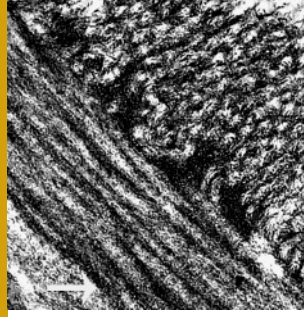
Mineralization of Bones and Teeth



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Bones and teeth consist of an inorganic calcium phosphate mineral approximated by hydroxylapatite and matrix proteins. The physical and chemical properties of these "bioapatite" crystals are different from those of geologic hydroxylapatite because of the way they are formed, and these unique properties are required for fulfilling the biological functions of bones and teeth. Recent biochemical studies provide insight into the factors controlling the formation and growth of bioapatite crystals and how alteration in the mineralization process can lead to diseases such as osteoporosis. New spectroscopic and microscopic techniques are enabling scientists to characterize changes in crystal properties in these diseases, providing potentially fruitful areas of collaboration between geochemists, mineralogists, and biological researchers and offering hope for the development of novel therapies.

KEYWORDS: biomineralization, mineralization mechanisms, calcium phosphate, hydroxylapatite

INTRODUCTION

Fossils not only provide the geologic record of evolution, they also remind us of the crucial role that mineralized tissues play in the biology of organisms. Mineralized tissues are composite structures consisting of an inorganic mineral phase, an organic phase, and cells. In this article, I provide an overview of the mineral–matrix relationships in bones and teeth, highlight the significant differences between biologic apatites and geological hydroxylapatite, and describe the recent advances and challenges in genetic, spectroscopic, and microscopic studies of the mineralization of bones and teeth. Biologic apatites are analogues of geologic hydroxylapatite but, especially in the case of bone and dentin, differ in having highly disordered, non-stoichiometric structures with numerous point deficiencies and carbonate substitutions. We will distinguish these structures in the present text by referring to bioapatite or apatite as distinct from stoichiometric hydroxylapatite. These topics have been reviewed recently in greater detail (Glimcher 2006).

The evolution of exoskeletons (shells, scales, etc.) some 500–600 million years ago during the "Cambrian explosion" allowed the preservation of this event in the form of fossils in the rock record. The subsequent development of endoskeletons (bones and teeth) gave vertebrates improved mobility and mechanical competence. Bones and teeth protect the internal organs, allow enhanced mobility, enable mastication of food, perform other mechanical functions, and are a ready source of the key regulatory inorganic ions calcium, magnesium, and phosphate. They also harbor a myriad of cells and growth factors that, in turn, control tissue properties. The sizes and shapes of bones reflect their function. For example, the flat skull bones protect the brain, the ribs protect the lungs, the pelvis protects other internal organs, the short tubular bones in the digits of the hands and feet provide specific grasping functions, the long bones enable locomotion. In this chapter, I provide a brief overview of bone and tooth structure as composite hierarchical materials, their formation under cellular control, and the important characteristics of bone and teeth mineral that distinguish them from geological hydroxylapatite.

STRUCTURE OF BONES AND TEETH

Bones and teeth are heterogeneous, hierarchical, composite structures (McKee et al. 2005). At the organ scale (centimeters), it is possible to distinguish different types of bones (e.g. long, flat) with distinct functions (FIG. 1A). Long bones consist of an outer cylinder of cortical bone surrounding a marrow cavity that includes struts of trabecular (cancellous) bone. Flat bones have variable structures; for example, the skull has lesser amounts of cancellous tissue whereas the spine consists mainly of cancellous bone.

As with bone, different components of the tooth (dentin, enamel, cementum) are distinguished at the organ scale (FIG. 1B). The periodontal ligament connects the tooth (via the cementum) to the underlying jawbone. The outer coating of the tooth as far as the gum line is enamel, a very hard material with little or no protein. Below the enamel is dentin, the major component of teeth. Separating the dentin from the surrounding jawbone is a bone–dentin composite material, cementum, and a periodontal membrane. The dentin surrounds a pulp cavity that holds the nerves and blood vessels necessary for tooth function.

