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NOT TO BE MISSED

Clinical and Basic Research Papers – March 2006 Selections

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

Bone Modeling and Remodeling

Abdallah BM, Haack-Sorensen M, Fink T, Kassem M. Inhibition of osteoblast differentiation but not adipocyte differentiation of mesenchymal stem cells by sera obtained from aged females. *Bone*. 2006 Mar 8; [Epub ahead of print] [Abstract]

> *The first 'abnormality' in the remodeling machinery leading to bone loss and bone fragility may be a decline in bone formation at the tissue and cellular levels; periosteal apposition declines after completion of longitudinal growth while mean wall thickness in the basic multicellular unit (reflecting synthesis of new bone) declines in midlife, if not sooner. The authors explore whether changes in the bone microenvironment contribute to impaired osteoprogenitor cell recruitment and differentiation. Effects of sera from 20-30 year-old and 70-84 year-old healthy female donors on human mesenchymal stem cell proliferation, differentiation into adipocytes and levels of adipocytic gene expression were no different, but 50% decreases in osteoblastic gene expression were observed in hMSC cultured in old donors, compared to sera from young donors (core binding factor/runt-related binding factor 2, alkaline phosphatase, collagen type I and osteocalcin).* —ES

Cobb J, Dierich A, Huss-Garcia Y, Duboule D. A mouse model for human short-stature syndromes identifies Shox2 as an upstream regulator of Runx2 during long-bone development. *Proc Natl Acad Sci U S A*. 2006 Mar 21;103(12):4511-5. [Abstract] [Full Text]

> *In humans, haploinsufficiency of the* SHOX *gene, as seen in Turner syndrome, is associated with short stature, however, the underlying pathophysiological mechanisms remained poorly understood.* Shox2*, the mouse paralog of* SHOX*, is highly expressed in the proximal domains of developing limbs. By generating a limb-specific* Shox2 *KO mouse, this study shows that absence of* Shox 2 *expression in limbs leads to the virtual absence of the humerus and femur. Moreover, analysis of in situ chondrocytic gene expression revealed that* Shox2 *functions upstream of* Runx2 *and* Indian hedgehog *(*Ihh*), its absence leading to a severe defect in chondrocyte differentiation. These findings further illustrate the complexity of transcriptional regulation at the growth plate, accounting for the variability in the relative length of long bones among tetrapods, and among humans potentially.* —SF

Lengner CJ, Steinman HA, Gagnon J, Smith TW, Henderson JE, Kream BE, Stein GS, Lian JB, Jones SN. Osteoblast differentiation and skeletal development are regulated by Mdm2-p53 signaling. *J Cell Biol*. 2006 Mar 13;172(6):909-21. [Abstract] [Full Text]

Zambetti GP, Horwitz EM, Schipani E. Skeletons in the p53 tumor suppressor closet: genetic evidence that p53 blocks bone differentiation and development. *J Cell Biol*. 2006 Mar 13;172(6):795-7. [Abstract] [Full Text]

> *Mdm2 is a negative regulator of the tumor suppressor p53; deletion of Mdm2 is expected to increase p53 activity. Conditional deletion of Mdm2 in osteoblasts, using the Col3.6 promoter, increases p53 activity and has an embryonic lethal phenotype, with reduced expression of Runx2 and markedly impaired osteoblast differentiation. Deletion of p53 in osteoblasts, on the other hand, leads to increased osteoblast proliferation and maturation and a strong predisposition to osteosarcoma. It is surprising that p53 would regulate cell maturation in this fashion – opposite of the usual paradigm in which p53 increases maturation – but the results agree with another recent paper that is not to be missed, Wang X, et al. J Cell Biol. 2006 Jan 2;172(1):115-25.* —GJS

Pathophysiology

Jones DH, Nakashima T, Sanchez OH, Kozieradzki I, Komarova SV, Sarosi I, Morony S, Rubin E, Sarao R, Hojilla CV, Komnenovic V, Kong YY, Schreiber M, Dixon SJ, Sims SM, Khokha R, Wada T, Penninger JM. Regulation of cancer cell migration and bone metastasis by RANKL. *Nature*. 2006 Mar 30;440(7084):692-6. [Abstract]

