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Biomimetic fabrication of apatite related biomaterials

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1. Introduction

Biomineralization is the process by which mineral crystals are deposited in an organized fashion in the matrix (either cellular or extracellular) of living organisms (Boskey, 1998). In simple terms, it can be described as the widespread and fascinating process by which living organisms produce minerals (Sigel et al., 2008; Stephen and Lowenstam, 1989). In this process, a living organism provides a chemical and physical environment that controls the nucleation and growth of a unique mineral phase. Often these materials exhibit hierarchical structural order, leading to superior physical properties not found in either their inorganic counterparts or in synthetic materials. The incorporation of inorganic compounds, such as salts, into biological structures often lends the structures hardness or rigidity. Almost 70 different mineral types are known to be formed by organisms from all the kingdoms. Examples include silicates in algae, carbonates in diatoms and invertebrates, and calcium phosphates and carbonates in vertebrates. These minerals adopt complex and genetically determined shapes, are often aligned to form arrays, and fulfill many different functions. These include the mechanical functions of exo- and endo-skeletons, temporary storage of minerals, stiffening of soft tissues, and much more. In vertebrates, especially mammals, bone and tooth are major biominerals.

Bones are living, growing tissue. During our lifetime, bone is constantly being renewed; there is localized removal of old bone (resorption) and replacement with newly formed bone. This coupled process is called bone remodeling. Biomineralization of bone—essential for its hardness and strength—involves a well orchestrated process in which crystals of calcium phosphate are deposited on the matrix produced by bone-forming cells (Weiner et al., 1999). Because bone formation consists of components including cells, matrix, and inorganics, the process is investigated by different research fields including cellular and molecular biology, organic and inorganic chemistry, crystallography, and material science (Figure 1).

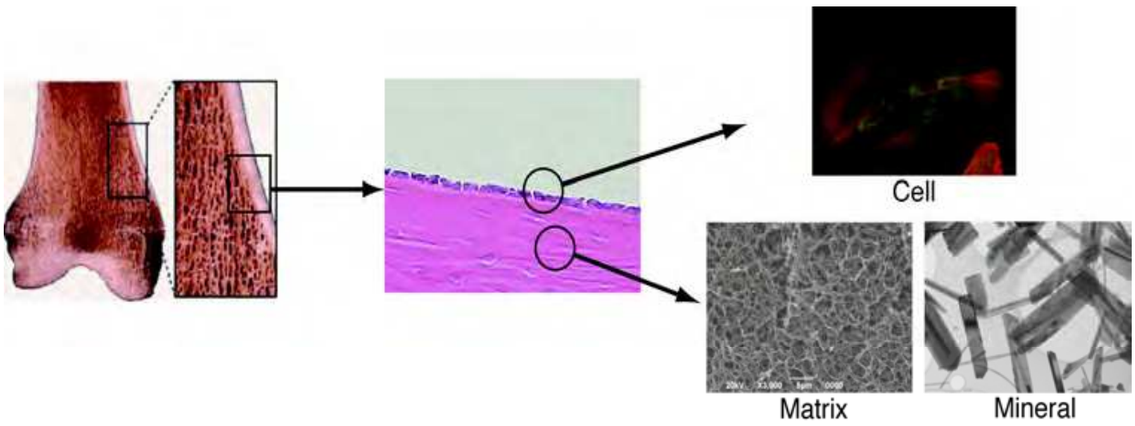

Fig. 1. Components of bone biomineralization. Bone forming cells (osteoblasts) produce extracellular matrix on which minerals are deposited.

Special attention has been paid to apatite materials because of their physicochemical properties, thermal stability, and biocompatibility that make them suitable for biomedical applications (Narasaraju et al., 1996). The usage of apatite-related biomaterials mainly focused on bone substitution or bone cements in the early years of study (Ono et al., 1990), however, the target has expanded to bone regeneration and drug delivery systems (Komleva et al., 2002). Therefore, material characteristics, including cellular and tissue compatibility, biodegradability, and drug loading capacity, should be improved. Moreover, it is desirable to create materials that can actively instruct cell fate in the area surrounding the material to enhance bone regeneration. To obtain such materials, research has focused on developing ideas based on biological mineralization systems. In this chapter, the latest research trends related to biomimetic apatite materials as well as biomimetic fabrication of apatite related biomaterials are introduced.

