with 316L-type stainless steel,[22] but the rates of formation and quantities are smaller than those of CP Ti and Ti alloys. In contrast, when Zr combines with HPO_4^{2-} it stabilizes and does not incorporate Ca, preventing the formation of Ca–P.[19,26] This is because the surface oxide film of Ti has a certain degree of reactivity, whereas that of Zr is highly stable.[6] Nb and Ta share the properties of Ti and Zr.[27]

This Ca–P formation is considered to be the cause of the callus formation on Ti alloys implanted into the human bone, and the assimilation of bone to implants, such as nails and screws. Ca–P formation can be suppressed by coating the Ti

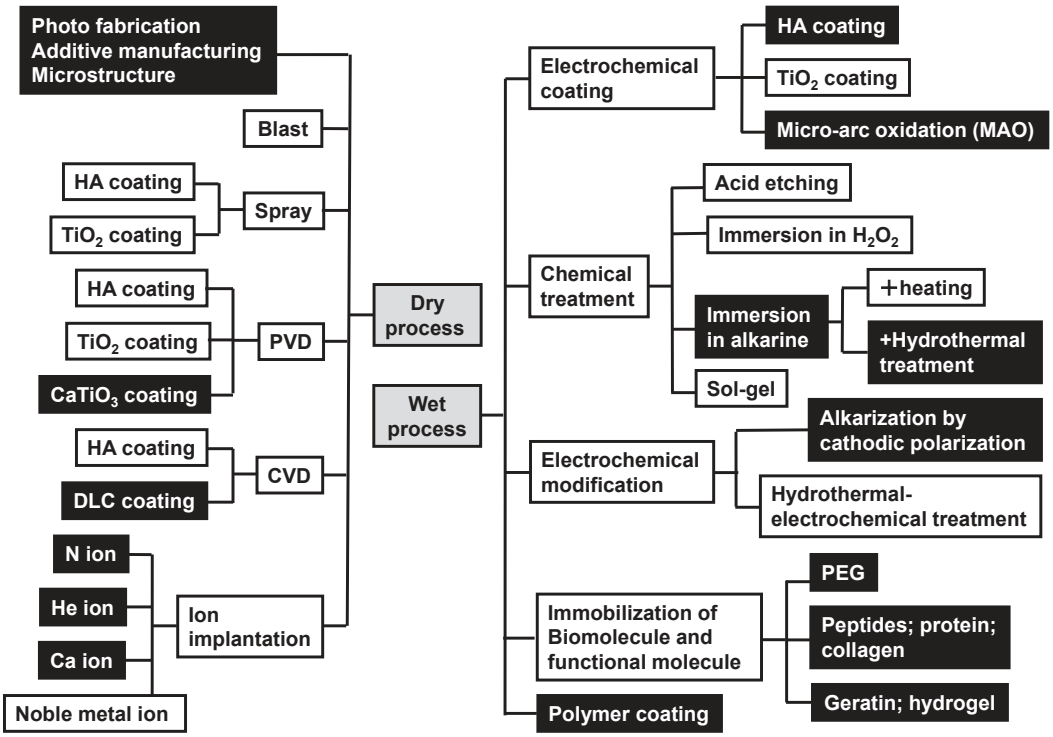

Fig. 4 Surface treatment and modification techniques of metals for medical application.

