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NOT TO BE MISSED

Clinical and Basic Research Papers – December 2004 Selections

Ego Seeman, Clinical Editor
Gordon J. Strewler, Editor

Bone Modeling and Remodeling

Miura M, Chen XD, Allen MR, Bi Y, Gronthos S, Seo BM, Lakhani S, Flavell RA, Feng XH, Robey PG, Young M, Shi S. A crucial role of caspase-3 in osteogenic differentiation of bone marrow stromal stem cells. *J Clin Invest.* 2004 Dec;114(12):1704-13. [Abstract] [Full Text]

> *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*

Stickens D, Behonick DJ, Ortega N, Heyer B, Hartenstein B, Yu Y, Fosang AJ, Schorpp-Kistner M, Angel P, Werb Z. Altered endochondral bone development in matrix metalloproteinase 13-deficient mice. *Development.* 2004 Dec;131(23):5883-95. [Abstract]

Inada M, Wang Y, Byrne MH, Rahman MU, Miyaura C, Lopez-Otin C, Krane SM. Critical roles for collagenase-3 (Mmp13) in development of growth plate cartilage and in endochondral ossification. *Proc Natl Acad Sci U S A.* 2004 Dec 7;101(49):17192-7. [Abstract] [Full Text]

> *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

Boucharaba A, Serre CM, Gres S, Saulnier-Blache JS, Bordet JC, Guglielmi J, Clezardin P, Peyruchaud O. Platelet-derived lysophosphatidic acid supports the progression of osteolytic bone metastases in breast cancer. *J Clin Invest.* 2004 Dec;114(12):1714-25. [Abstract] [Full Text]

> *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*

Burt-Pichat B, Lafage-Proust MH, Duboeuf F, Laroche N, Itzstein C, Vico L, Delmas PD, Chenu C. Dramatic decrease of innervation density in bone after ovariectomy. *Endocrinology.* 2005 Jan;146(1):503-10. [Abstract] [Full Text]

> *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*

Hu H, Hilton MJ, Tu X, Yu K, Ornitz DM, Long F. Sequential roles of Hedgehog and Wnt signaling in osteoblast development. *Development.* 2005 Jan;132(1):49-60. [Abstract]

> *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*

Nalla RK, Kruzic JJ, Kinney JH, Ritchie RO. Effect of aging on the toughness of human cortical bone: evaluation by R-curves. *Bone.* 2004 Dec;35(6):1240-6. [Abstract]

> *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*

Thomas DM, Johnson SA, Sims NA, Trivett MK, Slavin JL, Rubin BP, Waring P, McArthur GA, Walkley CR, Holloway AJ, Diyagama D, Grim JE, Clurman BE, Bowtell DD, Lee JS, Gutierrez GM, Piscopo DM, Carty SA, Hinds PW. Terminal osteoblast differentiation, mediated by runx2 and $p27^{kip1}$, is disrupted in osteosarcoma. *J Cell Biol.* 2004 Dec 6;167(5):925-34. [Abstract] [Full Text]

> *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 $p27^{kip1}$. Growth and differentiation in osteosarcoma cell lines are reciprocal, with runx2 induction of $p27^{kip1}$ 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

Fukata S, Hagino H, Okano T, Yamane I, Kameyama Y, Teshima R. Effect of intermittent administration of human parathyroid hormone on bone mineral density and arthritis in rats with collagen-induced arthritis. *Arthritis Rheum.* 2004 Dec;50(12):4060-9. [Abstract]

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

Rejnmark L, Vestergaard P, Kassem M, Christoffersen BR, Kolthoff N, Brixen K, Mosekilde L. Fracture risk in perimenopausal women treated with Beta-blockers. *Calcif Tissue Int.* 2004 Nov;75(5):365-72. [Abstract]

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

Venkatesan N, Barre L, Benani A, Netter P, Magdalou J, Fournel-Gigleux S, Ouzzine M. Stimulation of proteoglycan synthesis by glucuronosyltransferase-I gene delivery: A strategy to promote cartilage repair. *Proc Natl Acad Sci U S A.* 2004 Dec 28;101(52):18087-92. [Abstract] [Full Text]

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

Beaudreuil J, Balasubramanian S, Chenais J, Taboulet J, Frenkian M, Orcel P, Jullienne A, Horne WC, de Vernejoul MC, Cressent M. Molecular characterization of two novel isoforms of the human calcitonin receptor. *Gene.* 2004 Dec 8;343(1):143-51. [Abstract]

Berenson JR. Recommendations for zoledronic acid treatment of patients with bone metastases. *Oncologist.* 2005;10(1):52-62. [Abstract]

Calvo MS, Whiting SJ, Barton CN. Vitamin D fortification in the United States and Canada: current status and data needs. *Am J Clin Nutr.* 2004 Dec;80(6 Suppl):1710S-6S. [Abstract]

Cantorna MT, Zhu Y, Froicu M, Wittke A. Vitamin D status, 1,25-dihydroxyvitamin D_3, and the immune system. *Am J Clin Nutr.* 2004 Dec;80(6 Suppl):1717S-20S. [Abstract]

Dawson-Hughes B. Racial/ethnic considerations in making recommendations for vitamin D for adult and elderly men and women. *Am J Clin Nutr.* 2004 Dec;80(6 Suppl):1763S-6S. [Abstract]

DeLuca HF. Overview of general physiologic features and functions of vitamin D. *Am J Clin Nutr.* 2004 Dec;80(6 Suppl):1689S-96S. [Abstract]

