

37 - SECTION 4 Disorders of Bone and Mineral Metabolism

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Bone and Mineral

Metabolism in Health

and Disease F. Richard Bringhurst, Henry M. Kronenberg,

Eva S. Liu, Marc N. Wein BONE STRUCTURE AND METABOLISM Bone is a dynamic tissue that is remodeled constantly throughout life. The arrangement of compact and cancellous bone provides strength and density suitable for both mobility and protection. Compact or cortical bone forms the roughly cylindrical shell of long bones; cancellous or trabecular bone forms the plate-like meshwork that internally supports the cortical shell. In addition, bone provides a reservoir for calcium, magnesium, phosphorus, sodium, and other ions necessary for homeostatic functions. Bone also hosts and regulates hematopoiesis by providing niches for hematopoietic cell proliferation and differentiation. The skeleton is highly vascular and receives ~10% of the cardiac output. Remodeling of bone is accomplished by two distinct cell types: osteoblasts produce bone matrix, and osteoclasts resorb the matrix. The activities of these cells are coordinated by osteocytes, long-lived regulatory cells embedded within bone matrix. The extracellular components of bone consist of a solid mineral phase in close association with an organic matrix, of which 90–95% is type I collagen (Chap. 425). The noncollagenous portion of the organic matrix is heterogeneous and contains serum proteins such as albumin as well as many locally produced proteins, whose functions are incompletely understood. Those proteins include cell attachment/signaling proteins such as thrombospondin, osteopontin, and fibronectin; calcium-binding proteins such as matrix gla protein and osteocalcin; and proteoglycans such as biglycan and decorin. Some of the proteins organize collagen fibrils; others influence mineralization and binding of the mineral

phase to the matrix. The mineral phase is made up of calcium and phosphate and is best characterized as a poorly crystalline hydroxyapatite. The mineral phase of bone is deposited initially in intimate relation to the collagen fibrils and is laid down in specific locations in the “holes” between the collagen fibrils. This architectural arrangement of mineral and matrix results in a two-phase material well suited to withstand mechanical stresses. The organization of collagen influences the amount and type of mineral phase formed in bone. Although the primary structures of type I collagen in skin and bone tissues are similar, there are differences in posttranslational modifications and distribution of intermolecular cross-links. The holes in the packing structure of the collagen are larger in mineralized collagen of bone and dentin than in unmineralized collagens such as those in tendon. Single amino acid substitutions in the helical portion of either the $\alpha 1$ (COL1A1) or $\alpha 2$ (COL1A2) chains of type I collagen disrupt the organization of bone in the disease, osteogenesis imperfecta. The severe skeletal fragility associated with this group of disorders highlights the importance of the fibrillar matrix in the structure of bone (Chap. 425). Osteoblasts synthesize and secrete the organic matrix and regulate its mineralization. They are derived from cells of mesenchymal origin (Fig. 421-1A). Osteoblast precursors derive from the periosteum, the bone marrow, or the hypertrophic chondrocytes at the end of the growth plate. Active osteoblasts are found on the surface of newly forming bone. As an osteoblast secretes matrix, which then is mineralized, the cell may become an osteocyte, still connected with its nutrient supply through a series of canaliculi. Osteocytes account for the vast majority of the cells in bone. They are thought to be the

mechanosensors that communicate signals to surface osteoblasts and osteoclasts and their progenitors through the canalicular network and thereby serve as master regulators of bone formation and resorption. Osteocytes also secrete fibroblast growth factor 23 (FGF23), a major hormonal regulator of phosphate metabolism (see below). Mineralization of the matrix, both in trabecular bone and in osteons of compact cortical bone (Haversian systems), begins soon after the matrix is secreted (primary mineralization) but is not completed for several weeks or even longer (secondary mineralization). Although this mineralization takes advantage of the high concentrations of calcium and phosphate, already near saturation in serum, mineralization is a carefully regulated process that is dependent on the activity of osteoblast-derived alkaline phosphatase, which probably works by hydrolyzing inhibitors of mineralization, such as pyrophosphate.

Bone and Mineral Metabolism in Health and Disease

CHAPTER 421 Genetic studies in humans and mice have identified several key genes that control osteoblast development. Runx2 is a transcription factor expressed specifically in chondrocyte (cartilage cells) and osteoblast progenitors as well as in hypertrophic chondrocytes and mature osteoblasts. Runx2 regulates the expression of several important osteoblast proteins, including osterix (SP7) (another transcription factor needed for osteoblast maturation), osteopontin, bone sialoprotein, type I collagen, osteocalcin, and receptor-activator of nuclear factor (NF)- κ B (RANK) ligand. Runx2 expression is regulated in part by bone morphogenetic proteins (BMPs). Runx2-deficient mice are devoid of osteoblasts, whereas mice with a deletion of only one allele (Runx2 +/–) exhibit a delay in formation of the clavicles and some cranial bones. The latter abnormalities are similar to those in the human disorder cleidocranial dysplasia, which is also caused by heterozygous inactivating mutations in Runx2. The paracrine signaling molecule, Indian hedgehog (Ihh), also plays a critical role in osteoblast development, as evidenced by Ihh-deficient mice that lack osteoblasts in the type of bone formed on a cartilage mold (endochondral ossification). Signals

originating from members of the wnt family of paracrine factors are also important for osteoblast proliferation and differentiation. Osteocytes regulate osteoblasts partly by secreting a potent inhibitor of wnt signaling called sclerostin. Numerous other growth-regulatory factors affect osteoblast function, including the three closely related transforming growth factor β s, fibroblast growth factors (FGFs) 2 and 18, platelet-derived growth factor, and insulin-like growth factors (IGFs) I and II. Hormones such as parathyroid hormone (PTH) and 1,25-dihydroxyvitamin D [1,25(OH)₂D] activate receptors expressed by osteoblasts to assure mineral homeostasis and influence a variety of bone cell functions. Osteoclasts that resorb bone (see below) also regulate osteoblasts by releasing growth factors from bone matrix and by synthesizing proteins that can directly regulate osteoblastogenesis. Resorption of bone is carried out mainly by osteoclasts, multinucleated cells that are formed by fusion of cells derived from the common precursor of macrophages and osteoclasts. Thus, these cells derive from the hematopoietic lineage, quite different from the mesenchymal lineage cells that become osteoblasts. Multiple factors that regulate osteoclast development have been identified (Fig. 421-1B). Factors produced by osteocytes, osteoblasts, and marrow stromal cells allow cells of the osteoblast lineage to control osteoclast development and activity. Macrophage colony-stimulating factor (M-CSF) plays a critical role during several steps in the pathway and ultimately leads to fusion of osteoclast progenitor cells to form multinucleated, active osteoclasts. RANK ligand, a member of the tumor necrosis factor (TNF) family, is expressed on the surface of osteocytes, osteoblasts, and stromal fibroblasts. In a process involving cell-cell interactions, RANK ligand binds to the RANK receptor on osteoclast progenitors, stimulating osteoclast differentiation and activation. Alternatively, a soluble decoy receptor, referred to as osteoprotegerin (OPG), can bind RANK ligand and inhibit osteoclast differentiation. Several growth factors and cytokines (including interleukins 1, 6, and 11; TNF; and interferon γ) modulate osteoclast differentiation and function. Most hormones that influence osteoclast function do not target these cells directly but instead target cells of the osteoblast lineage to increase production of M-CSF and RANK. Both PTH and 1,25(OH)₂D increase osteoclast number and

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