At the tissue scale (millimeters to micrometers), in general, bones and teeth consist of cells, an organic matrix, and an inorganic matrix. The cells control the initial production of the mineralized tissue. In bone, osteoblast cells control the mineralization of the extracellular collagen protein matrix. When osteoblasts become engulfed in mineral, they become a different type of cell, called osteocytes, which communicate with each other via interconnecting long channels (canaliculae) that can send messages throughout the tissue. Finally, osteoclast cells remove bone mineral and bone matrix. Thus, bone cells regulate the formation and turnover or resorption of bone, a key step in regulating

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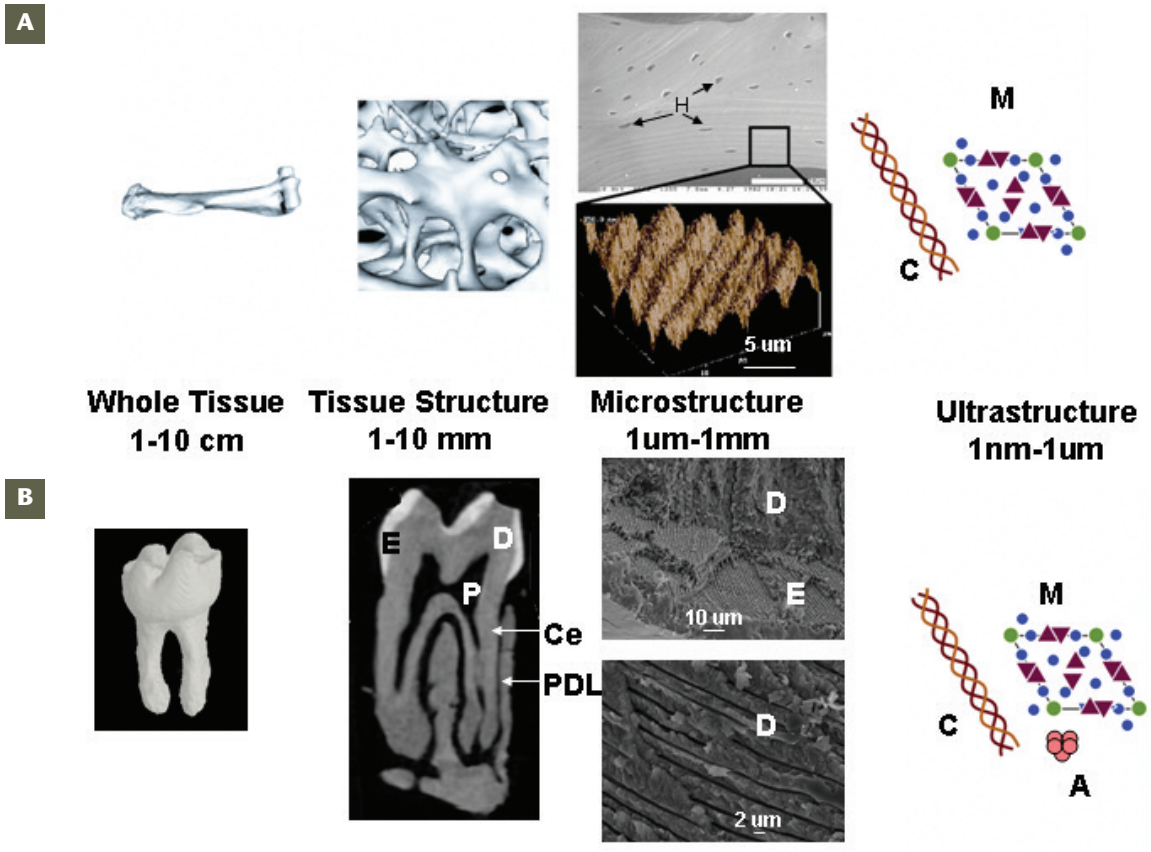

FIGURE 1 The hierarchical nature of bones (**A**) and teeth (**B**), illustrated using mouse tissues. (**A**) shows a mouse humerus (whole tissue), a high-power micrograph of the struts in trabecular bone (tissue structure), an electron micrograph of lamellar bone and an AFM image showing the peaks and troughs of the lamellae (microstructure), and a cartoon (ultrastructure) illustrating the major components of the matrix, triple-helical collagen (rope-like structure, C) and apatite (M). The apatite structure is a projection of the hydroxylapatite unit cell. Ca^{2+}, blue circles; OH^- or vacancy, green circles; PO_4^{3-}, red triangles. In (**B**), the mouse second molar structure (whole tissue) is also shown in cross section (tissue structure), with regions of enamel (E), dentin (D), pulp (P), cementum (Ce) and periodontal ligament (PDL) indicated. SEM images (microstructure) show dentin (D) with lamellar peritubular and intertubular dentin and enamel (E). The cartoon (ultrastructure) includes amelogenin nanospheres (A, pink cluster) from enamel. IMAGES IN (A) CONTRIBUTED BY DR. EVE DONNELLY AND IN (B) BY DRS. KOSTAS VERDELIS AND J. TIMOTHY WRIGHT.

body calcium, magnesium, and phosphate levels. This maintenance of inorganic ion levels, or homeostasis, is one of the major non-mechanical functions of bone. It is disrupted in a variety of common human diseases such as osteoporosis and osteomalacia.

