Roles of Metals on Regenerative Medicine

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Abstract: Metals are thought to be independent of regenerative medicine, while biodegradable polymers, biopolymers, calcium phosphate ceramics, and their composites are conventionally used as scaffold materials. However, importance of durability and strength of regenerative organs is increasing because size and morphology of target organs increase. Metals are effective materials for scaffolds for tissue engineering. Surface modification of metals is essential technique for the utilization to tissue engineering because metal surface must be controlled for adhere of cells and adsorption of biomolecules. Also, flexibility of metals is necessary.

1. Property of metals

The demand for metals in medical and dental devices is large. These materials are used because of their high durability, strength, and formability. Conventionally, metals are essential for orthopedic implants, bone fixators, artificial joints, external fixators, etc., since they can substitute for the function of hard tissues in orthopedics. Over 70% of implant devices consists of metals. Metals in medical devices cannot be replaced with ceramics or polymers at present, mainly because the metallic materials have greater strength and toughness. However, metals are generally not expected to be the biomaterials of the future at the research level because they do not have bioactive and biofunctional properties.

2. Biofunctionalization

Biofunctions are required for metals recently. For example, stents are placed at stenotic blood vessels for dilatation, and blood compatibility or prevention of adhesion of platelet is necessary. In guide wires and guiding cathetels, sliding lubrication in blood vessel is important when those are inserted into there. In addition, if metals were used for a sensing device, the control of cell adhesion is necessary. For these purpose, the fundamental property is inhibition of protein adsorption. Immobilization of biofunctional polymers on gold is usual by using the bonding –SH or –SS- group while this technique is only used for gold. On the other hand, the adhesion of platelet and adsorption of protein, peptide, antibody, and DNA are controlled by modifications. These goals are application to biomaterials, biosensors, and drug delivery system.

For utilization of metals to tissue engineering, cell adhesion and tissue induction properties are required. These properties are not obtained by the conventional metallurgical process but surface modification, such as immobilization of biofunctional polymers and biopolymers, calcium phosphate ceramics coatings, hibridization with biodegradable polymers.

3. Surface modification

When a metallic material is implanted into a human body, immediate reaction occurs between its surface and the living tissues. In other words, immediate reaction at this initial stage straightaway determines and defines a metallic material's tissue compatibility. Since conventional metallic biomaterials are usually covered with metal oxides, surface oxide films on metallic materials play an important role not only against corrosion but also in tissue compatibility. Surface properties of a metallic material may be controlled with surface modification techniques. To develop and apply the appropriate surface modification technique, knowledge of the material's surface composition is absolutely necessary. This is because surface modification is a process that improves surface property by changing the composition and structure, while leaving the mechanical properties of the material intact. Since surface properties are critically important in biomaterials, issues closely related to this aspect of metallic biomaterials are discussed here: Surface compositions of metallic biomaterials; How surface compositions change due to interaction with human tissues; and How to control surface compositions and morphologies using surface modification techniques.

Surface modification is a process that changes a material's surface composition, structure and morphology, leaving the bulk mechanical properties intact. With surface modification, chemical and mechanical durability, as well as tissue compatibility of surface layer could be improved. Surface property is particularly significant for biomaterials, and thus surface modification techniques are particularly useful to biomaterials. Dry-process (using ion beam) and hydro-process (which is performed in aqueous solutions) are predominant surface modification techniques. Apatite coating on titanium with plasma spray, titanium nitride coating with sputter deposition, and titanium oxide growth with morphological control by electrolysis are already available for commercial use.

The chief purpose for surface modification of titanium is to improve its hard-tissue compatibility. This is done by forming a calcium phosphate film on the titanium surface. Currently, plasma spraying of apatite on metallic materials is widely used to form the apatite layer, which is the nucleus for active bone formation and conductivity. In the case of plasma-sprayed apatite, however, the apatite-titanium interface or apatite itself may fracture under relatively low stress because of low interface bonding strength and low toughness of the sprayed layer itself. To overcome this weakness, dynamic ion mixing is applied to form an apatite with high interface bonding strength. Calcium ions are implanted during the mixing process to induce strong bonding between the apatite film and the titanium substrate, with implanted calcium ions serving as a binder. Sputter-deposition of apatite is now done by using RF magnetron sputtering and laser-pulse deposition.

Hard-tissue compatibility can be improved by modifying the titanium surface instead of the apatite film. In this section, various

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techniques to modify the titanium surface are given as follows:
- Immersion in alkaline solution and heating;
- Immersion in hydrogen peroxide solution;
- Immersion and hydrothermal treatment in calcium-containing solution; and
- Calcium ion implantation.

In the design of bone-substituting and blood-contacting materials for both medical implants and bioaffinity sensors, it is a major challenge to generate surfaces and interfaces that are able to withstand proteins adsorption.