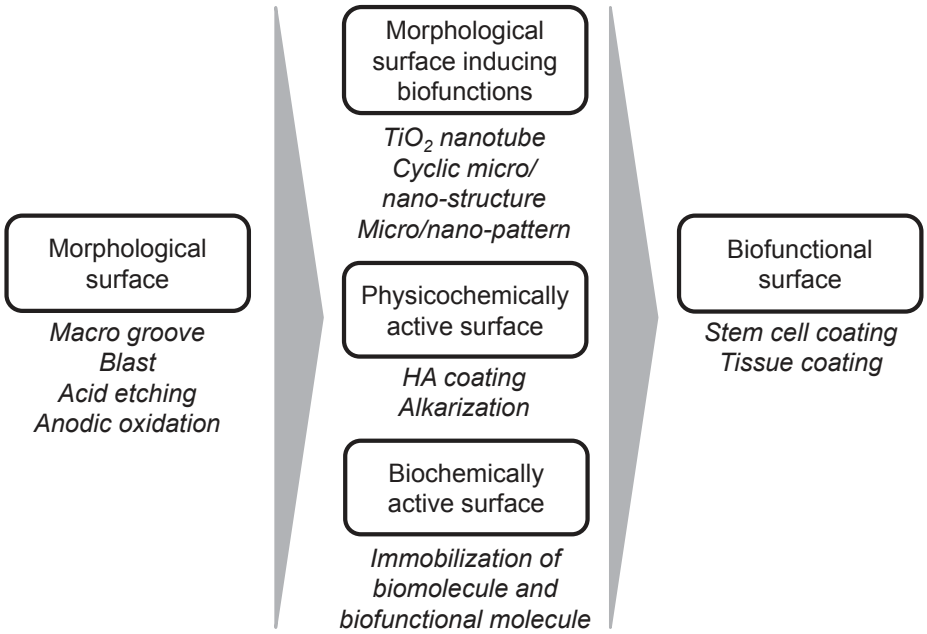

Fig. 5 Category of surface finishing and their functions.

surface with Zr, which inhibits Ca–P formation[28] and osteogenesis on Ti–6Al–4V alloy implanted in the tibia of rats.[29]

5. Surface Treatment

5.1 Transition and future prospects of surface treatments

There are many positive remarks on surface treatments for their potential medical applications.[7,8,30–33] Figure 4 summarizes the surface treatment techniques that have been performed on metallic biomaterials to date.

The classification of the surface treatment techniques, based on the type and function of the surface to be formed, is shown in Fig. 5. Currently, most of the techniques that have been extended to practical use include surfaces that have been morphologically controlled to incorporate roughness or pores. As the technology evolves, cyclic structures formed by micro- or nano-fabrication are expected to be the means of developing inorganic biofunctional surfaces in the future.

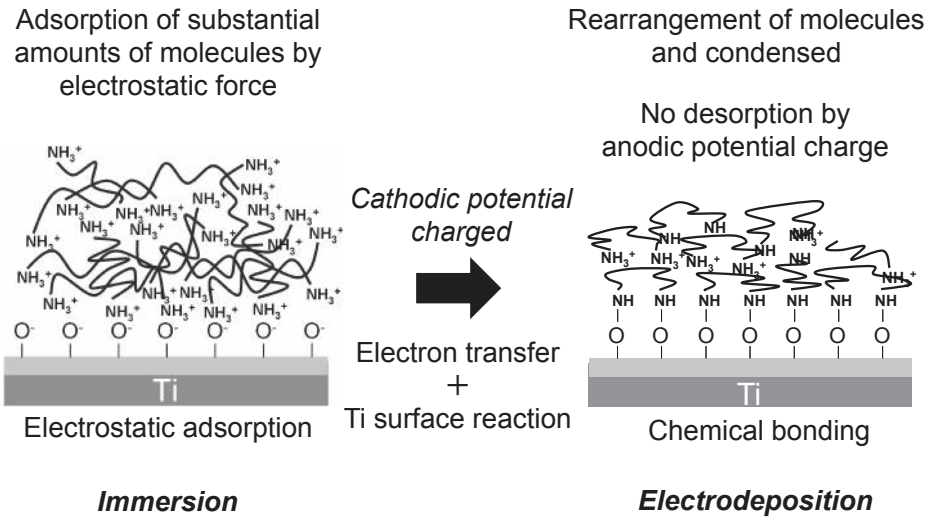

Fig. 6 Schematic illustration of electrodeposition process.

5.2 Osteogenesis and bone bonding

When Ca^{2+} is implanted into Ti, a surface modified layer consisting of CaO and $CaTiO_3$ is formed.[34] This is accompanied by the precipitation of Ca–P in a simulated body fluid,[35] and a rapid acceleration of chondroid tissue formation on osteoblastic MC3T3–E1 cell.[36] When implanted in rat tibia, the Ca^{2+}-implanted surface forms osseous tissue faster than an unimplanted surface, and new bone tissue adheres to the material surface.[37] These results can be explained by the presence of the point of zero charge and surface electric charge of $CaTiO_3$ produced by Ca^{2+} implantation.[38,39] While Ti-ion implantation with the sputter deposition of $CaTiO_3$ to Ti have been devised,[40] the high crystallinity of $CaTiO_3$ promotes osteogenesis.[41] The rapid immersion in $Ca(OH)_2$ solution,[42] autoclaving,[43] and repassivation in a simulated body fluid[44] of Ti have been studied extensively to address this. In addition, by performing Ca–P formation treatment on Ti, it is possible to form a periodontal ligament in rat tibia using a periodontal fiber-derived cell sheet.[45]