At the microstructure scale (micrometers), bone consists of structural units such as the individual struts (trabeculae) found in the marrow connecting the bone structure, the thin plates (lamellae) in cortical bone, and the bone formed around blood vessels (osteons). In the tooth, structural units include the tubules that permeate the dentin and the intertubular dentin that surrounds the extensions of the dentin-forming odontoblasts.

At the ultrastructural scale (nanometers), individual tissue components, namely the mineral crystals and the organic matrix, can be discerned. The organic matrix of bone consists primarily of a fibrous protein, collagen, and lesser amounts of other noncollagenous proteins (discussed later). In tooth, collagen is also the major organic constituent of dentin and cementum, but there is no collagen in enamel. Collagen is the same protein that gives flexibility to ligaments and tendons, but the addition of mineral to the collagen matrix makes it rigid and gives bones and teeth their greater load-bearing capacity. The mineral that reinforces bone and dentin matrices and is also the major constituent of enamel is an analogue of the mineral hydroxylapatite. At the element scale, bone apatite nanocrystals exhibit a variety of substitutions and vacancies that make the Ca/P molar ratio distinct from the stoichiometric hydroxylapatite ratio of 1.67 (Boskey 2006). Enamel apatite has fewer substitutions than bone or dentin mineral and more closely approximates stoichiometric hydroxylapatite.

Crystal Morphology, Size, and Composition

The crystals in bone have a plate-like habit and are nano-sized, with a length of ~20–50 nm and a width of 12–20 nm, depending on age and species (Glimcher 2006). The crystals in dentin are of similar size, but enamel crystals are ~10 times larger in all dimensions (Kirkham et al. 1998). In all these tissues, the initial crystals tend to be round but grow longer with age, suggesting the existence of factors that regulate bioapatite crystal habit. In bone, cementum, and dentin, apatite crystals develop with their long *c*-axes parallel to the collagen fibril axis (FIG. 2). The collagen and associated proteins play an important role in determining nucleation, growth, and proliferation of these crystals.

Because of bone remodeling or turnover, bone composition differs with animal age and tissue age, environmental factors, and health status. There is an age-dependent variation in chemical composition, crystal size, and amount of mineral present in different sites within the osteons and trabeculae in bone. Different parts of the tooth also have variable structure and composition. The outer coating, enamel, is not formed on a collagen matrix, and the organic matrix of enamel is degraded when the tooth is mature (Margolis et al. 2006). Enamel composition may be changed by bacteria

that cause dental caries and by chemical agents used to remineralize the damaged enamel. Dentin and cementum are not remodeled, so studies of their age-dependent maturation provide a picture of the dynamics of mineral deposition (Verdelis et al. 2007).

Differences between Bone and Dentin Hydroxylapatite and Geologic Hydroxylapatite

Almost a century ago, broad and poorly defined X-ray diffraction patterns from ground bone were recognized to be similar to those of geologic hydroxylapatite, $Ca_5(PO_4)_3(OH)$ (de Jong 1926). Later studies showed bone and dentin Ca/P molar ratios to be different from the 1.67 value for geologic hydroxylapatite (Zipkin 1970). A noncrystalline, X-ray-amorphous calcium phosphate phase (ACP) with a Ca/P molar ratio of 1.5 was found to precipitate spontaneously from highly supersaturated solutions and to convert at physiologic pH to apatite. This phase was suggested to be a precursor to bone and dentin mineral, thus explaining the non-stoichiometric Ca/P ratio in bones and teeth (Eanes et al. 1965). However, more sophisticated structural analyses based on radial distribution functions failed to demonstrate the presence of ACP in young bone (Grynpas et al. 1984). Recently the discovery of a stable amorphous calcium carbonate in sea urchin spines (Politi et al. 2004) reawakened the suggestion that a transient amorphous phase might also exist in bone (Weiner 2006). Structural studies based on nuclear magnetic resonance analysis argue against this and suggest that the presence of surface HPO_4^{2-} ions could explain the broad diffraction peaks (Jager et al. 2006), without a need to invoke the presence of ACP. While the controversy has not been put to rest, we are comfortable in stating that in all but the youngest bone and dentin, the only phase present is a highly disordered, highly substituted apatite. The small crystal size, high degree of carbonate substitution, substantial OH deficiency, presence of lattice vacancies, and the resultant increased solubility make apatite in bone, dentin, cementum, and even enamel distinct from geologic hydroxylapatite. The small crystal size means that a large percentage of the atoms are on the surface of the crystal, providing a large specific surface area for sorption of ions, proteins, and drugs. Another key distinction is that hydroxylapatite grows and incorporates inclusions over geological timescales compared to the changes in bone and tooth mineral that occur over short time spans (days to months). With time, depending on tissue site and animal diet, bone and dentin mineral progresses from a poorly crystalline apatite with high HPO_4^{2-} content and a low level of crystallinity to a mineral with somewhat higher crystallinity, lower acid phosphate content, and a more organized structure, albeit with more carbonate substitutions (Carden and Morris 2000; Boskey 2006; Verdelis et al. 2007).