> *Why do breast and prostate cancer metastasize to bone? Functional RANK is expressed on both cell types, and RANKL triggers migration of breast and prostate cancer cells, as well as primary mammary epithelial cells. RANKL is also expressed on B16F10 melanoma cells, and the RANKL antagonist osteoprotegerin (OPG) blocks bone metastasis of B16F10 after intracardiac injection. The ability of OPG to inhibit bone metastasis was previously attributed to osteoclast inhibition and reduced bone turnover, but zoledronic acid did not inhibit metastasis of B16F10. That RANK expression targets metastasis to bone is a nice idea, but other experiments, e.g. induction of bone metastasis by expression of RANK on naive tumor cells, will be required to prove it.* —GJS

Physiology and Metabolism

Shah S, Islam MN, Dakshanamurthy S, Rizvi I, Rao M, Herrell R, Zinser G,Valrance M, Aranda A, Moras D, Norman A, Welsh J, Byers SW. The molecular basis of vitamin D receptor and beta-catenin crossregulation. *Mol Cell*. 2006 Mar 17;21(6):799-809. [Abstract]

> *The vitamin D receptor (VDR) inhibits β-catenin signaling, and deletion of the VDR from bone produces a high bone mass phenotype; conversely, β-catenin promotes vitamin D signaling through the VDR. The molecular basis of this interaction involves the AF-2 domain of the VDR and the C-terminus of β-catenin; acetylation of β-catenin reciprocally regulates interactions with the VDR and TCF, a transcription factor in the Wnt signaling pathway. An E420Q mutation of the AF-2 domain of the VDR blocks classical VDR action but permits interactions with β-catenin. The same mutation causes hereditary vitamin D-dependent rickets without alopecia in humans, raising the possibility that β-catenin in the hair follicle is involved. The work thus provides molecular insights into the roles of vitamin D in bone and skin.* —GJS

Treatment and Drug Effects

Bischoff-Ferrari HA, Orav EJ, Dawson-Hughes B. Effect of cholecalciferol plus calcium on falling in ambulatory older men and women: a 3-year randomized controlled trial. *Arch Intern Med*. 2006 Feb 27;166(4):424-30. [Abstract]

> *There appears to be reasonable evidence that supplementation with calcium and vitamin D reduces fracture risk in institutionalized individuals. Here is some evidence for a reduction in falls in home dwelling women, not men. Whether fractures are reduced is not known. 3 years of treatment with 700 IU cholecalciferol and 500 mg calcium or placebo was assessed in 199 men and 246 women 65 years or older and living at home; 55% of women and 45% of men reported at least 1 fall. Treatment reduced the odds of falling in women (OR = 0.54, 0.30-0.97), but not in men (OR = 0.93, 0.50-1.72).* —ES

Daly RM, Brown M, Bass S, Kukuljan S, Nowson C. Calcium- and vitamin D3-fortified milk reduces bone loss at clinically relevant skeletal sites in older men: a 2-year randomized controlled trial. *J Bone Miner Res*. 2006 Mar;21(3):397-405. [Abstract]

> *This is a nicely executed study suggesting a decline in bone loss in the appendicular skeleton. What is needed is anti-fracture efficacy studies, as there are none. In this 2-year, randomized, controlled study of 167 men >50 years of age, supplementation with calcium- and vitamin D3-fortified milk suppressed PTH and slowed bone loss at the femoral neck, total hip, and ultradistal radius, but not spine.* —ES

Land C, Rauch F, Glorieux FH. Cyclical intravenous pamidronate treatment affects metaphyseal modeling in growing patients with osteogenesis imperfecta. *J Bone Miner Res*. 2006 Mar;21(3):374-9. [Abstract]

> *This is interesting because it drives home the existence and potential importance of periosteal bone resorption that occurs in growth, and maybe in adulthood. Fifty children (mean age, 6.7) with osteogenesis imperfecta received 2-4 years of pamidronate, resulting in abnormalities in the shape of the distal femoral metaphyses. Pamidronate interferes with periosteal resorption responsible for shaping the distal femoral metaphysis. The clinical implications are not known.* —ES