Fleet JC. Genomic and proteomic approaches for probing the role of vitamin D in health. *Am J Clin Nutr.* 2004 Dec;80(6 Suppl):1730S-4S [Abstract]

Greer FR. Issues in establishing vitamin D recommendations for infants and children. *Am J Clin Nutr.* 2004 Dec;80(6 Suppl):1759S-62S. [Abstract]

Heaney RP. Functional indices of vitamin D status and ramifications of vitamin D deficiency. *Am J Clin Nutr.* 2004 Dec;80(6 Suppl):1706S-9S. [Abstract]

Holick MF. Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. *Am J Clin Nutr.* 2004 Dec;80(6 Suppl):1678S-88S. [Abstract]

Logothetis CJ, Lin SH. Osteoblasts in prostate cancer metastasis to bone. *Nat Rev Cancer.* 2005 Jan;5(1):21-8. [Abstract]

Pawley N, Bishop NJ. Prenatal and infant predictors of bone health: the influence of vitamin D. *Am J Clin Nutr.* 2004 Dec;80(6 Suppl):1748S-51S. [Abstract]

Pettifor JM. Nutritional rickets: deficiency of vitamin D, calcium, or both? *Am J Clin Nutr.* 2004 Dec;80(6 Suppl):1725S-9S. [Abstract]

Raiten DJ, Picciano MF. Vitamin D and health in the 21st century: bone and beyond. Executive summary. *Am J Clin Nutr.* 2004 Dec;80(6 Suppl):1673S-7S. [Abstract]

Santoro M, Melillo RM, Carlomagno F, Vecchio G, Fusco A. Minireview: RET: normal and abnormal functions. *Endocrinology.* 2004 Dec;145(12):5448-51. [Abstract] [Full Text]

Specker B. Vitamin D requirements during pregnancy. *Am J Clin Nutr.* 2004 Dec;80(6 Suppl):1740S-7S. [Abstract]

Tangpricha V, Turner A, Spina C, Decastro S, Chen TC, Holick MF. Tanning is associated with optimal vitamin D status (serum 25-hydroxyvitamin D concentration) and higher bone mineral density. *Am J Clin Nutr.* 2004 Dec;80(6):1645-9. [Abstract]

Weaver CM, Fleet JC. Vitamin D requirements: current and future. *Am J Clin Nutr.* 2004 Dec;80(6 Suppl):1735S -9S. [Abstract]

Weinstein LS, Liu J, Sakamoto A, Xie T, Chen M. Minireview: GNAS: normal and abnormal functions. *Endocrinology.* 2004 Dec;145(12):5459-64. [Abstract] [Full Text]

Weisberg P, Scanlon KS, Li R, Cogswell ME. Nutritional rickets among children in the United States: review of cases reported between 1986 and 2003. *Am J Clin Nutr.* 2004 Dec;80(6 Suppl):1697S-705S. [[Abstract]

Welsh J. Vitamin D and breast cancer: insights from animal models. *Am J Clin Nutr.* 2004 Dec;80(6 Suppl):1721S-4S. [[Abstract]

Other Studies of Potential Interest

Amcheslavsky A, Zou W, Bar-Shavit Z. Toll-like receptor 9 regulates tumor necrosis factor-alpha expression by different mechanisms. Implications for osteoclastogenesis. *J Biol Chem.* 2004 Dec 24;279(52):54039-45. [Abstract] [Full Text]

Boström K, Zebboudj AF, Yao Y, Lin TS, Torres A. Matrix GLA protein stimulates VEGF expression through increased transforming growth factor-beta1 activity in endothelial cells. *J Biol Chem.* 2004 Dec 17;279(51):52904-13. [Abstract] [Full Text]

Chaisson ML, Branstetter DG, Derry JM, Armstrong AP, Tometsko ME, Takeda K, Akira S, Dougall WC. Osteoclast differentiation is impaired in the absence of inhibitor of kappa B kinase alpha. *J Biol Chem.* 2004 Dec 24;279(52):54841-8. [Abstract] [Full Text]

Crans GG, Silverman SL, Genant HK, Glass EV, Krege JH. Association of severe vertebral fractures with reduced quality of life: Reduction in the incidence of severe vertebral fractures by teriparatide. *Arthritis Rheum.* 2004 Dec;50(12):4028-34. [Abstract]

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]

Liu W, Xu D, Yang H, Xu H, Shi Z, Cao X, Takeshita S, Liu J, Teale M, Feng X. Functional identification of three receptor activator of NF-kappa B cytoplasmic motifs mediating osteoclast differentiation and function. *J Biol Chem.* 2004 Dec 24;279(52):54759-69. [Abstract] [Full Text]

Luo Q, Kang Q, Si W, Jiang W, Park JK, Peng Y, Li X, Luu HH, Luo J, Montag AG, Haydon RC, He TC. Connective tissue growth factor (CTGF) is regulated by Wnt and bone morphogenetic proteins signaling in osteoblast differentiation of mesenchymal stem cells. *J Biol Chem.* 2004 Dec 31;279(53):55958-68. [Abstract] [Full Text]

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Wang Y, Middleton F, Horton JA, Reichel L, Farnum CE, Damron TA. Microarray analysis of proliferative and hypertrophic growth plate zones identifies differentiation markers and signal pathways. *Bone.* 2004 Dec;35(6):1273-93. [Abstract]

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