2. Basics of biominralization of bones

To obtain biomimetic apatite materials or to develop biomimetic methods of fabricating them, it is crucial to understand the natural biomineralization process of bones. The biomineralization process of bone can be simply divided into three parts at the microscopic level as follows, though the process differs depending on the ossification manner (e.g. osteochondral, intramembranous), stage (e.g. development, fracture healing), region, or age.
1) Osteogenic differentiation of mesenchymal stem cells (MSCs).
2) Organization of matrix proteins secreted from osteoblasts.
3) Nucleation and crystal growth of apatite minerals on matrix.

2.1. Osteogenic differentiation of mesenchymal stem cells (MSCs):

As a result of the capacity for self-renewal and differentiation, bone marrow derived stromal cells were first considered as stem cells and named mesenchymal stem cells (MSCs). However, in the bone marrow, stromal cells are a rare and heterogeneous population of cells that contain a mixture of progenitors at different stages of commitment to the mesodermal lineage and only a very small number of multipotential self-renewing stem cells (Caplan,

1991). It is now accepted that most bone marrow derived progenitor stromal cells can be considered, after *in vitro* proliferation, to be MSCs (Horwitz et al., 2005). Consequently, MSCs are typically defined as adherent, fibroblastoid-like cells that differentiate to osteoblasts, adipocytes, and chondrocytes *in vitro*. Despite their functional heterogeneity, *in vitro* MSCs are defined as nonhematopoietic cells (CD45-, CD14-, CD34-) but express other molecules, the combination of which is largely used for their description: CD73+, CD44+, CD105+, CD90+ and CD146+.

Key factors	***In vivo* and *in vitro* effects**
TGFbeta	Can induce osteoblast differentiation at the early stage of immature cells but can also inhibit osteogenesis in committed cells.
BMP2	Osteochondrogenic factor; might initiate bone formation and bone healing and can induce expression of other BMPs
BMP4	Osteochondrogenic factor in vivo and *in vitro*
BMP7	Osteogenic factor in vivo and *in vitro*; active on more mature osteoblasts
Noggin	Suppresses osteoblastic differentiation
FGFb	Mutations induce chondrodysplasia and craniosynostosis; can stimulate Sox9; might be a negative regulator of postnatal bone growth and remodeling
IGF-I, II	Stimulates growth plate formation, endochondrate ossification and bone formation by osteoblasts
VEGF	Most potent angiogenic and vasculogenic factor; crucial at the onset of bone formation
PlGF	Induces proliferation and osteogenic differentiation of MSCs; crucial for vascularization
Wnts	Depending on Wnt type, crucial for osteoprogenitor proliferation; can also inhibit final osteoblast maturation
Ihh	Pivotal role for growth plate and endochondral formation; can inhibit osteoblast differentiation; might induce PTHrP expression
PTHrP	Pivotal role for growth plate and endochondral formation; can induce or inhibit osteogenesis
OPG	Strongly inhibits bone resorption and has a pivotal role in bone Remodeling.
RANKL	Strongly stimulates bone resorption and has a pivotal role in bone remodeling
MAPKs	Crucial for regulation of intracellular signaling induced by osteogenic factors (still controversial)
Runx2	Master regulator of early osteogenesis; runx2_/_ mice died, with no bone formation
Osterix	Master regulator of late osteogenesis, inhibiting chondrogenesis
Dlx5	Induces osteoblast maturation but inhibits osteocyte formation
Msx2	Induces proliferation of immature cells; responses depend on Dlx5 quantity
NF-kB	Inhibits the differentiation of MSCs and committed osteoblastic cells

Table 1.Molecules involved in bone formation (Modified from Deschaseaux et al., 2009)

As shown in Table 1 a range of cytokines modulate osteoblast differentiation, including bone matrix-derived transforming growth factor beta (TGF-β), bone morphogenetic protein2 (BMP-2), BMP-4, and BMP-7, and their inhibitors noggin, chordin, gremlin, etc. Transcription factors that regulate the osteoblast include a range of homeodomain proteins: the activator protein (AP) family members Jun, Fos, and Fra, Smads, CCAAT/enhancer binding proteinβ (C/EBPβ) and C/EBP δ , lymphoid-enhancing factor (a Wnt effector), activating transcription factor 4, Runt-related transcription factor 2 (Runx2), and osterix, the last 3 of which are considered master genes for osteoblast differentiation. Runx2 is critical for osteoblast differentiation and two homeobox protein Dlx5 and Msx2 regulate Runx2 activity via a protein-protein binding interactions (Shirakabe et al., 2001). Thus, owing to the specific signal activation including transcriptional dynamics, MSCs differentiate into osteoblasts (Figure 2).