To accelerate bone formation surrounding implant materials, the materials are modified with biomolecules. Several phospholic acids were synthesized and grafted onto titanium. Proliferation, differentiation and protein production of rats' osteoblastic cells on the titanium were then investigated. Type I collagen production increased with modification by ethane-1,1,2-triphospholic acid and methylenediphosphonic acid. To improve hard tissue response, bone morphogenetic protein-4 (BMP-4) was immobilized on Ti-6Al-4V alloy through lysozyme. To improve tissue compatibility, attempts were made for silane chemistry to couple proteins to the oxidized metal surfaces of Co-Cr-Mo, Ti-6Al-4V, Ti and Ni-Ti.

Platelets adhesion, adsorption of proteins, peptides and antibodies, and DNA can likewise be controlled by modifications. A class of copolymers based on poly (L-lysine)-g-poly (ethylene glycol), PLL-g-PEG, was found to spontaneously adsorb from aqueous solutions onto TiO_2, $Si0.4Ti0.6O2$ and $Nb2O5$ to develop blood-contacting materials and biosensors. Poly(ethylene glycol)-poly(DL-lactic acid) (PEG-PLA) copolymeric micelles were attached on functionalized TiO_2 and Au. The micelle layer enhanced the protein resistance of the surfaces by up to 70%.

4. Morphology

Many studies were conducted to examine the effect of pores on the ingrowth of tissues or cells to titanium. The host bone came into contact with a surface relief of the plasma-sprayed coating, which was then characterized using an open microstructure with variable height at any part of a surface. Animal tests confirmed the advantage of a rough surface. Several studies have been made on bone ingrowth into porous systems with different pore sizes. The diameter of interconnecting pores seems to dictate the quality of tissue growing into porosity space. When pore sizes were down to 50mm, there was effective bone ingrowth into porous coatings. However for regeneration of mineralized bone, the interconnections of porosity must be larger than 100 mm. When the pore size was larger than 1mm, fibrous tissues were sometimes formed. Based on these readings, the optimal pore size for mineralized bone ingrowth was concluded at 100-400 mm.

Titanium fiber mesh was used as a scaffold for tissue engineering with cultured osteogenic cells. After titanium fiber mesh was seeded with osteogenic cells, bone formation was generated more effectively in a shorter culture time.

5. Future metallic biomaterials

Metallic materials are widely used in medicine not only for orthopedic implants, but also as cardiovascular devices and for other purposes. Biomaterials are always used in close contact with living tissues. Therefore, interactions between material surfaces and living tissues must be well understood. This knowledge is essential to developing the utilization to tissue engineering.

In particular, metal surface-biomolecule reactions and/or metal surface-cell reactions are important. A good knowledge of these reactions can help to add biofunctions to metallic materials that already have excellent mechanical properties. Finally through surface modification techniques such as multi-layer coating and patterning of multi-functional layers, it is possible to arrive at an optimal range of biofunctions in a biomaterial.
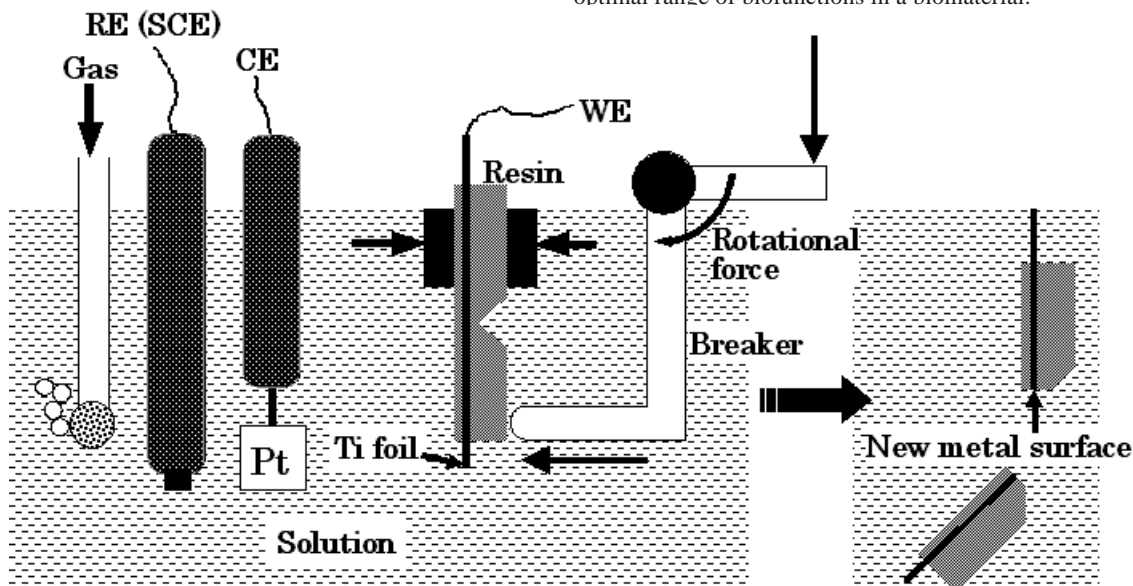