Alkaline treatment is more efficient than immersion in an alkali solution, and is achieved by creating an alkaline environment on the surface through cathodic polarization of Zr. As a result, the Zr surface is covered with OH groups that serve as reaction sites for protein adsorption and cell adhesion, hence promoting the osteogenic ability of the Zr surface.[46]

Poly(ethylene glycol) (PEG) is a functional molecule that has the tendency to suppress protein adsorption, and when it is immobilized on a solid surface, it may produce biofunctional surface. The arginine-glycine-aspartic (RGD) acid sequence promotes cell adhesion. When PEG that is modified with amino and carboxyl groups at the terminals (NH_2–PEG–COOH) is electrodeposited on the Ti surface, the RGD peptides are stably immobilized at pH 12.[47] The extent of calcification by MC3T3–E1 cells was larger in Ti with the RGD immobilized than that in untreated Ti, and the extent of calcification of cells on RGD/PEG/Ti was large.[48] The osteoblasts are able to easily recognize the RGD because the NH_2–PEG–COOH chain molecule fluctuates in the solution. The implantation of this RGD/PEG/Ti specimen in the tibia of rabbits has been found to promote osteogenesis.[49]

5.3 Soft tissue adhesion, antibacterial property, and antithrombotic property

Type I collagen has been strongly electrodeposited, with a mesh form, on a Ti surface using a sine wave with a positive and negative potential to improve soft tissue.[50]

The electrodeposition of PEG diamine (NH_2–PEG–NH_2), modified with amine groups on both terminals, results in a U-shaped immobilization (as shown in Fig. 6).[51,52] The active OH groups on the Ti surface oxide film play an important role in electrodeposition, and the thickness of the PEG-immobilized layer increases as the concentration of OH groups increases.[53] When PEG is electrodeposited on Ti, this results in the suppression of protein adsorption, platelet adhesion, which is an indicator of antithrombotic properties,[54] and bacterial adhesion together with biofilm formation.[55] Electrodeposition of PEG is also effective in controlling friction and adhesion between materials.[56] The mechanism of electrodeposition of PEG diamine onto the Ti surface has been precisely elucidated.[57]

Electrodeposition is also applicable to other molecules, such as the 2-methacryloyloxyethyl phosphorylcholine (MPC) polymer, which has a structure similar to that of a cell membrane. Adhesion of the MPC polymer to the Ti surface suppresses platelet adhesion.[58,59]

On the other hand, platelet adhesion on the Ti surface is suppressed by He^+ injection,[60] and can also be suppressed by anodic oxidation.[61]

5.4 Dual-functional surface

Micro-arc oxidation (MAO) is an effective method for forming porous oxide layers on the surface of valve metals, and has successfully been applied to dental implants. Porous TiO_2 contains Ca^{2+} and HPO_4^{2-} ions (the latter notation is used because, although phosphate ions in other forms are also present, they are neutral, and hence this ion has the highest probability of existence). Consequently, when a layer of porous TiO_2 is formed on the surface of the Ti–24Nb–13Ta–

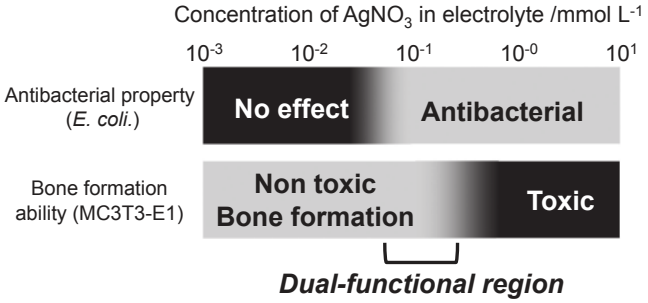

Fig. 7 Concept of dual-function of MAO-treated Ti surface with Ag for antibacterial property and bone formation.