2.2. Secretion of matrix proteins by osteoblasts

Recruited and differentiated osteoblasts play a key role in biomineralization by secreting matrix proteins including collagen and non-collagenous proteins (NCP). Most tissues have been shown to contain a mixture of different collagen types. Bone, however, appears to contain almost exclusively type I collagen, with some type V (Broek et al., 1985). Type I collagen is the most common of the collagens in vertebrates. It comprises up to 90% of the skeletons of mammals and is also widespread all over the body, giving various tissues their mechanical strength and providing the major biomechanical scaffold for cell attachment and anchorage of macromolecules. Though type I collagen has multisectorial tasks, in bones type I collagen is mineralized with apatite crystals and gives mechanical strength and bone flexibility, and, moreover, it facilitates bone mineralization (Mirja et al., 2001).

Other important matrix proteins secreted by osteoblasts are NCP, including osteopontin (OP), bone sialoprotein (BSP), osteonectin (ON), and osteocalcin (OC). OP has important roles in immune functions, acts as an important anti-apoptotic factor in many circumstances (Denhardt et al., 2001), and also functions as an adhesion protein involved in cell attachment and wound healing (Wang et al., 2008). It plays a pivotal role in anchoring osteoclasts or hematopoietic stem cells to the mineral matrix of bones and thereby regulates their fate (Nilsson et al., 2005). OP contains a string of polyaspartic acid residues as well as an RGDS sequence near the middle of the primary sequence, where it has higher affinity with hydroxyapatite (HAp). BSP is a phosphoprotein that contains large stretches of polyglutamic acids as well as the RGD integrin-binding sequence at its carboxy terminus (Ganss et al., 1999). Its expression is generally limited to the later stages of osteoblast differentiation and early stages of mineralization. BSP also has a high affinity for calcium ions. ON is an acidic, secreted extracellular matrix glycoprotein. ON binds strongly to HAp (Romberg et al., 1985) even in the presence of 4M guanidinium hydrochloride. Alkaline phosphatase (ALP) secreted by osteoblasts is responsible for increasing local inorganic phosphate concentration during apatite formation (Hoffmann et al., 2008). Notably, these NCP can adhere to collagen fibers via strong physical adsorption or covalent bindings. Therefore, NCP coupling with type I collagen is considered to be an important template for mineralization. Indeed, numerous studies indicate that HAp orientation correlates with collagen orientation (Iijima et al., 1997b). OC is abundant in the synthesized osteogenic matrix, binds to phospholipid vesicles in the presence of Ca^{2+}, and also binds HAp. It has been stipulated that OC may function as a negative regulator of bone formation, although its exact role is unknown.

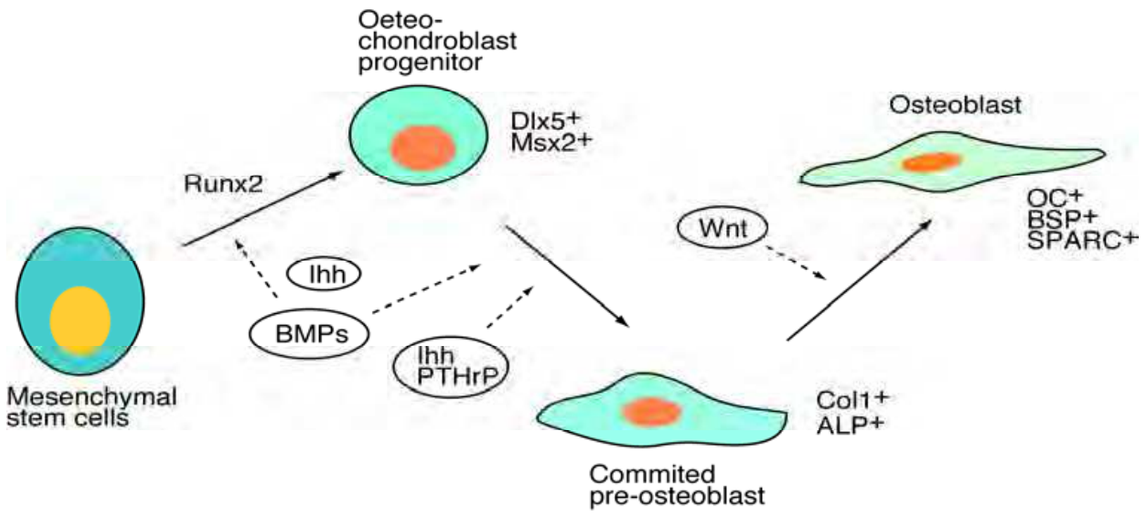

Fig. 2. Schematic illustration of differentiation of mesenchymal stem cells.

