NOT TO BE MISSED

Clinical and Basic Research Papers – December 2004 Selections

Ego Seeman, Clinical Editor
Gordon J. Strewler, Editor

Bone Modeling and Remodeling


Removal of the gene for caspase-3 blocks a key step in apoptosis and causes delayed skeletal ossification; casp3(+/-) mice have low bone mass. Replicative senescence of osteoblast precursors is increased by deficiency of caspase-3, perhaps because of overexpression of p21; thus, there may be a tradeoff of osteoblast senescence for protection against apoptosis. A caspase-3 inhibitor accelerates bone loss after ovariectomy. The balance between senescence and apoptosis in osteoblasts needs to be understood. —GJS


MMP-13 (collagenase-3) is one of the principal extracellular proteases of cartilage and bone. Removal of MMP-13 from cartilage causes delayed exit of hypertrophic chondrocytes, broadens the hypertrophic cartilage zone, and delays ossification of growth cartilage. Trabecular bone is increased, and conditional inactivation of MMP-13 specifically in cartilage and bone shows that the trabecular phenotype is independent of cartilage matrix degradation. MMP-13 is synergistic with MMP-9; double knockout mice have a severe phenotype. —GJS

Pathophysiology


The bioactive lipid lysophosphatidic acid has receptors on and is a mitogen for breast cancer cells. Bone metastasis of breast cancer cells is specifically enhanced by expression of lysophosphatidic acid receptors. Breast cancer cells induce the aggregation of platelets, an important source of lysophosphatidic acid. Inhibition of platelet aggregation with integrilin, an antagonist of the platelet thrombin receptor αIIbβ3, markedly inhibits bone metastasis. Similar results were shown using CHO cells. The results, if they can be generalized to other tumor cells, point to platelets as a possible point of attack on bone metastasis. —GJS
**BoneKEy-Osteovision. 2005 January;2(1):1-5**
http://www.bonekey-ibms.org/cgi/content/full/ibmske;2/1/1
DOI: 10.1138/20050142


  Central control of bone mass involves the β-adrenergic nervous system in bone. In a carefully controlled study, these investigators demonstrate a profound reduction in innervation density in rat tibiae after ovariectomy. Innervation of muscle and skin was unaffected. This work opens to investigation possible neural mediation of bone loss in estrogen deficiency. —GJS


  β-catenin was removed from all progenitors of cartilage and bone cells using Dermo1-Cre. Osteoblasts are absent, because canonical wnt signaling is abolished. Genetic results in mice and experiments in C3H10T1/2 cells are consistent with wnt being downstream of the hedgehog signal that is required for osteogenesis; the wnt involved in osteogenesis in the perichondrium is likely to be wnt7b. A landmark study that identifies the role of wnt signaling in bone modeling, with implications for bone remodeling. —GJS


  Why and how bones break remains poorly defined -- so poorly understood that we don't even appreciate that we don't know. This study describes ex vivo fracture experiments to quantitatively assess the effect of aging on the fracture toughness properties of human cortical bone in the longitudinal direction. Both the ex vivo crack-initiation and crack-growth toughness deteriorate with age; initiation toughness decreases some 40% over six decades (from 40 to 100 years), while growth toughness is eliminated. —ES


  Osteosarcomas are generally composed of poorly differentiated and rapidly proliferative cells. Poorly differentiated osteosarcoma cell lines have either reduced runx2 protein or impaired runx2 action, because functional retinoblastoma protein (pRb) is lost. Introduction of runx2 induces growth arrest by a mechanism involving induction of p27kip1. Growth and differentiation in osteosarcoma cell lines are reciprocal, with runx2 induction of p27kip1 and a direct interaction of pRb and runx2 as key control points. —GJS

**Physiology**

◆ Bouillon R, Bex M, Vanderschueren D, Boonen S. Estrogens are essential for male pubertal periosteal bone expansion. *J Clin Endocrinol Metab*. 2004 Dec;89(12):6025-9. [Abstract] [Full Text]

  The mechanisms regulating periosteal apposition are not well defined. Androgens are thought to account for greater periosteal apposition in males, and so greater bone size than in females. Another mechanism may be that testosterone is aromatized to estrogen, and estrogen effects on insulin-like growth factor 1 may promote periosteal bone formation. In this study, estrogen given to a 17-year-old boy with congenital aromatase
deficiency, until the age of 20 years, normalized total and free testosterone and reduced remodeling. BMD of the spine and femoral neck increased, but pQCT of the ultradistal radius revealed no gain of trabecular or cortical volumetric BMD. The authors infer that the increase in areal BMD is driven by an increase in periosteal apposition and bone size, which requires estrogen. —ES

**Treatment and Drug Effects**


  In the PTH-treated rats with collagen-induced arthritis (CIA), the incidence and severity of arthritis was similar to vehicle-treated rats with CIA. The decrease of BMD caused by CIA was suppressed by PTH. Bone formation was higher and bone resorption was lower in the PTH-treated arthritic rats. Mechanical properties were also maintained in the PTH-treated rats. —ES


  Treatment with beta-blockers has been reported to be associated with higher BMD and lower fracture risk in some (but not all) studies. In this study, treatment was associated with a threefold increased fracture risk, a lower serum osteocalcin, and no difference in BMD. The controversy will be resolved when a randomized double-blind placebo controlled trial is performed with fracture rate as an endpoint. Until then, the findings of all studies with lower levels of evidence will be too difficult to interpret. —ES


  Osteoarthritis is a degenerative disease in which the resiliency of cartilage is compromised by loss of glycosaminoglycans (GAGs). Here a delivery system is devised to express the GAG-synthesizing enzyme β1,3-glucuronosyltransferase-I in chondrocytes in culture and in cartilage explants. Expression of the enzyme protects cartilage explants from loss of GAGs after treatment with interleukin 1. —GJS

**Reviews, Perspectives, and Editorials**


Other Studies of Potential Interest


- Green AD, Colon-Emeric CS, Bastian L, Drake MT, Lyles KW. Does this woman have osteoporosis? *JAMA.* 2004 Dec 15;292(23):2890-900. [Abstract]


