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NOT TO BE MISSED

Clinical and Basic Research Papers – May 2007 Selections

Serge Ferrari, Associate Editor
Ego Seeman, Clinical Editor
Gordon J. Strewler, Editor

Bone Modeling and Remodeling

Ardeshirpour L, Dann P, Adams DJ, Nelson T, Vanhouten J, Horowitz MC, Wysolmerski JJ. Weaning triggers a decrease in RANKL expression, widespread osteoclast apoptosis and rapid recovery of bone mass after lactation in mice. *Endocrinology*. 2007 May 10; [Epub ahead of print]

> *Puberty, pregnancy and lactation are all states in which large amounts of calcium are incorporated into bone with minimal reliance on dietary calcium. Calcium is delivered to the newborn during lactation at the expense of bone loss that is completely reversible after weaning. In this paper, it is shown that within three days after weaning in mice there is a fall in RANKL levels, a dramatic wave of osteoclast apoptosis, and a fall in urinary CTX, with preservation of bone formation and rapid subsequent recovery of bone mass. How does the adaptation of bone to lactation and weaning differ from menopause – where, in contrast to lactation, estrogen-deficient bone loss is irreversible?* —GJS

Armstrong VJ, Muzylak M, Sunters A, Zaman G, Saxon LK, Price JS, Lanyon LE. Wnt/beta-catenin signaling is a component of osteoblastic bone cells' early responses to load-bearing, and requires estrogen receptor alpha. *J Biol Chem*. 2007 May 8; [Epub ahead of print]

> *There is now good evidence that the Wnt-LRP5 signaling pathway is an important mediator of the skeletal response to loading in vivo. This study attempts to relate these findings to the role of estrogens in the maintenance of the osteoblastic response to mechanical stimuli. Here it is shown that in the presence of a SERM or in the absence of estrogen receptor (ER)α, activation of the β-catenin pathway in osteoblasts by shear strain is reduced. Moreover, in vivo expression of genes related to the Wnt-LRP5 pathway was also reduced in the loaded tibia of ERα KO mice. These data suggest that loss of estrogen may lead to a lower Wnt-LRP5 response to mechanical stimulation, which in turn might contribute to the negative bone mineral balance after menopause. Most interestingly, this study provides new insights into the mechanisms by which estrogen could elicit some anabolic bone responses (i.e., by favoring β-catenin signaling).* —SF

Eijken M, Swagemakers S, Koedam M, Steenbergen C, Derkx P, Uitterlinden AG, van der Spek PJ, Visser JA, de Jong FH, Pols HA, van Leeuwen JP. The activin A-follistatin system: potent regulator of human extracellular matrix mineralization. *FASEB J*. 2007 Apr 20; [Epub ahead of print]

> *Through an elegant series of experiments the authors provide compelling evidence that activin A acts as an autocrine inhibitor of osteoblast differentiation and mineralization, the latter not only by bone cells. This is to be related to the recent discovery (Nat Genet. 2006 May;38(5):525-7) that activin receptor (ACVR1) mutations cause fibrodysplasia ossificans progressiva, i.e., massive ectopic calcifications.* —SF

Wang Y, Wan C, Deng L, Liu X, Cao X, Gilbert SR, Bouxsein ML, Faugere MC, Guldberg RE, Gerstenfeld LC, Haase VH, Johnson RS, Schipani E, Clemens TL. The hypoxia-inducible factor alpha pathway couples angiogenesis to osteogenesis during skeletal development. *J Clin Invest*. 2007 Jun 1;117(6):1616-26. [Abstract] [Full Text]

Towler DA. Vascular biology and bone formation: hints from HIF. *J Clin Invest*. 2007 Jun;117(6):1477-80. [Abstract] [Full Text]

> *Abrogation of hypoxia-sensing has major effects on chondrogenesis but little is known about hypoxia in bone. Here, removal of the VHL gene from osteoblasts upregulates the hypoxia-responsive transcription factors HIF1-α and HIF2-α. Massive overgrowth of long bones (but not the skull bones) results; removal of HIF1-α has a reciprocal effect. This bony overgrowth is associated with high VEGF levels and massive angiogenesis, and in bone explants angiogenesis can be blocked by VEGF antibodies. Removal of VHL from osteoblasts thus induces angiogenesis and bone overgrowth by cell non-autonomous mechanisms. The authors propose that in the pseudohypoxic state that results from upregulation of HIF1-α, exuberant angiogenesis induced by VEGF introduces osteoblast precursors into bone, leading to excessive bone formation, but this remains to be demonstrated directly.* —GJS