2.3. Nucleation and crystal growth of apatite minerals on matrix

It now appears clear that type I collagen alone is biologically insufficient to induce mineralization. It is thought that in bone, an interaction between anionic proteins and type I collagen fibrils may provide a stereochemical orientation of negatively charged groups that acts as a HAp nucleator. *In vitro* studies of organic matrix on biological crystal formation have proved a powerful complement to ultrastructural approaches in the ongoing attempt to determine the mechanism of calcification in bone and epiphyseal cartilage. However, much confusion has been generated by the fact that anionic matrix molecules often act as calcification inhibitors in these systems by complexing calcium ions and, in some cases, inhibiting crystal growth by adsorption onto specific crystal faces. For example, an aspartate-rich protein adsorbs to specific faces of growing apatite crystal, inhibiting the development of these faces and hence altering the crystal morphology (Addadi and Weiner, 1985). An important conceptual breakthrough has been the realization that macromolecules with a high density of negatively charged groups may act as crystal nucleators if immobilized onto solid-phase surfaces (Linde et al., 1989).

Similarly, amphipathic lipid monolayers or bilayers may promote calcification in an adjacent solution phase. Matrix vesicles secreted from osteoblasts are also considered to be a major site of biomineral nucleation (Figure 3). There are electron microscopy reports from researchers claiming that the mineralization process may involve the mobilization and translocation of insoluble mitochondrial calcium phosphate to the plasma membrane. According to this scheme, ions are 'packaged' and pinched off within trilaminar membrane-bound vesicles that are enriched and complexed with acidic phospholipid and contain NCP/proteolipid (Glinder et al., 1989). The phosphate-containing ALP within these new extracellular matrix vesicles is a species that is electrophoretically distinct from the form of the enzyme that is restricted to intracellular sites (Arsenis et al., 1976). Then, mineral formation penetrates the vesicle membrane and, in the presence of Ca^{+2}, PO_4^{-3}, and pyrophosphate, serves as the nuclei for formation of needle-shaped apatite. Finally, proliferation of the apatite spreads outwards into the matrix, rupturing the matrix vesicle (Anderson et al., 1969).

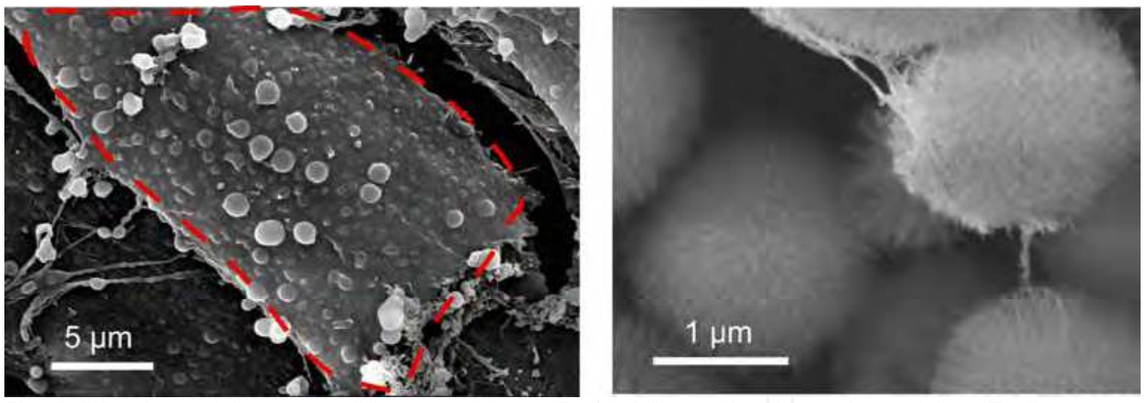

Fig. 3. Matrix vesicle secreted by osteoblasts (Left). Mineralized matrix vesicles (Right).

3. Bone minerals

The crystals of bone apatite are extremely small (crystallites). By x-ray diffraction, crystal size has been found to range in its long dimension (c-axis) from 10–25 nm (Boskey et al., 1985; Grynpas et al., 1986). By electron microscopy, bone crystal length has been found to vary from 30–70 nm (Landis et al., 1978). Therefore, bone mineral has a huge surface area of between 85 and 170 m^2/g (Ortner, 2003).