Lindsay R, Cosman F, Zhou H, Bostrom MP, Shen VW, Cruz JD, Nieves JW, Dempster DW. A novel tetracycline labeling schedule for longitudinal evaluation of the short-term effects of anabolic therapy with a single iliac crest bone biopsy: early actions of teriparatide. *J Bone Miner Res*. 2006 Mar;21(3):366-73. [Abstract]

> *It is not clear whether PTH-induced bone formation is dependent on previous remodeling or occurs de novo. A quadruple tetracycline labeling method allows assessment of changes in bone formation in a single biopsy. 1 month hPTH(1-34) extends the bone-forming surface, increases mineral apposition rate, and initiates modeling-based formation. New bone was deposited on previously quiescent surfaces (i.e., modeling-based formation), but a proportion of this could occur by encroachment from adjacent resorption cavities.* —ES

Reviews, Perspectives and Editorials

Deroo BJ, Korach KS. Estrogen receptors and human disease. *J Clin Invest*. 2006 Mar;116(3):561-70. [Abstract] [Full Text]

Jones ME, Boon WC, Proietto J, Simpson ER. Of mice and men: the evolving phenotype of aromatase deficiency. *Trends Endocrinol Metab*. 2006 Mar;17(2):55-64. [Abstract]

Papapoulos SE. Bisphosphonate actions: Physical chemistry revisited. *Bone*. 2006 Feb 24; [Epub ahead of print] [Abstract]

Reid IR, Cornish J, Baldock PA. Nutrition-related peptides and bone homeostasis. *J Bone Miner Res*. 2006 Apr;21(4):495-500. [Info]

Russell RG. Ibandronate: Pharmacology and preclinical studies. *Bone*. 2006 Apr;38(4 Suppl 1):S7-S12. [Abstract]

Tashjian AH Jr, Gagel RF. Teriparatide [human PTH(1-34)]: 2.5 years of experience on the use and safety of the drug for the treatment of osteoporosis. *J Bone Miner Res*. 2006 Mar;21(3):354-65. [Info]

Other Studies of Potential Interest

Aguirre JI, Plotkin LI, Stewart SA, Weinstein RS, Parfitt AM, Manolagas SC, Bellido T. Osteocyte apoptosis is induced by weightlessness in mice and precedes osteoclast recruitment and bone loss. *J Bone Miner Res*. 2006 Apr;21(4):605-15. [Abstract]

Desai J, Shannon ME, Johnson MD, Ruff DW, Hughes LA, Kerley MK, Carpenter DA, Johnson DK, Rinchik EM, Culiat CT. Nell1-deficient mice have reduced expression of extracellular matrix proteins causing cranial and vertebral defects. *Hum Mol Genet*. 2006 Apr 15;15(8):1329-41. [Abstract]

Gaur T, Rich L, Lengner CJ, Hussain S, Trevant B, Ayers D, Stein JL, Bodine PV, Komm BS, Stein GS, Lian JB. Secreted frizzled related protein 1 regulates Wnt signaling for BMP2 induced chondrocyte differentiation. *J Cell Physiol*. 2006 Mar 30; [Epub ahead of print] [Abstract]

Ke HZ, Crawford DT, Qi H, Simmons HA, Owen TA, Paralkar VM, Li M, Lu B, Grasser WA, Cameron KO, Lefker BA, Dasilva-Jardine P, Scott DO, Zhang Q, Tian XY, Jee WS, Brown TA, Thompson DD. A nonprostanoid EP4 receptor selective prostaglandin E(2) agonist restores bone mass and strength in aged, ovariectomized rats. *J Bone Miner Res*. 2006 Apr;21(4):565-75. [Abstract]

Tylzanowski P, Mebis L, Luyten FP. The Noggin null mouse phenotype is strain dependent and haploinsufficiency leads to skeletal defects. *Dev Dyn*. 2006 Apr 5; [Epub ahead of print] [Abstract]

Venken K, De Gendt K, Boonen S, Ophoff J, Bouillon R, Swinnen JV, Verhoeven G, Vanderschueren D. Relative impact of androgen and estrogen receptor activation in the effects of androgens on trabecular and cortical bone in growing male mice: a study in the androgen receptor knockout mouse model. *J Bone Miner Res*. 2006 Apr;21(4):576-85. [Abstract]

Conflict of Interest: Dr. Ferrari and Dr. Strewler report that no conflicts of interest exist. 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.