Epidemiology

Burge R, Dawson-Hughes B, Solomon DH, Wong JB, King A, Tosteson A. Incidence and economic burden of osteoporosis-related fractures in the United States, 2005–2025. *J Bone Miner Res*. 2007 Mar;22(3):465–75. [Abstract]

> *The burden of fragility fractures in the United States was >2 million fractures, costing about $17 billion in 2005. Total costs including prevalent fractures are > $19 billion. Men account for 29% of fractures and 25% of costs. Total incident fractures by site were vertebral (27%) and hip (14%) with the remaining ~50% being wrist (19%), pelvic (7%), and other (33%). Total costs by fracture type were vertebral (6%), hip (72%), wrist (3%), pelvic (5%), and other (14%). By 2025, annual fractures and costs are projected to rise by almost 50%. Fracture prevention should address all skeletal sites.* —ES

Genetics

Wellcome Trust Case Control Consortium. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. *Nature*. 2007 Jun 7;447(7145):661-78. [Abstract]

> *No bone diseases studied here, but the ultimate demonstration of what a combination of the most advanced genotyping technologies, biostatistics and large case-control cohorts (and many millions of dollars!) can do to identify susceptibility loci for common diseases. At one stroke, the Trust performed a genome-wide association (GWA) analysis of nearly 500k SNPs in 3,000 controls and about 2,000 affected individuals for each of the seven following disorders: bipolar disorder, coronary artery disease, Crohn's disease, rheumatoid arthritis, type 1 diabetes, type 2 diabetes and hypertension. One or more gene loci (21 in total) were found to be associated with each of these disorders, except hypertension, at the $p < 5 \times 10^{-7}$ level of significance (not the least interesting aspect of this paper is the discussion about the issue of multiple testing). As several groups have now performed 500k GWA in osteoporosis (yet to be reported), reading of the Trust paper is essential to understand the power and limitations of this approach, including the*

fact that gene variants contributing to less than 20% of the increase in risk for the disease are unlikely to be detected, despite very large numbers of individuals. —SF

Physiology and Metabolism

Cianferotti L, Cox M, Skorija K, Demay MB. Vitamin D receptor is essential for normal keratinocyte stem cell function. *Proc Natl Acad Sci U S A*. 2007 May 29;104(22):9428-33. [Abstract] [Full Text]

Absence of the VDR is associated with alopecia in humans and mice but vitamin D deficiency is not, suggesting that the VDR has a ligand-independent role in hair follicle development. In this paper it is shown that keratinocyte stem cells in the VDR-deficient hair follicle niche have impaired self-renewal. Wnt signaling, known to be important in hair follicle development, is also impaired – β-catenin fails to induce anagen in VDR-deficient hair follicles. In co-immunoprecipitation experiments, the unliganded VDR participates in a complex with β-catenin and Lef1. Wnt signaling in stem cells requires the VDR, at least partly as a component of transcriptional complexes. —GJS

Treatment and Drug Effects

Carter PH, Liu RQ, Foster WR, Tamasi JA, Tebben AJ, Favata M, Staal A, Cvijic ME, French MH, Dell V, Apanovitch D, Lei M, Zhao Q, Cunningham M, Decicco CP, Trzaskos JM, Feyen JH. Discovery of a small molecule antagonist of the parathyroid hormone receptor by using an N-terminal parathyroid hormone peptide probe. *Proc Natl Acad Sci U S A*. 2007 Apr 17;104(16):6846-51. [Abstract] [Full Text]

The chase for an orally available PTH agonist (and/or antagonist) continues. This study first describes optimization of PTH(1-14), the shortest PTH receptor agonist developed so far, so that both the in vitro and in vivo properties of the optimized compound get closer to PTH(1-34). Then this compound was used to screen a library of chemical compounds, leading to identification of a small molecule with selective antagonistic properties for the PTH receptor. The structure of this antagonist is compatible with its oral administration. Future studies will tell whether this oral molecule is effective as a PTH antagonist in vivo and also whether it can be modified to become an oral agonist. —SF