There are essentially five solid phases of calcium phosphate that have been linked to biological mineralization (Table 2). Of these, HAp ($Ca_{10}(PO_4)_6(OH)_2$) (Figure 4) is universally recognized as the final solid mineral phase of bone. All others have been implicated as minor or precursor phases; they are acid stable and will convert to the thermodynamically stable and insoluble HAp at a high pH. HAp alone is stable at neutral or basic pH. Tricalcium phosphate ($Ca_3(PO_4)_2$, TCP) requires the presence of Mg for its formation at room temperature. Both dicalcium phosphate dihydrate ($CaHPO_4 \cdot 2H_2O$, DCPD) and octacalcium phosphate ($Ca_8H_2(PO_4)_6 \cdot 5H_2O$, OCP) have acid phosphate groups (HPO_4) and a structural plane on which HAp can be grown epitaxially (Neuman and Neuman, 1958). Studies suggest that platelets are the dominant morphology of bone apatite (Traub et al., 1989). The formation of plate-like crystals in the mineralized collagen fibrils is still not fully understood. One possible explanation for this mineral morphology in bone is that crystal growth occurs via an OCP intermediate (Brown et al., 1962; Weiner and Traub, 1992). OCP has nearly the same crystal structure as HAp but contains an extra hydrated layer that may be responsible for the observed plate-shaped crystals in natural bone. Amorphous calcium phosphate (ACP) was also found to spontaneously precipitate to apatite at physiological values *in vitro* (Eanes et al., 1965). However, Grynpas et al. could not detect the presence of ACP in young bone (Grynpas et al., 1984). Improved methods of imaging and structure determination have since led to the identification of stable and transient forms of amorphous precursors in biomineralization of calcium carbonate in sea urchin spines and spicules (Addadi et al., 2003; Politi et al., 2004; Politi et al., 2006). As a result, the role of amorphous phases in mineralization of HAp in biological tissues such as bone continues to be a subject of great research interest.

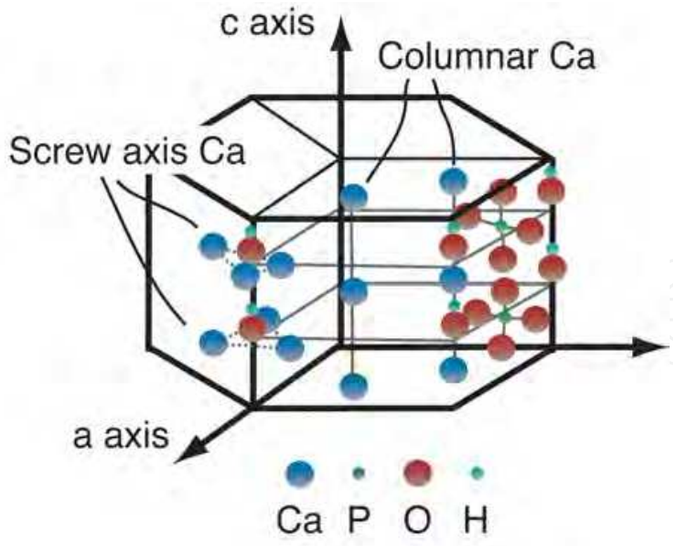

Fig. 4. Hydroxyapatite crystal

Phosphates (PO_4) in the general formula of HAp can be CO_3, SO_4, VO_4, AsO_4, or SiO_4. A variety of metals can take the place of Ca in the formula. In case of natural apatites, the main cation is Ca and Mg is secondary. The last group $(OH)_2$ can be F_2, Cl_2, Br_2, or CO_3 (Zipkin, 1973). Chemical analysis has shown that in hard biological tissues, i.e., bone, enamel, and dentine, the biological apatites are not pure HAp, but contain a mixture of minor elements, including CO_3, HPO_4, F, Cl, Mg, and Na ions (Yoshikawa and Myoui, 2005). Based on the knowledge derived from biological mineralization systems, researchers, especially material scientists and chemists, are now seeking biomimetic apatite-related biomaterials.

Name	Formula	Abbreviation	Molar ratio
Hydroxyapatite	$Ca_{10}(PO_4)_6(OH)_2$	HAp	1.67
Tricalcium phosphate	$Ca_3(PO_4)_2$	TCP	1.50
Octacalcium phosphate	$Ca_8H_2(PO_4).5H_2O$	OCP	1.33
Dicalcium phosphate dihydrate	$CaHPO_4 \cdot 2H_2O$	DCPD	1.00
Amorphous calcium phosphate		ACP	1.30-1.50

