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## Controlled release of strontium ions from a bioactive Ti metal with a Ca-enriched surface layer

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### ABSTRACT

A nanostructured sodium hydrogen titanate layer  $\sim 1 \mu\text{m}$  in thickness was initially produced on the surface of titanium metal (Ti) by soaking in NaOH solution. When the metal was subsequently soaked in a mixed solution of  $\text{CaCl}_2$  and  $\text{SrCl}_2$ , its Na ions were replaced with Ca and Sr ions in an Sr/Ca ratio in the range 0.18–1.62. The metal was then heat-treated at  $600^\circ\text{C}$  to form strontium-containing calcium titanate (SrCT) and rutile on its surface. The treated metal did not form apatite in a simulated body fluid (SBF) even after 7 days. When the metal formed with SrCT was subsequently soaked in water at  $80^\circ\text{C}$ , the treated metal formed bone-like apatite on its surface within 1 day in SBF since the Ca ions were partially replaced with  $\text{H}_3\text{O}^+$  ions. However, it released only 0.06 ppm of Sr ions even after 7 days in phosphate-buffered saline. When the metal was soaked after the heat treatment in 1 M  $\text{SrCl}_2$  solution instead of water, the treated metal released 0.92 ppm of Sr ions within 7 days while maintaining its apatite-forming ability. The Ti formed with this kind of bioactive SrCT layer on its surface is expected to be highly useful for orthopedic and dental implants, since it should be able to promote bone growth by releasing Sr ions and tightly bond to the bone through the apatite formed on its surface.

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### 1. Introduction

Titanium metal and its alloys are widely used as orthopedic and dental implants because of their high level of mechanical strength and good biocompatibility. However, they cannot bond to living bone. It has been reported that Ti with a polished surface forms a thin fibrous tissue at the interface of living bone and the metal [1]. Ti with a roughened surface is able to come into direct contact with living bone, but does not bond. It would thus be valuable to introduce a bone-bonding capacity into Ti and its alloys for the purpose of stable fixation. A coating of calcium phosphate using a plasma spray is often used to acquire such bone-bonding capacity. However, this method does not produce a uniform bioactive surface layer because only the surface exposed to the plasma becomes coated, and the calcium phosphate is thus liable to decompose in the living body over time. Coating with calcium phosphate has been also achieved by sputtering, the sol-gel method or alternative soaking [2,3]. However, the resulting coatings are not stable over a long period in a physiological environment. The incorporation of calcium ions into the surface of Ti has been attempted using ion implantation, micro-arc oxidation and

hydrothermal treatment [4–7] to provide the capacity for apatite formation on the metal, while titania nanotubes have been formed by anodic oxidation to stimulate osteoblast cells [8]. However, these techniques require special apparatus and are not suitable for devices with a complicated structure and/or on a large scale.

Solution treatment with subsequent heat treatment allows the formation of a uniform bioactive surface layer, even on the inner surface of a porous body [9,10], and does not need any special apparatus. It has been shown that Ti forms a sodium titanate surface layer when soaked in NaOH solution at  $60^\circ\text{C}$  for 24 h and then heat-treated at  $600^\circ\text{C}$  for 1 h. This metal with a surface sodium titanate layer spontaneously forms bone-like apatite on its surface in a physiological environment and bonds directly to living bone through this layer [1,11–14]. Such treatment was applied to the porous Ti layer of an artificial hip joint that was commercialized in Japan in 2007 [15]. Recently, it was shown that a greater apatite-forming capacity was conferred on Ti when the metal was soaked in  $\text{CaCl}_2$  solution after the NaOH treatment, then subjected to heat and water treatments so as to form calcium-deficient calcium titanate on its surface [16]. This Ca treatment resulted in stable apatite formation on the Ti even after storage in a humid environment for a long period of time, in contrast with the NaOH and heat treatment. Furthermore, it was effective even for the Ti–Zr–Nb–Ta alloy [17,18], which is free from cytotoxic elements

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[19] and exhibits a high level of mechanical strength and low elastic modulus after proper processing [20]. The NaOH and heat treatment was not effective at inducing apatite formation on such alloys [21]. When Ca-treated Ti–15Zr–4Nb–4Ta, Ti–29Nb–13Ta–4.6Zr alloys as well as pure Ti were implanted into rabbit tibia, they bonded tightly with the living bone without forming any fibrous tissue, and their failure load under tensile stress increased over time [22]. It was concluded that the large bone-bonding capacity of the metals was attributable to their large apatite-forming capacity.