The most significant way in which bone and dentin apatite crystals are distinct from geologic hydroxylapatite is the way in which they form and, as a consequence of this, the association of the mineral phase with an organic matrix. All mineralization in living organisms (biomineralization) is controlled to some extent by cells, and the organic matrices made by those cells facilitate the deposition of crystals. The extracellular matrix proteins associated with mineralized collagen in bone and dentin also change with time. Initially, the mineral crystals are formed in an environment rich in the so-called SIBLING (Small Integrin-Binding LIgand N-linked Glycoprotein) proteins. As bone crystals grow, there is greater association with proteins, such as osteocalcin, that regulate remodeling. This points to the final, key distinction between bone apatite and geologic hydroxylapatite—bone mineral is always in a dynamic state

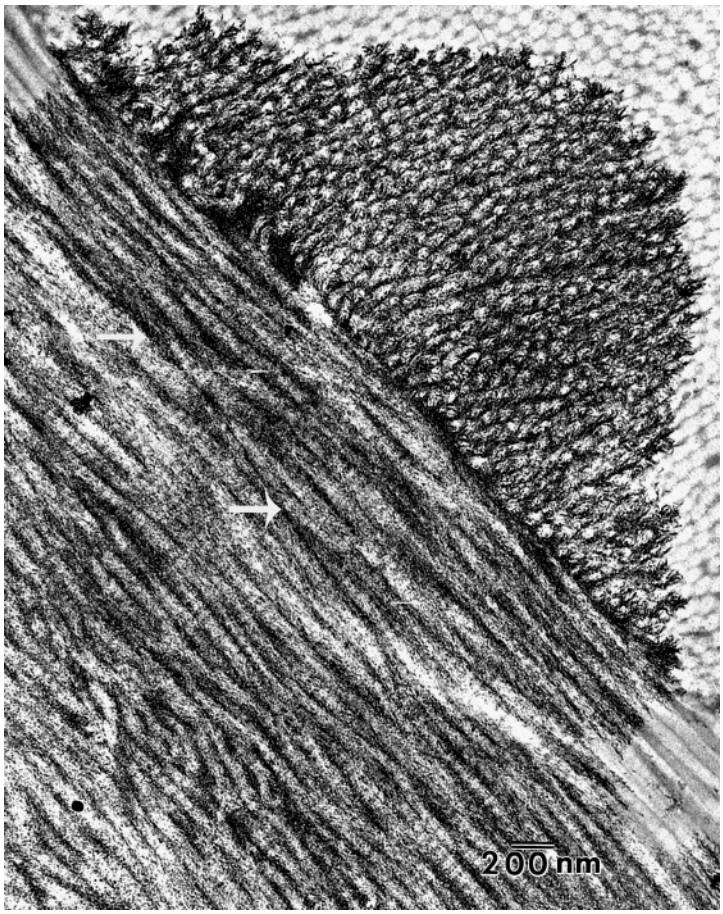

FIGURE 2 Transmission electron micrograph showing the alignment of electron-dense mineral crystals along the collagen fibrils in fish scales. The fish scale image matches that of the newest-formed mineral in bone and dentin in mammals and allows viewing of the earliest mineral deposits; although the same orientation is found in bone and dentin, it is more difficult to visualize in these more highly mineralized tissues. Arrows point to typical electron-dense crystals and the lighter structures represent collagen fibrils. The collagen fibrils can also be seen in cross-section adjacent to the mineralized tissue. IMAGE COURTESY OF DR. STEPHEN B. DOTY

and is remodeled (removed and redeposited) by cellular activity, whereas geologic hydroxylapatite is modified only by physicochemical processes such as dissolution, reprecipitation, and incorporation of foreign ions.