Table 2. Solid phases of biological calcium-phosphate

4. *In vitro* approaches to fabricating biomimetic inorganic materials

4.1. Biomimetic apatite: Ionically substituted apatite

Apatite powders can be synthesized via numerous production routes with a range of different reactants. Processing techniques include wet chemical methods (precipitation), hydrothermal techniques, hydrolysis of other calcium phosphates, and sol-gel methods. Since biological minerals, especially the apatite found in bone, are often ionically substituted apatite, apatite materials substituted by ions have been synthesized to control the

characteristics of apatite materials. When HAp is synthesized in the presence of Mg, Fe, CO_3, or F, these ions are readily and partly substituted at certain positions (e.g., Mg and Fe at the Ca site, CO_3 at the PO_4 site, and CO_3 and F at the OH site) in HAp crystals. The ionically substituted HAp exhibits different characteristics than normal HAp. For example, the solubility of apatite containing Mg, Fe, or CO_3 substitution increases with the increase in the concentration of the substitute ion (Gibson and Bonfield, 2002; Suchanek et al., 2004; Morrissey et al., 2005), whereas the stability of crystals increases and solubility decreases in apatite with F substitution (Okazaki et al., 1998; Okazaki et al., 1981). In addition to those, Sr- or Zn-substituted HAp crystals were synthesized by researchers. Sr-containing HAp enhanced the proliferation and differentiation of osteoblasts (e.g., MG63) (Capuccini et al., 2008). It also facilitated the nucleation of HAp, therefore, Sr-containing HAp is might be usable as a template for growing new bone (Pan et al., 2009). Zn-containing HAp increases the specific surface area (Tonegawa et al., 2007) and decreases the thermal stability of HAp (Li et al., 2008). Thus, ionic substitution, which occurs in natural apatite, is effective for controlling both material and biological characteristics of apatite.

4.2. Apatite formation via biomimetic mineralization

Researchers are also developing new synthetic, biomimetic systems to obtain apatite materials with biomimetic crystal morphology and size. Iijima et al. focused on the OCP crystal growth methods similar to the biological system. A collagen disk prepared from bovine Achilles tendon, which shows specific uniaxial alignment, was used as the template for OCP crystal formation. Consequently, the researchers were able to reproduce a ribbon-like OCP crystal formation morphologically close to the biological apatite precursors (Iijima et al., 1997b) (Figure 5a).

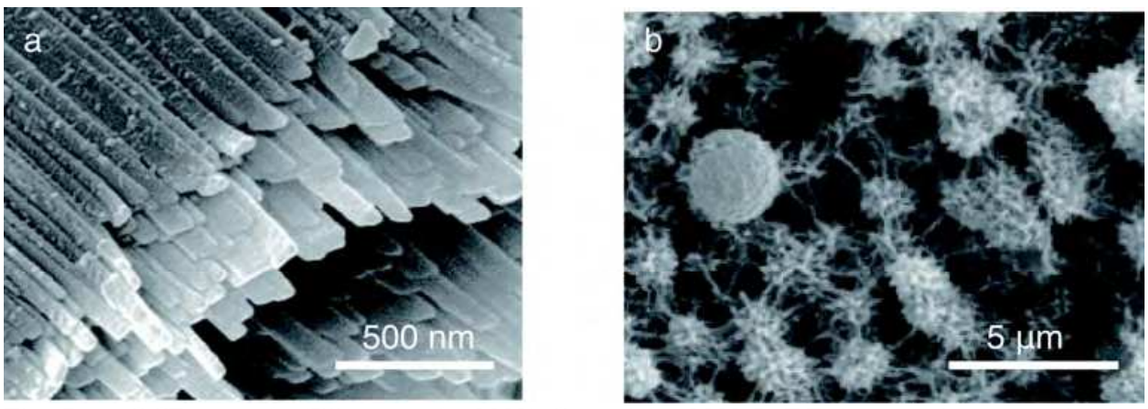

Fig. 5. a) OCP crystals (Iijima et al., 2002) Copyright 2002 IADR, b) Apatite formation on metal substrate. Copyright 2008 Elsevier.

Since simulated body fluid (SBF) containing inorganic ions similar to those in human plasma has been developed, SBF is considered to be a robust tool for reproducing biological apatite formation *in vitro*. Coating a bone-like apatite layer on substrate is expected to be a useful technique for inducing bioactivity on the substrate. The bone-like apatite layer can be formed on the surface of substrates in SBF solution when several specific functional groups are introduced to the substrates. Coating bone-like apatite layers through this biomimetic

process has received much attention in the fabrication of novel bioactive composites (Kamitakahara et al., 2007). Often, the biomimetic apatite coating is developed on the surface of titanium and its alloys. Gu et al. developed a method for biomimetic deposition of apatite coating on surface-modified NiTi alloy. They prepared a TiO_2 coating on NiTi alloy by heat treatment in air. The heat-treated NiTi alloy was then immersed in SBF for the biomimetic deposition of the apatite layer onto the surface of the TiO_2 coating. XPS and Raman results showed that this apatite layer was a carbonated and non-stoichiometric apatite with a Ca/P ratio of 1.53, which is similar to human bone (Gu et al., 2005). Ohtsuki et al. reported *in vitro* formation of small crystallities of carbonate-containing apatite on the surface of Ceravital-type glass ceramics soaked in SBF (Ohtsuki et al., 1991).