The strontium ion is an attractive candidate for enhancing bone healing due to its therapeutic effect on osteoporotic bone, which it achieves by increasing new bone formation while reducing bone resorption [23–25]. Cell studies have shown that Sr incorporation promotes the proliferation and differentiation of osteoblastic cells in porous ceramic scaffolds [26,27]. Pre-clinical studies have indicated that Sr ions derived from strontium ranelate increase bone mineral density at various skeletal sites, including the lumbar spine, femoral neck and total hip, resulting in the prevention of osteoporosis [28].

It is expected that the growth of new bone surrounding Ti will be promoted when Ti releases appropriate concentrations of Sr ions in a living body. Once the apatite is formed on the Ti surface, the newly grown bone bonds tightly to the metal through the apatite. In the present study, the preparation of bioactive Ti with the capacity to release Sr ions was undertaken by modifying the conventional Ca treatment method. Apatite formation on the surface of the resultant product in a simulated body fluid (SBF) and release of Sr ions in phosphate-buffered saline (PBS) are discussed in terms of the surface structure.

## 2. Materials and methods

### 2.1. Surface treatment

Pure Ti (Ti > 99.5%, medical grade; ISO5832-2, Nilaco Co., Japan) was cut into rectangular samples with dimensions of  $10 \times 10 \times 1 \text{ mm}^3$ , abraded with #400 diamond plates and washed with acetone, 2-propanol and ultrapure water in an ultrasonic cleaner for 30 min, then dried at 40 °C. The Ti plates were soaked in 5 ml of 5 M NaOH (Reagent grade; Kanto Chemical Co., Inc., Tokyo, Japan) aqueous solution at 60 °C in an oil bath, then shaken at a speed of 120 strokes  $\text{min}^{-1}$  for 24 h and gently rinsed with ultrapure water for 30 s. They were subsequently soaked in 10 ml of a mixed solution of 100 – X mM  $\text{CaCl}_2$  (reagent grade; Kanto Chemical Co., Inc., Tokyo, Japan) and X mM  $\text{SrCl}_2$  (reagent grade; Kanto Chemical Co.) at 40 °C, where X is the range from 0 to 100, designated as “100 – XCa + XSr”, shaken at 120 strokes  $\text{min}^{-1}$  for 24 h, washed with ultrapure water for 30 s and dried at 40 °C. They were subsequently heated to 600 °C at a rate of 5 °C  $\text{min}^{-1}$  and kept at 600 °C for 1 h, followed by natural cooling in an Fe–Cr electrical furnace. After the heat treatment, they were soaked in 10 ml of water or 1 M  $\text{SrCl}_2$  solution (Reagent grade; Kanto Chemical Co., Inc., Tokyo, Japan) at 80 °C, shaken at 120 strokes  $\text{min}^{-1}$  for 24 h, washed for 30 s and dried.

### 2.2. Surface analysis

#### 2.2.1. Scanning electron microscopy

The surface and cross-sections of the metal samples subjected to the chemical and heat treatments were coated with a Pt–Pd thin film and observed under field emission scanning electron microscopy (FE-SEM; S-4300, Hitachi Co., Tokyo, Japan) at a voltage of 15 kV.

#### 2.2.2. Energy-dispersive X-ray analysis

The surface chemical compositions of the metal samples subjected to the chemical and heat treatments were analyzed with an energy-dispersive X-ray spectrometer (EDX; EMAX-7000, Horiba Ltd., Kyoto, Japan) at 9 kV–K for Ca, Sr, O and Ti in five areas, and their averaged value was used for analysis.