Reid IR, Cundy T, Grey AB, Horne A, Clearwater J, Ames R, Orr-Walker BJ, Wu F, Evans MC, Gamble GD, King A. Addition of monofluorophosphate to estrogen therapy in postmenopausal osteoporosis - a randomized controlled trial. *J Clin Endocrinol Metab*. 2007 Apr 17; [Epub ahead of print]

Is fluoride back? Should lower doses be assessed in large clinical trials? 80 women with osteoporosis taking estrogen were randomized to monofluorophosphate (fluoride 20 mg/day) or placebo over 4 years. There were large increases in spine BMD. Hyperosteoidosis was present in biopsies from 5 of 7 subjects, with osteomalacia in 2 of 7. The hazards ratio for vertebral fractures was 0.20 (95% confidence interval, 0.05-1.30) and the incidence rate ratio was 0.12 (95% confidence interval, 0.06-0.23, P<0.01). The hazards ratio for non-vertebral fractures was 3.3 (95% CI, 0.8-12.0). —ES

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Reviews, Perspectives and Editorials

Glass DA, Karsenty G. In vivo analysis of Wnt signaling in bone. *Endocrinology*. 2007 Jun;148(6):2630-4.

Hofbauer LC, Brueck CC, Singh SK, Dobnig H. Osteoporosis in patients with diabetes mellitus. *J Bone Miner Res*. 2007 May 14; [Epub ahead of print] [Abstract]

Jilka RL. Molecular and cellular mechanisms of the anabolic effect of intermittent PTH. *Bone*. 2007 Jun;40(6):1434-46. [Abstract]

Jilka RL, Weinstein RS, Parfitt AM, Manolagas SC. Quantifying osteoblast and osteocyte apoptosis: challenges and rewards. *J Bone Miner Res*. 2007 Jun 1; [Epub ahead of print] [Abstract]

Lei SF, Jiang H, Deng FY, Deng HW. Searching for genes underlying susceptibility to osteoporotic fracture: current progress and future prospect. *Osteoporos Int*. 2007 May 30; [Epub ahead of print] [Abstract]

Pittas AG, Lau J, Hu FB, Dawson-Hughes B. The role of vitamin d and calcium in type 2 diabetes. A systematic review and meta-analysis. *J Clin Endocrinol Metab*. 2007 Jun;92(6):2017-29. [Abstract] [Full Text]

Other Studies of Potential Interest

Baldock PA, Allison SJ, Lundberg P, Lee NJ, Slack K, Lin EJ, Enriquez RF, McDonald MM, Zhang L, During MJ, Little DG, Eisman JA, Gardiner EM, Yulyaningsih E, Lin S, Sainsbury A, Herzog H. Novel role of Y1 receptors in the coordinated regulation of bone and energy homeostasis. *J Biol Chem*. 2007 May 9; [Epub ahead of print]

Ball SG, Shuttleworth CA, Kielty CM. Vascular endothelial growth factor can signal through platelet-derived growth factor receptors. *J Cell Biol*. 2007 May 7;177(3):489-500. [Abstract] [Full Text]

Barna M, Niswander L. Visualization of cartilage formation: insight into cellular properties of skeletal progenitors and chondrodysplasia syndromes. *Dev Cell*. 2007 Jun;12(6):931-41. [Abstract]

Buckbinder L, Crawford DT, Qi H, Ke HZ, Olson LM, Long KR, Bonnette PC, Baumann AP, Hambor JE, Grasser WA, Pan LC, Owen TA, Luzzio MJ, Hulford CA, Gebhard DF, Paralkar VM, Simmons HA, Kath JC, Roberts WG, Smock SL, Guzman-Perez A, Brown TA, Li M. Proline-rich tyrosine kinase 2 regulates osteoprogenitor cells and bone formation, and offers an anabolic treatment approach for osteoporosis. *Proc Natl Acad Sci U S A*. 2007 May 30; [Epub ahead of print]

Chattopadhyay N, Quinn SJ, Kifor O, Ye C, Brown EM. The calcium-sensing receptor (CaR) is involved in strontium ranelate-induced osteoblast proliferation. *Biochem Pharmacol*. 2007 Apr 27; [Epub ahead of print] [Abstract]