Dentin mineral is remodeled to a much lesser extent, although the roots are remodeled as a response to disease, and the remodeling is under cellular control. Enamel mineral is not remodeled, but enamel matrix is degraded as mineralization takes place. Enamel mineral may be lost due to dissolution by bacterial acids resulting in dental cavities. It is crucial to appreciate these differences between biologic apatite and geologic hydroxylapatite, and extreme caution must be exercised if attempting to use results obtained in vitro from highly crystalline hydroxylapatites to explain biological in vivo processes.

Organic Matrices of Bones and Dentin

Bone and dentin are composite materials that consist of apatite crystals deposited in an oriented fashion on a scaffolding provided by an organic matrix, predominantly collagen. Collagen, an insoluble fibrous protein, is one of the most abundant proteins in the body. Of the more than 27 types of collagen, type I is the most prevalent and is associated with bone, dentin, cementum, skin, ligament, and tendon.

The collagen macromolecule has a unique structure, consisting of three collagen polypeptide chains wound into a repeating triple-helical fibril (Ramachandran and Venkatachalam 1966). The fibrils line up head-to-tail to form repeating arrays that give flexibility to the nonmineralized tissues. When reinforced with mineral particles, the resulting composite increases in strength and becomes capable of bearing weight. The mineral particles align themselves with their long axes parallel to the fibril axis of the collagen (FIG. 2). Spaces (holes) between the individual collagen molecules and between the collagen fibrils can accommodate these mineral particles (Hodge 1989). The apatite crystals appear to deposit first within the holes and then to spread throughout the matrix.

Noncollagenous proteins are found tightly associated with the collagen. If one removes the mineral from the collagen matrix with solvents that also extract the noncollagenous proteins, the matrix cannot be remineralized (Termine et al. 1981). Similarly, if one removes the organic phosphate–ester residues from the already demineralized matrix, the dephosphorylated matrix cannot be remineralized (Glimcher 1989). Observations such as these led to the concept that noncollagenous proteins are important for the control of bone and dentin mineralization. Zhu et al. (2007) provide extensive data concerning the properties, modifications, functions, and effect on in vitro apatite formation of noncollagenous extracellular matrix proteins in bone and dentin.

Many noncollagenous proteins are phosphorylated proteins, again suggesting a role for the protein-linked phosphate–ester groups in the mineralization process. The major proteins associated with enamel are not phosphorylated, and include amelogenins, ameloblastins, enamelins. The role of these proteins in initial enamel mineral formation and growth was recently reviewed (Bartlett et al. 2006; Margolis et al. 2006).

To mimic the process of bone and tooth formation, tissue engineers are developing scaffolds that can be directly implanted into mineralized tissue defects or can be seeded with cells prior to implantation (Holland and Mikos 2006; Cerruti and Sahai 2006; Jones et al. 2007 this issue). Some of these implants contain model collagen scaffolds. Others have a structure resembling that of native collagen but do not contain any collagen molecules. Many of the scaffolds being tested include peptide mimetics that can recruit cells and control cell remodeling of the matrix. The peptide mimetics are designed from those native compounds that have proven functions in the mineralization process.

CELLULAR REGULATION OF THE MINERALIZATION PROCESS

Cells produce the organic matrix that becomes mineralized, control the flux of ions into the extracellular matrix, and register signals that indicate when the mineralization process should commence and end (TABLE 1). The extracellular matrix surrounding the cells provides an oriented surface for mineral deposition and defines both the sites where mineralization will commence and the size to which the crystals will grow. Collagen provides the template for mineral deposition in dentin and bone, and the size and organization of the collagen fibrils limits the dimensions that mineral crystals can attain. However, as noted above, without the noncollagenous proteins, the mineralization process does not occur in a measurable time period.