Moreover, there are reports about biomimetic methods of apatite formation using simpler solutions than SBF. For example, Bigi et al. reported a new fast method for the development of nanocrystalline HAp coatings on Ti6Al4V substrates using a slightly supersaturated Ca/P solution with an ionic composition simpler than that of SBF (Bigi et al., 2005). Shi et al. also followed the same biomimetic approach to synthesize an apatite layer on the surface of NaOH-modified titanium coatings in supersaturated solutions containing Ca^{2+} and HPO_4^{2-} ions. They observed that, depending on the ion composition and concentration of the solution, apatite layers were formed with preferred orientation and a composition similar to that found in bone (Shi et al., 2001) (Figure 5b).

5. *In vitro* approaches to fabricate biomimetic organic/inorganic composite materials

5.1. HAp containing organics

Improvement of physico-chemical characteristics (e.g., crystallinity, solubility, adsorptive properties, etc.) of apatite is important for using apatite-based materials for biomedical applications such as bone regeneration. Since acidic molecules have a well documented affinity to HAp, researchers synthesized HAp in the presence of organics, including acidic molecules and sugars. Previous reports indicated that HAp synthesized with acidic amino acids (e.g., aspartic acid, glutamic acid) has decreased crystallinity and increased solubility (Kevin, et al., 2007; Matsumoto et al., 2002). FTIR analysis indicated that these HAp crystals contained acidic amino acids and showed selective loading capacity of positively charged molecules (Uddin et al., 2009) and enhanced osteogenic differentiation of cells (Boanini et al, 2006). Stupp et al. synthesized HAp using macromolecules such as poly(l-lysine) and poly(l-glutamic acid). Poly(l-lysine) generated large single crystals that were flat and thin, whereas poly(l-glutamic acid) generated nanoscale crystallites (Stupp et al., 1997). Stupp et al. also demonstrated biomimetic mineralization of bone apatite using self-assembling molecules known as peptide amphiphiles (Hartgerink et al., 2001). Since the peptide design is flexible, this approach would be robust for obtaining HAp crystals with desired structure and size.

5.2. Biomimetic mineralization in organic gel to fabricate organic/inorganic composite material

Basically, the methods originate from biochemical studies investigating the effect of matrix proteins on biomineralization. Silverman and Boskey developed a gel diffusion precipitation

technique for growing large HAp crystals in collagen gel. This group has shown the *inter alia* promotion of HAp formation and growth by acidic phospholipids, biglycan, and BSP (Silverman and Boskey, 2004). On the other hand, inhibition of mineralization was observed for OP, dentin sialoprotein, aggrecan, and dentin matrix protein-1 (Tartaix et al., 2004). Hunter and Goldberg used a variation of the double diffusion gel method (using double diffusion of ions from opposite directions into a gel that contains the matrix molecule of interest) to explore apatite nucleation and inhibition by a number of matrix proteins (Hunter and Goldberg, 1993). Their system uses an agarose gel separated from calcium and phosphate reservoirs by diffusion membranes. SDS-polyacrylamide electrophoretic gel was also used as gel diffusion precipitation system. Calcium and phosphate ions were diffused naturally or propelled by electric potential. Calcium phosphate was precipitated in the gel. The precipitation was affected by proteins in the gel that had been separated by electrophoresis.

From a different stand-point, gels containing precipitated minerals developed in these methods are considered to be organic/inorganic composite gel material. Yoh et al. performed *in vitro* fabrication of fibrin/apatite composite material by using gel diffusion systems at various pH conditions. The minerals generated in fibrin gel varied with the pH conditions: DCPD in the noncontrolled pH solution, a DCPD and OCP mixture at pH 7.4, and an OCP and HAp mixture at pH 9.0. The composition of minerals in the gel can be regulated by their reaction period or diffusion rate (Yoh et al., 2008) (Figure 6). Watanabe et al. demonstrated anisotropic HAp formation in an agarose gel using an electrophoretic approach and an alternate soaking process to obtain the composite materials for bone regeneration (Watanabe et al., 2007).