4.6Zr alloy, the osteogenic ability is improved.[62] MAO is also effective for Zr and can promote osteogenesis by forming a porous ZrO_2 layer.[63] The combination of MAO with chemical treatment,[64] and the addition of Sr,[65] are also effective in promoting calcification on Ti and improving the wettability of the Ti surface.[66]

When Ti is subjected to MAO treatment, the addition of a sufficient quantity of Ag together with Ca^{2+} and HPO_4^{2-} to the electrolyte results in evidence of antibacterial activity. There is an overlap between this range of concentrations and that in which osteogenic cells show calcification. This achieves the dual function of promoting both the antibacterial activity and osteogenesis (Fig. 7).[67] Zn and Cu are also effective antibacterial elements,[68,69] and their modes of action have been elucidated, together with the degree of antibacterial activity of the constituent elements of Ti alloys.[70] However, in the future, it may be necessary to incorporate both soft tissue adhesion and antibacterial properties to prevent peri-implantitis (inflammation around dental implants).

5.5 Metal-polymer composite

By combining polymers with metals, it is possible to develop materials that possess both the desirable properties of polymers and the strength of metals. Ti and segmented polyurethane (SPU) can be composited via the silane coupling agent γ-MPS,[71] and the effects of UV irradiation[72] and surface hydroxyl groups[73] on the adhesive property have been determined. It is also possible to combine the Ti–29Nb–13Ta–4.6Zr alloy with SPU.[74–76]

5.6 Corrosion resistance, wear resistance, and lubricity

When a Ni–Ti shape-memory/superelastic alloy is electrochemically charged in an aqueous solution containing glycerol, lactic acid, sulfuric acid, and ethanol, a titanium oxide film without Ni is formed, ensuring corrosion resistance and safety.[17] In addition, an improvement in the wear resistance of Co–Cr alloys is achieved by N^+ implantation,[77–79] and an improvement in the lubricity is achieved through the formation of a diamond-like carbon (DLC) film on the Ti surface.[80]

5.7 Promotion of stem cell adhesion and differentiation

The surface morphology of a material is an important factor for tissue adhesion. A fine periodic structure can be formed on a surface by means of a femtosecond laser. In addition to promoting calcification on the Ti surface,[81] the antithrombotic property of Ni–Ti alloys,[82] and the cell extension on the Ti surface,[83,84] this can also promote the adhesion and differentiation of stem cells.[85,86] This technology is necessary for the development of next-generation implants covered by stem cells.

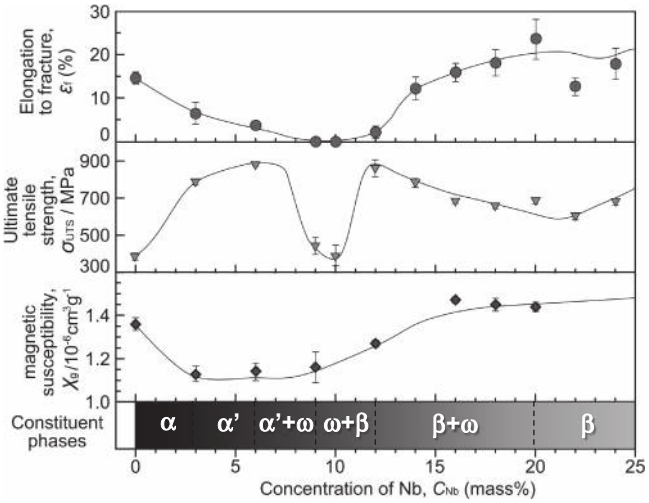

Fig. 8 Relationship among Nb content, constituent phase, elongation to fracture, ultimate tensile strength, and magnetic susceptibility in Zr–Nb alloy (reproduced from a previous paper[90]).