Macromolecules that Control Mineral Formation and Crystal Growth in Bone and Dentin

As noted above, several families of proteins associated with the collagen matrix are involved in regulation of the mineralization process. Some of these proteins have multiple functions beyond their role in mineralization (Zhu et al. 2007). The proteins include phosphorylated proteins, proteoglycans, glycoproteins, gamma-carboxy-glutamic-acid-containing (gla) proteins. Among the phosphorylated proteins, the SIBLINGs are the most widely studied (Qin et al. 2004). The genes for all these proteins are on the same chromosome. These proteins all have cell-binding domains and multiple phosphorylation sites. They all interact with fibrillar collagen, and they can be cleaved enzymatically into smaller fragments. Investigations by our group have focused on how these posttranslational modifications (phosphorylation, binding, fragmentation) can affect the formation and growth of bioapatite in solution (Zhu et al. 2007). Some of these proteins act as both inhibitors and promoters of mineralization (see online table as supplementary data at www.elements.geoscienceworld.org) depending on the extent of posttranslational modification and/or their concentration. Similarly, small leucine-rich proteoglycans (SLRPs) interact with fibrillar collagen, can be cleaved and variably sulfated, and sometimes are excreted in larger forms requiring fragmentation for activation (Waddington et al. 2003). The gla-protein family has fewer members than the SLRP and SIBLING families, but these too have anionic components that are subject to posttranslational modifications (Laizé et al. 2005).

Several properties must be demonstrated in order to prove that a material isolated from mineralized tissue is directly involved in the mineralization process. First, the component must be shown to be present, to be modified, or to disappear, concurrent with its hypothesized role in the nucleation of mineral crystals or in the regulation of crystal growth. Second, it must be shown to have a role in the mineralization process. This can be demonstrated by cell-free solution studies, by studies in cell, tissue, or organ culture, or by analyses of animal models (or patients) in which the protein is overexpressed, underexpressed or improperly modified after it is expressed. The most convincing proof is a combination of all the above.

The noncollagenous proteins found in the mineralized tissues occur at or near the mineralization front in bones and teeth. Their presence has been demonstrated by using a radioisotope during synthesis to label the protein and identify it by its emitted radiation; by immunohistochemistry where antibodies localize the protein in tissue sections; and/or by localizing the gene or the protein at specific sites in the tissue. A variety of methods can be used to study the effects of the protein in the absence of cells. In studies of mineral formation, the protein is exposed to a metastable calcium phosphate solution that is supersaturated with respect to hydroxylapatite but in which precipitation does not occur for months or even years until a nucleator is added (Takeuchi et al. 2005). The presence of the protein promotes faster nucleation relative to the metastable protein-free controls. In a different type of experiment exploring crystal-growth kinetics, one can determine the effect of proteins on the growth rates of preformed seed crystals in metastable solution and monitor the resulting crystal morphologies (Moradian-Oldak et al. 1998; Wesson and Ward 2007 this issue). Mineral accumulation in these studies is based on chemical analysis of changes in the dissolved calcium and phosphate concentrations, measurement of the amount of mineral accrued, or physicochemical assessment of crystal size (by electron microscopy, X-ray diffraction, or some other spectroscopic method). These same types of mineral analysis methods are often used to assess the properties of the mineral in genetically modified animals.

TABLE 1 PRINCIPAL CELLS MINERALIZED TISSUES IN VERTEBRATES

Cell	Tissue	Function and Properties
Chondrocyte	Calcified Cartilage	Secretes matrix and prepares matrix for calcification
Osteoblast	Bone	Round or flat-bone forming cell that synthesizes matrix and orchestrates the coupling of bone formation and bone remodeling
Osteocyte	Bone	Osteoblast surrounded by mineral; linked to other similar cells by thin processes (canaliculae)
Osteoclast	Bone	Multinucleated large-bone resorbing cell; binds to bone surface and releases acid and enzymes that respectively remove mineral and matrix in response to signals
Odontoblast	Dentin	Tooth matrix-forming cell; produces dentin matrix in a predefined direction
Cementoblast	Cementum	Cell involved in synthesis of cementum mineral and matrix
Ameloblast	Enamel	Cell that produces enamel

Studying Mineralization Processes in the Bones of Genetically Modified Animals

In recent years, techniques for ablating (knockout) or overexpressing (knockin) genes in mice and other species have been widely applied to elucidate the functions of the proteins produced by these genes (Boskey et al. 2005). Gene modification may also occur naturally or may be designed to occur in a specific tissue (conditional knockout or knockin). There are certain limitations to these methods: (1) the gene may be essential for life, and gene modification could create a condition such that no new animals are born and none can be evaluated; (2) gene modulation may cause the over- or underexpression of compensatory genes, thus preventing any visible changes in the organism; or (3) the modulation of the gene may have effects not directly related to the protein function because of the way in which the modulation occurred. Despite these potential limitations, gene-modification techniques have provided considerable insight into the functions of numerous extracellular matrix genes.