Dackor RT, Fritz-Six KL, Smithies O, Caron KM. Receptor activity modifying proteins 2 and 3 have distinct physiological functions from embryogenesis to old age. *J Biol Chem*. 2007 Apr 30; [Epub ahead of print]

Guo RT, Cao R, Liang PH, Ko TP, Chang TH, Hudock MP, Jeng WY, Chen CK, Zhang Y, Song Y, Kuo CJ, Yin F, Oldfield E, Wang AH. Bisphosphonates target multiple sites in both cis- and trans-prenyltransferases. *Proc Natl Acad Sci U S A*. 2007 Jun 12;104(24):10022-7. [Abstract] [Full Text]

Huang MS, Morony S, Lu J, Zhang Z, Bezouglaia O, Tseng W, Tetradis S, Demer LL, Tintut Y. Atherogenic phospholipids attenuate osteogenic signaling by BMP-2 and PTH in osteoblasts. *J Biol Chem*. 2007 May 22; [Epub ahead of print]

Kim SY, Lee JY, Kim HY, Oh B, Kimm K, Kim HL, Park BL, Shin HD, Park EK, Koh JM, Kim GS. Association of KIT gene polymorphisms with bone mineral density in postmenopausal Korean women. *J Hum Genet*. 2007;52(6):502-9. [Abstract]

Lundberg P, Allison SJ, Lee N, Baldock PA, Brouard N, Rost S, Enriquez R, Sainsbury A, Lamghari M, Simmons P, Eisman JA, Gardiner EM, Herzog H. Greater bone formation of Y2 knockout mice is associated with increased osteoprogenitor numbers and altered Y1-receptor expression. *J Biol Chem*. 2007 May 9; [Epub ahead of print]

Nehring JA, Zierold C, Deluca HF. Lithocholic acid can carry out in vivo functions of vitamin D. *Proc Natl Acad Sci U S A*. 2007 Jun 12;104(24):10006-9. [Abstract] [Full Text]

Okoumassoun LE, Russo C, Denizeau F, Averill-Bates D, Henderson DJ. Parathyroid hormone-related protein (PTHrP) inhibits mitochondrial-dependent apoptosis through CK2. *J Cell Physiol*. 2007 Apr 18; [Epub ahead of print] [Abstract]

Ono N, Nakashima K, Schipani E, Hayata T, Ezura Y, Soma K, Kronenberg HM, Noda M. Constitutively active parathyroid hormone receptor signaling in cells in osteoblastic lineage suppresses mechanical unloading-induced bone resorption. *J Biol Chem*. 2007 May 11; [Epub ahead of print]

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Provot S, Zinyk D, Gunes Y, Kathri R, Le Q, Kronenberg HM, Johnson RS, Longaker MT, Giaccia AJ, Schipani E. Hif-1alpha regulates differentiation of limb bud mesenchyme and joint development. *J Cell Biol*. 2007 May 7;177(3):451-64. [Abstract] [Full Text]

Tai K, Dao M, Suresh S, Palazoglu A, Ortiz C. Nanoscale heterogeneity promotes energy dissipation in bone. *Nat Mater*. 2007 Jun;6(6):454-62. [Abstract]

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Yamashita T, Yao Z, Li F, Zhang Q, Badell IR, Schwarz EM, Takeshita S, Wagner EF, Noda M, Matsuo K, Xing L, Boyce BF. NF-kB p50 and p52 regulate RANKL and TNF-induced osteoclast precursor differentiation by activating c-Fos and NFATc1. *J Biol Chem*. 2007 Jun 22;282(25):18245-53. [Abstract] [Full Text]

Zhao Y, Ding S. A high-throughput siRNA library screen identifies osteogenic suppressors in human mesenchymal stem cells. *Proc Natl Acad Sci U S A*. 2007 Jun 5;104(23):9673-8. [Abstract] [Full Text]

Conflict of Interest: Dr. Ferrari reports that he receives research support from Amgen and consultancy/speaker's fees from Merck Sharp & Dohme, Eli Lilly, and Amgen. Dr. Seeman reports that he is an advisory committee member for Sanofi-Aventis, Eli Lilly, Merck Sharp & Dohme, Novartis, and Servier, and that he lectures occasionally at conference symposia for those companies. Dr. Strewler reports that no conflict of interest exists.