6. New Alloys and Manufacturing Processes

6.1 Zirconium alloys that decrease MRI artifacts

Since the magnetic susceptibility of conventionally used metals is higher than that of the surrounding living tissue, the metallic materials are magnetized under the strong magnetic field of magnetic resonance imaging (MRI), and the images of organs and tissues are disturbed or lost around the metallic materials; this is called an artifact. The volume of an MRI artifact depends on the shape,[87] and is proportional to the magnetic susceptibility.[88] To prevent MRI artifacts, it is therefore necessary to develop a metallic material with a low magnetic susceptibility close to that of the surrounding living tissue. Zr has a lower magnetic susceptibility than those of Ti, Ti alloys, Co, and Fe. Nb, Mo, and Ta are extremely safe solid-solute elements that can strengthen Zr. Zr–Nb alloys[89–91] have a low magnetic susceptibility, and the Zr–14Nb alloy shows a small MRI artifact volume.[92] However, as shown in Fig. 8, at a minimum value of the magnetic susceptibility, an ω-phase is formed which has poor mechanical properties. Therefore, it is necessary to consider the balance between the magnetic susceptibility and mechanical properties. The addition of Pd or Pt is effective in increasing the corrosion resistance of Zr–Nb alloys. Zr–Mo alloys have a good balance between low magnetic susceptibility and mechanical properties in the range of 0.5–1 mass% Mo.[93–95] In addition, mass melting, hot forging, and cold swaging of the Zr–1Mo alloy have been successfully carried out for achieving a good balance between low magnetic susceptibility and mechanical properties.[96,97] After cold swaging with an 84% area reduction, the alloy is well-balanced, with a tensile strength of 1001 MPa, an elongation to fracture of 10%, and a mass magnetic susceptibility of

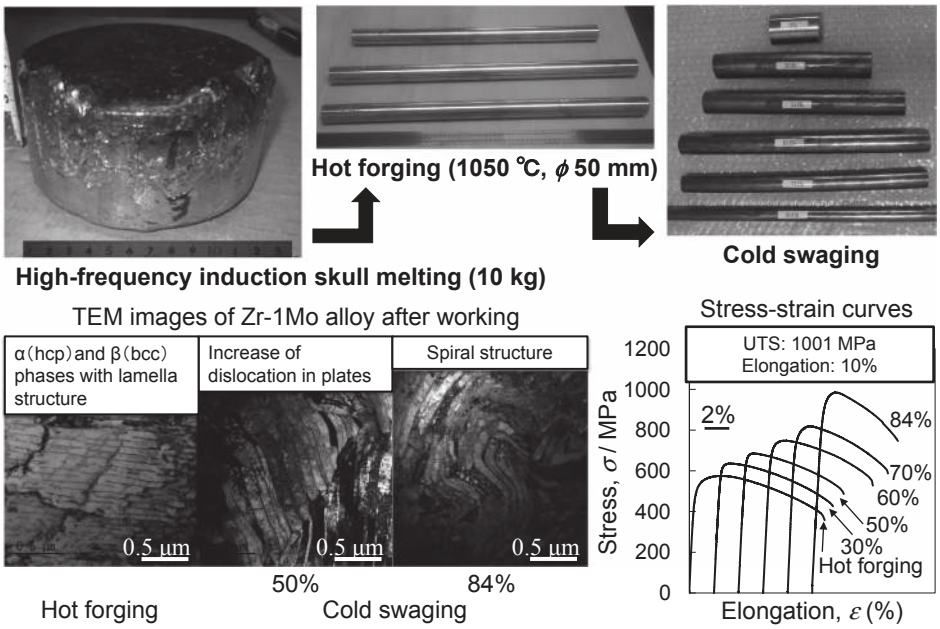

Fig. 9 Strengthening of Zr–1Mo alloy by hot forging and cold swaging.

$13.85 \times 10^{-9} - 4.87 \times 10^{-9}\,m^3kg^{-1}$. As a result of cold swaging, the α- and β-phase striped structures are deformed with an undulation (Fig. 9).[97] Superior mechanical properties are achieved with a Zr–1Mo alloy by means of additive manufacturing,[98] and the magnetic susceptibility is reduced further in a Zr–Ag alloy.[99]

The surface of the Zr–14Nb alloy can be whitened using high-temperature oxidation, and this can be applied to the abutment of dental implants.[100] In addition, dental casting shows sufficient mechanical properties[101] and has a high bonding strength with porcelain,[102] and therefore it can be applied as a dental restoration and prosthesis. Furthermore, the Zr–14Nb–5Ta–1Mo alloy, designed on the basis of d-electron alloy design theory, shows better mechanical properties than those of the Ti–6Al–4V alloy with low magnetic susceptibility.[103]