The most obvious bone changes have occurred in animals lacking osterix and cbfa1/Runx2—master genes that are required for the initiation of cartilage calcification and bone formation (Okazaki and Sandel 2004). Mice with abnormalities in the genes that express bone (type I) collagen have a condition known as osteogenesis imperfecta, which is characterized by brittle, fragile bones. These bones contain abnormal collagen fibrils with abnormally small, poorly oriented crystals. Genetic studies on patients with osteoporosis showed a polymorphism (i.e. variation in a gene expressing one chain of the collagen molecule) that is associated with fracture incidence (Stewart et al. 2006). More subtle bone and tooth changes occur in mice lacking the extracellular matrix proteins. When examined by light microscopy, bones and teeth of these animals often do not show any visible changes, but analysis by sophisticated techniques, such as magnetic resonance imaging (MRI), microcomputed tomography (micro-CT), and other two- and three-dimensional spectroscopic techniques (Judex et al. 2003), reveal changes that provide insight into the function(s) of the protein.

Fourier transform infrared (FTIR) spectroscopic imaging and Raman microspectroscopic imaging can be used to provide information on the spatial distribution of molecular vibrations in tissues such as bone and dentin (Carden and Morris 2000; Boskey 2006). The spectra arise from vibrations in the bonds of the component molecules (mineral, collagen, lipid) within the tissue (FIG. 3A) and indicate the quantity of the component as well as changes in the molecular environments. Parameters have been defined in both FTIR and Raman studies that are indicative of tissue mineral content, mineral crystal size, mineral HPO_4^{2-} content, mineral carbonate content, and collagen matrix maturity. For example, the peak height ratio of the 1030 cm^{-1} band in stoichiometric apatite to the 1020 cm^{-1} band in non-stoichiometric apatite can be used to estimate the crystal size or crystallinity index.

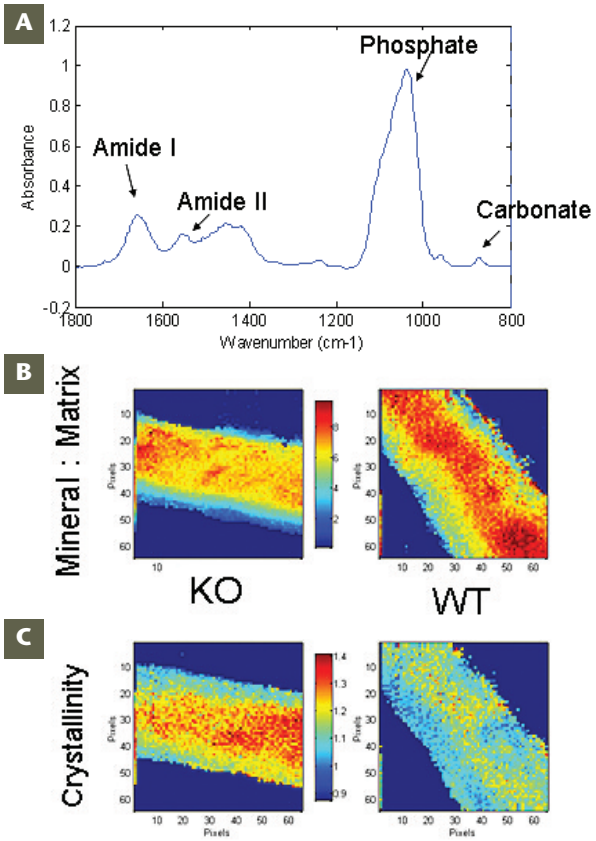

FIGURE 3 FTIR analysis of bones illustrating the effect of dentin matrix protein 1 (DMP1) deficiency on mineral content and crystallinity. (**A**) Typical spectrum of bone showing the vibrational bands used to calculate mineral and matrix parameters. (**B**) Images of mineral/matrix ratio in bone shafts of knockout (KO) and wild-type (WT) mice. This parameter, calculated as the ratio of the integrated areas under the phosphate (900–1200cm^{-1}) vibration to the integrated area under the amide I band (1585–1720cm^{-1}) is linearly related to the mineral content of the tissue as determined by ash weight (Faibish et al. 2005). (**C**) Images of crystallinity (crystal size/perfection) distribution in in the same bone of KO and WT mice. 1 pixel ~6.3 µm. The "crystallinity" parameter is calculated from the peak height intensity of subbands at 1030 cm^{-1} and 1020cm^{-1} and is correlated to the particle size as determined by X-ray diffraction (Boskey 2006). The color scales correspond to the values for the parameter shown, where blue is lowest and red is highest.