#### 2.2.3. Thin-film X-ray diffraction and Fourier transform confocal laser Raman spectrometry

The Ti sample surfaces subjected to the chemical and heat treatments were analyzed by thin-film X-ray diffractometry (TF-XRD; model RNT-2500, Rigaku Co., Japan) and Fourier transform confocal laser Raman spectrometry (FT-Raman; LabRAM HR800, Horiba Jovin Yvon, France). TF-XRD was performed using a  $\text{Cu K}\alpha$  X-ray source operating at 50 kV and 200 mA. The glancing angle of the incident beam was set to an angle of 1° against the sample surface. In the FT-Raman measurements, an Ar laser with a wavelength of 514.5 nm and an exciting laser power of 16 mW was used as the laser source.

#### 2.2.4. X-ray photoelectron spectroscopy

The element distribution of the metal samples subjected to the chemical and heat treatments was analyzed at a near-surface depth using X-ray photoelectron spectroscopy (XPS; Quantera SXM, Physical Electronics Inc., USA) under Ar sputtering at a rate of 37  $\text{nm min}^{-1}$  ( $\text{SiO}_2$  conversion). In this analysis, an Al  $\text{K}\alpha$  radiation line was used as the X-ray source. The XPS take-off angle was set at 45°, which enabled the system to detect photoelectrons to a depth of 1–5 nm from the surface. Narrow scan spectra of  $\text{Ca}2p$  and  $\text{Sr}3d$  were also collected using XPS (ESCA-3300KM, Shimadzu Co., Japan), with an Mg  $\text{K}\alpha$  radiation line as the X-ray source. The XPS take-off angle was set at 45°. The binding energy of the measured spectra was calibrated by reference to the C1s peak of the surfactant  $\text{CH}_2$  groups on the substrate occurring at 284.6 eV.

### 2.3. Ion release

The samples subjected to the chemical and heat treatments were soaked in 2 ml of PBS at a specific concentration ( $\text{Na}^+$  158.14,  $\text{K}^+$  1.06,  $\text{Cl}^-$  155.17 and  $\text{HPO}_4^{2-}$  4.03 mM) and the pH was adjusted to 7.4 at 36.5 °C, then gently shaken at a speed of 50 strokes  $\text{min}^{-1}$  for various periods up to 7 days. Once soaked in the PBS, the Ca and Sr ion concentrations in the PBS were measured by inductively coupled plasma emission spectroscopy (ICP; SPS3100, Seiko Instruments Inc., Japan). Three samples were independently prepared for each soaking condition, and the averaged value was used for analysis.

### 2.4. Soaking in SBF

The samples subjected to the chemical and heat treatments were soaked in 24 ml of SBF with ion concentrations ( $\text{Na}^+$  142.0,  $\text{K}^+$  5.0,  $\text{Ca}^{2+}$  2.5,  $\text{Mg}^{2+}$  1.5,  $\text{Cl}^-$  147.8,  $\text{HCO}_3^-$  4.2,  $\text{HPO}_4^{2-}$  1.0 and  $\text{SO}_4^{2-}$  0.5 mM) nearly equal to those of human blood plasma at 36.5 °C. The SBF was prepared by dissolving reagent-grade NaCl,  $\text{NaHCO}_3$ , KCl,  $\text{K}_2\text{HPO}_4 \cdot 3\text{H}_2\text{O}$ ,  $\text{MgCl} \cdot 6\text{H}_2\text{O}$ ,  $\text{CaCl}_2$  and  $\text{Na}_2\text{SO}_4$  (Nacalai Tesque Inc., Kyoto, Japan) in ultrapure water, then buffering it at pH 7.4 with tris(hydroxymethyl)aminomethane and 1 M HCl (Nacalai Tesque Inc., Kyoto, Japan) at 36.5 °C [29]. After soaking in the SBF for various periods up to 7 days, the samples were gently rinsed with ultrapure water and dried. Surface apatite formation was examined by TF-XRD, FE-SEM and EDX.

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