BoneKEy. 2007 August;4(8):204-208
http://www.bonekey-ibms.org/cgi/content/full/ibmske;4/8/204
DOI: 10.1138/20070267

NOT TO BE MISSED

Clinical and Basic Research Papers – July 2007 Selections

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

Bone Modeling and Remodeling

Aguirre JI, Plotkin LI, Gortazar AR, Martin Millan M, O'brien CA, Manolagas SC, Bellido T. A novel ligand-independent function of the estrogen receptor is essential for osteocyte and osteoblast mechanotransduction. *J Biol Chem*. 2007 Jul 3; [Epub ahead of print]

> *Mechanical stimulation promotes osteocyte (and osteoblast) survival by activating the extracellular signal regulated kinases ERKs. Estrogens have similar effects and adaptation to mechanical forces is defective in mice lacking the estrogen receptor (ER) a or the ERb. ERKs are not activated by stretching in osteocytic and osteoblastic cells in which both ERa and ERb have been knocked out. This is reversed partially by transfection of either one of the two ERs and fully by transfection of both. The ER antagonist ICI 182,780 abrogates ERK activation and the anti-apoptotic effect of mechanical stimulation. ERs participate in the transduction of mechanical forces into pro-survival signaling in bone cells, albeit in a ligand-independent manner*. —ES

Almeida M, Han L, Martin-Millan M, Plotkin LI, Stewart SA, Roberson PK, Kousteni S, O'brien CA, Bellido T, Parfitt AM, Weinstein RS, Jilka RL, Manolagas SC. Skeletal involution by age-associated oxidative stress and its acceleration by loss of sex steroids. *J Biol Chem*. 2007 Jul 10; [Epub ahead of print]

> *The authors propose a unified mechanism of reduced protection of oxidative stress reflected in increased reactive oxygen species levels, decreased glutathione reductase activity, and increases in the phosphorylation of p53 and p66shc, two key components of a signaling cascade that influences apoptosis and lifespan. The same changes in oxidative stress were reproduced by gonadectomy and reversed by estrogens or androgens.* —ES

Macdonald BT, Joiner DM, Oyserman SM, Sharma P, Goldstein SA, He X, Hauschka PV. Bone mass is inversely proportional to Dkk1 levels in mice. *Bone*. 2007 Sep;41(3):331-9. [Abstract]

> *Dickkopf-1 (DKK1) is a Wnt inhibitor that binds LRP5 and LRP6. A decrease in DKK1 increases Wnt activity and bone mass. Dkk1(d) (double ridge) alleles express low amounts of Dkk1 so crossing Dkk1(+/-) and Dkk1(+/d) mice results in genotypes with decreasing Dkk1 expression levels: +/+, +/d, +/- and d/-. Trabecular bone volume increased in 8-week-old mutants in a fashion inversely proportional to the level of Dkk1 expression. Trabecular number and thickness were higher in the low Dkk1 expressing genotypes. Cortical bone thickness and cross-sectional area of the femoral diaphysis correlated with lower Dkk1 expression. DKK1 is a negative regulator of bone homeostasis in vivo.* —ES

Wan DC, Pomerantz JH, Brunet LJ, Kim JB, Chou YF, Wu BM, Harland R, Blau HM, Longaker MT. Noggin suppression enhances in vitro osteogenesis and accelerates in vivo bone formation. *J Biol Chem*. 2007 Jul 2; [Epub ahead of print]

> *A balance exists between bone morphogenetic protein (BMP) agonists and antagonists and osteogenesis. Reduction of Noggin enhanced BMP signaling and in vitro osteoblast bone formation. Radiographic and histological analyses revealed more bone regeneration at 2 and 4 weeks post-injury. Enhanced osteogenesis through downregulation in Noggin is a novel approach to accelerate bone formation*. —ES

Yang S, Li YP. RGS10-null mutation impairs osteoclast differentiation resulting from the loss of [Ca2+]i oscillation regulation. *Genes Dev*. 2007 Jul 15;21(14):1803-16. [Abstract]