FIGURES 3B AND 3C show FTIR images and their corresponding histograms from the cortical bone in a knockout (KO) mouse that lacks the SIBLING protein DMP1 (dentin matrix protein 1) compared to those of its age- and sex-matched wild-type (WT) litter mate. The images show that the mineral content is decreased and crystallinity is increased in the bones of the KO mouse. These images led to the suggestion that DMP1 is important for both initiation of mineral for-

mation and regulation of mineral accumulation (Ling et al. 2005). DMP1 depletion has recently been shown to alter phosphate metabolism, adding new dimensions to its role in mineralization (Lorenz-Depiereux et al. 2006; Feng et al. 2006). Computer modeling also indicates how DMP1 and other anionic matrix proteins may interact with mineral crystals and crystal nuclei (Huq et al. 2005), thus controlling crystal size and shape.

CLINICAL RELEVANCE

Knowledge of mineralization processes and mechanisms in bones and teeth is important for the prevention and treatment of both common and rare diseases, ranging from osteoporosis to dental caries. Animal models often provide insight into human diseases with similar characteristics. Conversely, suggestions that a human disease may involve a particular genetic abnormality have, in some cases, led to the development of animal models that can be used to study the effects of proposed therapies and to perform detailed analyses that cannot be done in humans. For example, mice lacking a protein related to a lipoprotein receptor had decreased bone density, providing a model that could be used for the study of osteoporosis (Baldock and Eisman 2004). Our understanding of the mineral differences in mutant animal models and the comparison of these changes to bone diseases in larger animal models have provided novel insights into the disease process and new therapeutic goals.

There are a variety of human diseases in which altered mineral properties occur in bones and teeth. Examples of these mineral changes are summarized in Table 2, which includes frequently encountered diseases such as osteoporosis and osteomalacia and less-common diseases such as osteopetrosis, osteonecrosis, and osteogenesis imperfecta and odontogenesis imperfecta. Some of these diseases are due to genetic abnormalities, but they may also be attributed, to varying degrees, to environmental factors such as diet, exposure to sunlight, and exercise (Ralston and de Crombrugghe 2006).

FUTURE DIRECTIONS

Scientists and engineers are working together with clinicians to design new materials that restore function and repair or replace mineralized tissues damaged by disease or injury (Tuan 2004; Fong et al. 2005; Jones et al. 2007). Despite the extensive knowledge base that allows such tissues to be engineered, there are still unsolved questions about bone and tooth mineral and the mineralization process in these tissues. For example, what factors control mineral deposition at discrete sites in normally mineralized tissues and not in others? Which trace elements are beneficial or harmful when incorporated in bones and teeth, in what chemical species form do they occur, and at what concentrations? Which factors and extracellular matrix proteins are essential for directing the process of mineralization, and which are redundant? Can bone lost to disease and repaired by a functional material attain the mechanical and biological properties of the original material? Which therapeutics will be able to restore diseased bones and teeth to their normal function? What role do stem cells play in controlling mineralization? While some of these questions may seem redundant, they set the stage for many future investigations. Mineralogists and geochemists interested in investigating nanocrystals will help to determine the answer to these questions.

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Table 2 TYPICAL MINERAL CHANGES IN HUMAN BONE AND DENTAL DISEASES RELATIVE TO AGE AND SEX-MATCHED HEALTHY INDIVIDUALS

Disease	Description	Prevalence	Mineral Content	Crystal Size	Other Features and Relevant Review
Osteoporosis	Increased porosity with tendency to fracture	High	Variable	Increased	Collagen maturity increased (Boskey et al. 2006)
Amelogenesis imperfecta	Impaired enamel mineralization	High	Decreased	Variable	Hypomineralization; oftenX-linked (higher prevalence in males) (Robinson et al. 2003)
Osteomalacia	Poorly mineralized bone with tendency to fracture	High	Decreased	Increased	Associated with vitamin D deficiency (Faibish et al. 2005)
Osteogenesis imperfecta	Brittle bone disease due to abnormal collagen synthesis	Low	Decreased	Decreased	Abnormal collagen gene expression (Zhu et al. 2007)
Osteopetrosis	Rock-like bone with increased tendency to fracture	Low	Increased	Decreased	Impaired bone remodeling (Boskey et al. 2006)
Osteonecrosis	Dead bone	Low	Increased	Variable	Lack of viable cells (Weinstein et al. 2000)
Renal osteodystrophy	Kidney malfunction leading to osteoporotic bone	Low	Decreased	Increased	(Sanchez 2006)

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