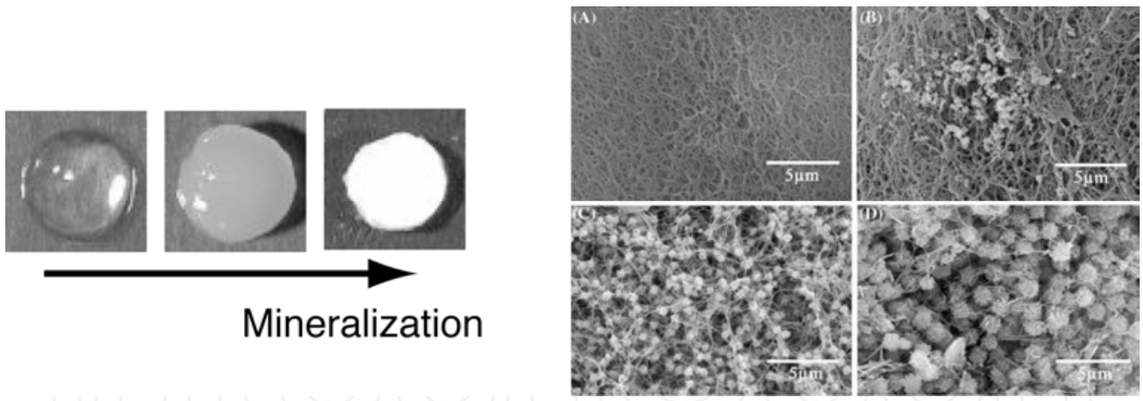

Fig. 6. Biomimetic mineralization of apatite in fibrin gel. Copyright 2008 Wiley.

5.3. Cell based fabrication of organic/inorganic composite gel

Synthesis of organic/inorganic composite materials generated by inorganic nucleation in a polymerized matrix is a unique system for obtaining biomimetic materials. Cells might also be great contributors to the synthesis of organic/inorganic composite material, because secreted proteins, especially those derived from osteogenic differentiated cells, supply regions where mineral crystals nucleate and grow. Our group demonstrated that culturing MSCs in three-dimensional (3D) gel matrix enhanced the precipitation of cell-derived matrix and minerals. The matrix and mineral content in the material can be regulated by cell culture

conditions including cell number and period. Moreover, 3D cell patterning in the gel has been found to be effective in controlling the matrix and mineral position and distribution in the gel. Thus, this type of cell-based fabrication technique would be a new approach to fabricating more biomimetic materials (Figure 7).

6. Conclusion

Biological tissue shows amazing characteristics and has functions that cannot be easily reproduced by artificial synthesis. For example, bone tissue shows fracture toughness though it is soft in nature. Therefore, learning from biological systems gives us tremendous opportunities to fabricate materials that we have not yet been able to produce. The ionically substituted HAp materials or organic-containing HAp materials introduced in this chapter are good candidates for drug delivery carriers for bone regeneration or bone-related diseases. Organic/inorganic composite gel materials fabricated by self-precipitation or by a cell-based method would be neo-bone tissue that could shorten the bone regeneration period. Thus, apatite related biomaterials inspired by nature have potential for numerical biomedical applications.

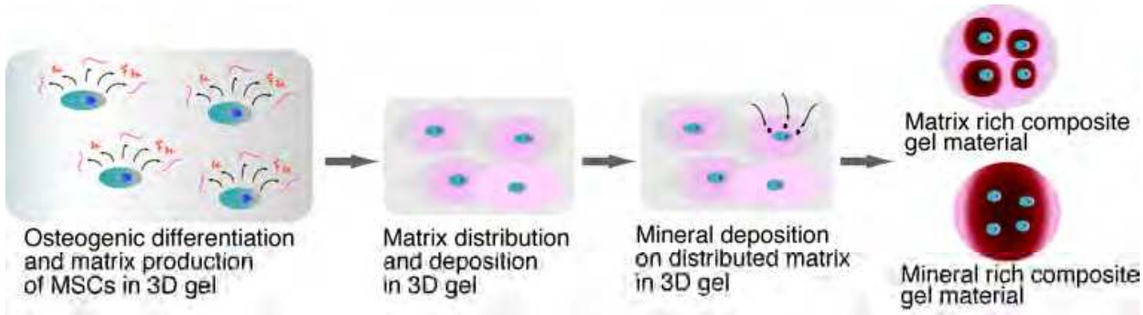

Fig. 7. Schematic illustration of biomimetic mineralization in fibrin gel culturing with MSCs.

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Nature's evolution has led to the introduction of highly efficient biological mechanisms. Imitating these mechanisms offers an enormous potential for the improvement of our day to day life. Ideally, by bio-inspiration we can get a better view of nature's capability while studying its models and adapting it for our benefit. This book takes us into the interesting world of biomimetics and describes various arenas where the technology is applied. The 25 chapters covered in this book disclose recent advances and new ideas in promoting the mechanism and applications of biomimetics.

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