> *Calcium oscillations are essential to the calcineurin-NFATc1 arm of RANKL signaling in osteoclasts. Mice that are deficient in the regulator of G-protein signaling (RGS) protein RGS10 exhibit impaired osteoclast differentiation and severe osteopetrosis. Ectopic expression of RGS10 increases the sensitivity of osteoclasts to RANKL signaling, but deficiency of RGS10 eliminates calcium oscillations and activation of NFATc1. Ectopic NFATc1 expression rescues osteoclast differentiation from the impairment that results from deletion of RGS10. Yet another wrinkle, but an important one, in the signaling of RANKL in the osteoclast.* —GJS

Genetics

Sobacchi C, Frattini A, Guerrini MM, Abinun M, Pangrazio A, Susani L, Bredius R, Mancini G, Cant A, Bishop N, Grabowski P, Del Fattore A, Messina C, Errigo G, Coxon FP, Scott DI, Teti A, Rogers MJ, Vezzoni P, Villa A, Helfrich MH. Osteoclast-poor human osteopetrosis due to mutations in the gene encoding RANKL. *Nat Genet*. 2007 Aug;39(8):960-2. [Abstract]

> *Some patients with autosomal recessive osteopetrosis (ARO) lack osteoclasts and cannot be rescued by hematopoietic stem cell transplantation, suggesting the absence of an osteoclast-autonomous molecular defect. These features are distinct from those found in osteopetrotic patients with mutations in the chloride channel (CLCN7), vacuolar proton pump (TCIRG1), transmembrane protein (OSTM1), and carbonic anhydrase (CA2). This paper now reports that mutations (single nucleotide changes and deletions) in RANKL, an indispensable cytokine for activation of osteoclastogenesis by osteoblasts and T cells, occur in this particular form of ARO. Proof-of-concept that RANKL therapy could restore osteoclastogenesis in these patients was demonstrated in vitro. Of note, subjects with autosomal RANKL mutations did not present obvious abnormalities of their immune system, a finding that may be of importance with regard to the ongoing development of RANKL inhibitors (denosumab) for the treatment of bone diseases*. —SF

Pathophysiology

Ruiz-Perez VL, Blair HJ, Rodriguez-Andres ME, Blanco MJ, Wilson A, Liu YN, Miles C, Peters H, Goodship JA. Evc is a positive mediator of Ihh-regulated bone growth that localises at the base of chondrocyte cilia. *Development*. 2007 Aug;134(16):2903-12. [Abstract]

> *The Ellis-van Creveld syndrome is characterized by short limbs, craniofacial abnormalities and ectodermal dysplasia. Causal mutations in two genes, EVC and EVC2, have been identified by positional cloning. It is shown here that EVC is expressed at the base of cilia and affects Indian hedgehog (Ihh) signaling in chondrocytes. Evc(-/-) mice,*

which recapitulate the human syndrome, display premature chondrocyte hypertrophy and deficient bone collar formation, consistent with defective Ihh action. Recent studies show that Smoothened (Smo) localizes to primary cilia and Gli transcription factor (Gli)3 processing is defective in intraflagellar transport mutants. Expression of Patched (Ptch)1 and Gli1 is markedly decreased in Evc(-/-) mice; experiments in Evc(-/-) cells indicate that the defect lies downstream of Smo. —GJS

Physiology and Metabolism

Lee NK, Sowa H, Hinoi E, Ferron M, Ahn JD, Confavreux C, Dacquin R, Mee PJ, McKee MD, Jung DY, Zhang Z, Kim JK, Mauvais-Jarvis F, Ducy P, Karsenty G. Endocrine regulation of energy metabolism by the skeleton. *Cell*. 2007 Aug 10;130(3):456-69. [Abstract]

The hypothalamus regulates the skeleton in response to nutrient intake.This exceptional paper shows that the reverse occurs as well. Mice deficient in the osteoblast-specific protein kinase OST-PTP have hyperinsulinemia, hypoglycemia and increased sensitivity to insulin, demonstrating that bone exerts humoral control over both pancreatic ß-cells and insulin target tissues. Osteocalcin(-/-) mice have an opposite phenotype, and removing one osteocalcin allele corrects the OST-PTP phenotype. Administration of osteocalcin improves glucose tolerance in vivo; only uncarboxylated osteocalcin is effective in ß-cells and adipocytes. Though the molecular relationship of OST-PTP and osteocalcin is not determined, uncarboxylated osteocalcin is a hormone that regulates metabolism. —GJS