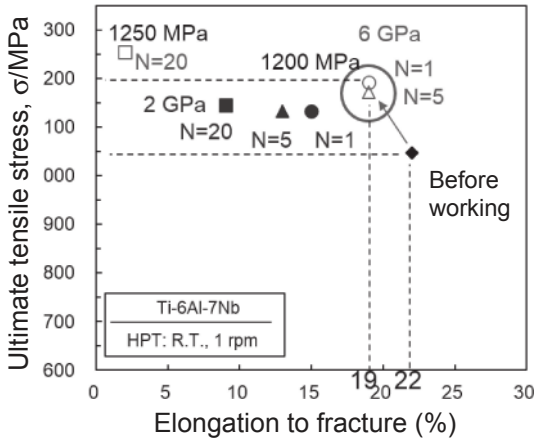

Fig. 10 Change in strength and elongation of Ti–6Al–7Nb alloy by high pressure process.

6.2 Nickel-free stainless steel production by nitrogen absorption

Ni tends to be a risk element related to metal allergies, necessitating the development of stainless steel that does not contain Ni for biomedical uses. In order to produce a Ni-free austenitic stainless steel, it is necessary to use austenitizing elements, such as C, Mn, N, Co, and Cu, in place of Ni.[104] Ni-free stainless steel has good corrosion resistance,[105,106] but has an extremely poor workability and a high manufacturing cost. Hence, a manufacturing process has been developed in which ferrite is first processed before it contains N, and then N is absorbed at 1473 K in order to austenitize it.[107–110] The alloy has a tensile strength of 931 MPa after annealing, an elongation to fracture of $\leq$49%, and an excellent cell compatibility.[111]

6.3 High-pressure torsion processing and high-pressure slide processing

Narrow implants with small diameters are manufactured to be used for patients with insufficient bone volume in the jawbone. In order to reduce the diameter, it is necessary to increase the strength. However, in conventional processing, increasing the strength decreases the elongation to fracture. When the Ti–6Al–7Nb alloy is subjected to high-pressure torsion (HPT) processing, to increase the strength while maintaining the elongation, the tensile strength increases to 1200 MPa, but the elongation is maintained at 19%, which is similar to the original value (Fig. 10).[112] Since it is necessary to process the rod material in order to apply it to a proper dental implant, high-pressure sliding (HPS) processing was conducted, and the same effect as that of HPT processing was observed.[113] The fatigue property and cytocompatibility of a biomedical Co–Cr–Mo alloy subjected to HPT processing, and a short subsequent time of annealing, has also been studied.[114]

6.4 Additive manufacturing

In applying additive manufacturing to the medical field, there is a high demand for the production of tailor-made

medical devices with particular sizes and shapes that suit the individual needs of the patients, as well as the production of fine surface structures. The Co–Cr alloy made by the additive manufacturing process has been studied with regard to the relationships between the structure and corrosion resistance,[115] and the building direction and anisotropy,[116] applied to the clasp of a partial denture, the fatigue strength,[117] and the effect of heat treatment.[118–121] The relationships between the crystal structure, mechanical properties, and corrosion resistance of austenitic stainless steel have been studied,[122] as well as the effects of process parameters on the mechanical properties of the additively manufactured Zr–1Mo alloy builds.[123]

7. The Future of Metallic Biomaterials Research

The material design, manufacturing process, and biological evaluation of biomaterials draw on science and technology from a variety of fields, and there is no academic field called "biomaterials". At one stage, Japan formed one of the three global leaders in biomaterials research, together with the United States and Europe, and was highly recognized internationally for the exceptional development of new materials and the proposal of new development concepts. However, the global position of Japan has declined with the rise of China and South Korea in the past 20 years, and the same trend has been observed in the field of materials science. Whether or not Japan can create a genuine "biomaterials" field in the future may be the key to securing international superiority and promoting innovation in the development of next-generation medical devices. In practical sciences, such as biomaterials, new disciplines may emerge in the process of elucidating the mechanisms involved in the newly developed-technology. In Japan, there is a misconception that technology is born deductively from the foundation of science, but in biomaterials, an inductive approach to defining a unified theory/general principle from individual technologies is also possible.

Acknowledgements

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