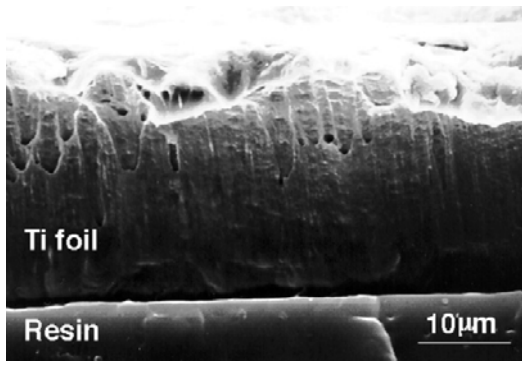Fig. 1 Schematic drawing of an electrochemical cell and fracturing of the specimen

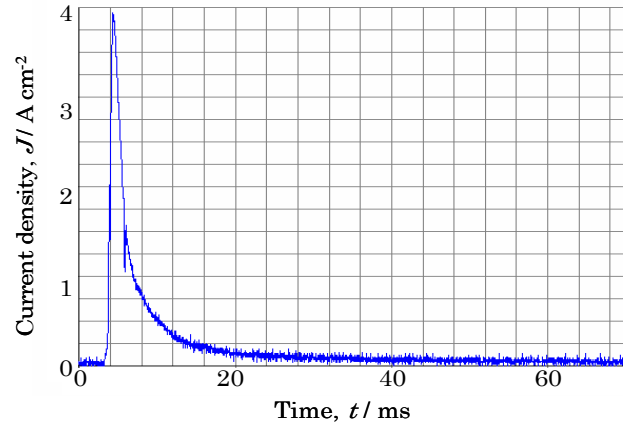Fig. 2   Scanning electron micrograph of a fractured surface of titanium foil.

Fig. 3   Time transient of current density of titanium by the fracture, formation of new metal surface, or repassivation in Hanks' solution at 0 V vs. SCE.
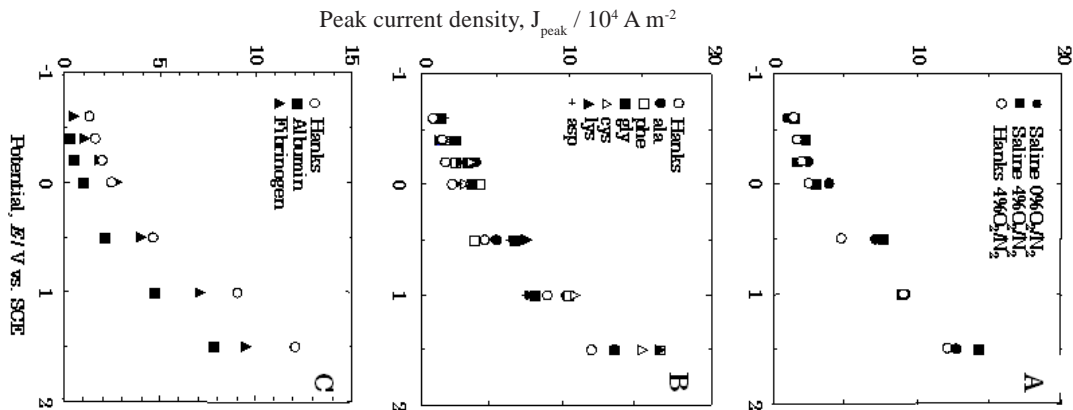

Fig. 4 Peak current densities of depassivated titanium in saline and Hanks' solution (A), Hanks' solution with and without amino acids (B), and Hanks' solution with and without proteins (C) as a function of the charged potential.
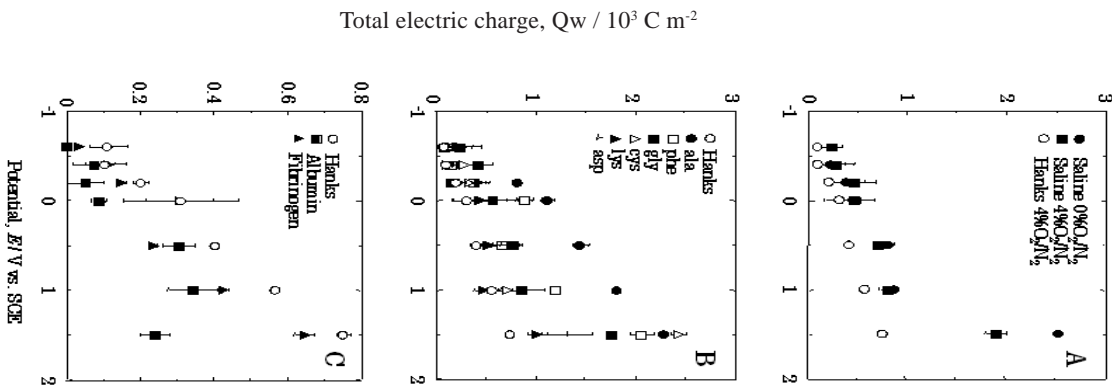

Fig. 5 Total charge of repassivation reaction obtained by the integration of the current with time in saline and Hanks' solution (A), Hanks' solution with and without amino acids (B), and Hanks' solution with and without proteins (C) as a function of the charged potential.