Treatment and Drug Effects

Kiel DP, Magaziner J, Zimmerman S, Ball L, Barton BA, Brown KM, Stone JP, Dewkett D, Birge SJ. Efficacy of a hip protector to prevent hip fracture in nursing home residents: the HIP PRO randomized controlled trial. *JAMA*. 2007 Jul 25;298(4):413-22. [Abstract]

Kannus P, Parkkari J. Hip protectors for preventing hip fracture. *JAMA*. 2007 Jul 25;298(4):454-5. [Info]

The efficacy of hip protectors to reduce hip fracture incidence remains uncertain, particularly since the publication of a Cochrane review concluding that comparisons between institutions with and without protectors (cluster randomization design) suffered from a systematic bias. In this study, 1042 residents from 37 US nursing homes were randomly assigned to hip protectors on one side (left or right), while the other side remained unprotected (hence each subject is his or her own control). The study was terminated after 20 months (mean participation time, 8 months) due to lack of efficacy. Even among the 30% of nursing home residents with greater than 80% adherence, the rate of hip fractures on the protected and unprotected side remained the same. Worse, more hip fractures (13) occurred on the side that was actually protected at the time of the fall than on the other side (7 hip fractures). Whether these negative results reflect biomechanical ineffectiveness of the protector, patient profiles and/or a lack of two-sided protection remains uncertain. The accumulating evidence, however, speaks against the systematic use of hip protectors in the institutionalized elderly. —SF

Manson JE, Allison MA, Rossouw JE, Carr JJ, Langer RD, Hsia J, Kuller LH, Cochrane BB, Hunt JR, Ludlam SE, Pettinger MB, Gass M, Margolis KL, Nathan L, Ockene JK, Prentice RL, Robbins J, Stefanick ML; WHI and WHI-CACS Investigators. Estrogen therapy and coronary-artery calcification. *N Engl J Med*. 2007 Jun 21;356(25):2591-602. [Abstract]

In 1064 women aged 50 to 59 years at randomization after a mean of 7.4 years of treatment, coronary-artery calcium (or Agatston) score was lower among women receiving estrogen (83.1) than placebo (123.1) (P=0.02). The multivariate odds ratios for coronary-artery calcium scores of more than 0, 10 or more, and 100 or more in the group receiving estrogen as compared with placebo, were 0.78 (95% confidence interval, 0.58 to 1.04), 0.74 (0.55 to 0.99), and 0.69 (0.48 to 0.98), respectively. The corresponding odds ratios among women with at least 80% adherence to the study were 0.64 (P=0.01), 0.55 (P<0.001), and 0.46 (P=0.001). For coronary-artery calcium scores of more than 300 (vs. <10), the multivariate odds ratio was 0.58 (P=0.03) in an intention-to-treat analysis and 0.39 (P=0.004) among women with at least 80% adherence. —ES

Stepan JJ, Burr DB, Pavo I, Sipos A, Michalska D, Li J, Fahrleitner-Pammer A, Petto H, Westmore M, Michalsky D, Sato M, Dobnig H. Low bone mineral density is associated with bone microdamage accumulation in postmenopausal women with osteoporosis. *Bone*. 2007 Sep;41(3):378-85. [Abstract]

Thirty-eight women with osteoporosis received ALN (10 mg/day or 70 mg/week for a mean duration of 63.6 months) while 28 were untreated. After adjustment for confounders, crack density (Cr.Dn) was elevated in ALN patients (P=0.028 and P=0.069 for crack surface density (Cr.S.Dn)). In ALN patients, lower femoral neck BMD (Cr.S.Dn, r=-0.58, P=0.003; Cr.Dn, r=-0.54, P=0.005) and increased age (Cr.S.Dn, r=0.43, P=0.03; Cr.Dn, r=0.43, P=0.03) were associated with microdamage accumulation. Femoral neck BMD was the only independent predictor for these correlations (P=0.04 for Cr.Dn and P=0.03 for Cr.S.Dn). Microdamage accumulation may occur in low BMD patients treated with alendronate. —ES

Reviews, Perspectives and Editorials

Seeman E. Is a change in bone mineral density a sensitive and specific surrogate of anti-fracture efficacy? *Bone*. 2007 Sep;41(3):308-17. [Abstract]

Wu-Wong JR. Vitamin D receptor: a highly versatile nuclear receptor. *Kidney Int*. 2007 Aug;72(3):237-9. [Abstract]

Other Studies of Potential Interest

Abzhanov A, Rodda SJ, McMahon AP, Tabin CJ. Regulation of skeletogenic differentiation in cranial dermal bone. *Development*. 2007 Sep;134(17):3133-44. [Abstract]

Almeida M, Han L, Martin-Millan M, O'brien CA, Manolagas SC. Oxidative stress antagonizes WNT signaling in osteoblast precursors by diverting B-catenin from TCF- to FOXO-mediated transcription. *J Biol Chem*. 2007 Jul 10; [Epub ahead of print]

Athanasopoulos AN, Schneider D, Keiper T, Alt V, Pendurthi UR, Liegibel UM, Sommer U, Nawroth PP, Kasperk C, Chavakis T. VEGF-induced upregulation of CCN1 in osteoblasts mediates proangiogenic activities in endothelial cells and promotes fracture healing. *J Biol Chem*. 2007 Jul 10; [Epub ahead of print]

Chen Q, Sivakumar P, Barley C, Peters DM, Gomes RR, Farach-Carson MC, Dallas SL. Potential role for heparan sulfate proteoglycans in regulation of TGF-beta by modulating

assembly of latent TGF-beta binding protein-1 (LTBP1). *J Biol Chem*. 2007 Jun 19; [Epub ahead of print]

Eswaran SK, Allen MR, Burr DB, Keaveny TM. A computational assessment of the independent contribution of changes in canine trabecular bone volume fraction and microarchitecture to increased bone strength with suppression of bone turnover. *J Biomech*. 2007 Jul 4; [Epub ahead of print] [Abstract]

Khosla S, Burr D, Cauley J, Dempster DW, Ebeling PR, Felsenberg D, Gagel RF, Gilsanz V, Guise T, Koka S, McCauley LK, McGowan J, McKee MD, Mohla S, Pendrys DG, Raisz LG, Ruggiero SL, Shafer DM, Shum L, Silverman SL, Van Poznak CH, Watts N, Woo SB, Shane E. Bisphosphonate-associated osteonecrosis of the jaw: report of a task force of the American Society for Bone and Mineral Research. *J Bone Miner Res*. 2007 Jul 30; [Epub ahead of print] [Abstract]

Malone AM, Anderson CT, Tummala P, Kwon RY, Johnston TR, Stearns T, Jacobs CR. Primary cilia mediate mechanosensing in bone cells by a calcium-independent mechanism. *Proc Natl Acad Sci U S A*. 2007 Aug 2; [Epub ahead of print] [Abstract] [Full Text]

Morita K, Miyamoto T, Fujita N, Kubota Y, Ito K, Takubo K, Miyamoto K, Ninomiya K, Suzuki T, Iwasaki R, Yagi M, Takaishi H, Toyama Y, Suda T. Reactive oxygen species induce chondrocyte hypertrophy in endochondral ossification. *J Exp Med*. 2007 Jul 9;204(7):1613-23. [Abstract]

Yamaguchi H, Sasaki K, Satomi Y, Shimbara T, Kageyama H, Mondal MS, Toshinai K, Date Y, González LJ, Shioda S, Takao T, Nakazato M, Minamino N. Peptidomic identification and biological validation of neuroendocrine regulatory peptide-1 and -2. *J Biol Chem*. 2007 Jul 3; [Epub ahead of print]

Yan L, Vatner DE, O'connor JP, Ivessa A, Ge H, Chen W, Hirotani S, Ishikawa Y, Sadoshima J, Vatner SF. Type 5 adenylyl cyclase disruption increases longevity and protects against stress. *Cell*. 2007 Jul 27;130(2):247-58. [Abstract]

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.