BoneKEy-Osteovision. 2007 February;4(2):25-29
http://www.bonekey-ibms.org/cgi/content/full/ibmske;4/2/25
DOI: 10.1138/20060246

NOT TO BE MISSED

Clinical and Basic Research Papers – January 2007 Selections

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

Bone Modeling and Remodeling

Tu X, Joeng KS, Nakayama KI, Nakayama K, Rajagopal J, Carroll TJ, McMahon AP, Long F. Noncanonical Wnt signaling through G protein-linked PKCdelta activation promotes bone formation. *Dev Cell*. 2007 Jan;12(1):113-27. [Abstract]

> *The canonical Wnt signaling pathway is securely implicated in endochondral bone formation and the regulation of bone turnover. Tu et al. report that noncanonical Wnt signaling also takes place in bone. Wnt3a induces protein kinase C* δ (PKCδ)*, apparently by Gi/Gq-dependent induction of phospholipase C, in a process that requires Disheveled-2 and involves co-localization of Disheveled-2 and PKC*δ *to the plasma membrane. Wnt7b signals via this noncanonical but not the canonical pathway; removal of either PKC*δ *or Wnt7b results in a modest delay in embryonic bone formation. This is the first demonstration of noncanonical Wnt signaling in bone. The relatively small effects on bone formation could reflect redundancy or a secondary role of the noncanonical pathway.* —GJS

Diagnosis

Lewis CE, Ewing SK, Taylor BC, Shikany JM, Fink HA, Ensrud KE, Barrett-Connor E, Cummings SR, Orwoll E; Osteoporotic Fractures in Men (MrOS) Study Research Group. Predictors of non-spine fracture in elderly men: the MrOS study. *J Bone Miner Res*. 2007 Feb;22(2):211-9. [Abstract]

> *As new algorithms for fracture (particularly hip) risk evaluation in women are being developed, based not only on BMD but also on simple clinical risk factors, this large study in men is worth a look: history of falls and its related risk factors, including depression and walking disability, are of great predictive value, and should not be forgotten.* —SF

Genetics

Ioannidis JP, Ng MY, Sham PC, Zintzaras E, Lewis CM, Deng HW, Econs MJ, Karasik D, Devoto M, Kammerer CM, Spector T, Andrew T, Cupples LA, Duncan EL, Foroud T, Kiel DP, Koller D, Langdahl B, Mitchell BD, Peacock M, Recker R, Shen H, Sol-Church K, Spotila LD, Uitterlinden AG, Wilson SG, Kung AW, Ralston SH. Meta-analysis of genome-wide scans provides evidence for sex- and site-specific regulation of bone mass. *J Bone Miner Res*. 2007 Feb;22(2):173-83. [Abstract]

> *Nine independent, genome-wide scans have identified quantitative trait loci (QTLs) related to bone mineral density in Caucasians. Due to major differences in study design and methods, i.e., in family structure (parents/offspring and relatives, sibs or twins), phenotype definition (continuous BMD or probands), and marker distribution, each*

individual study was limited by low power and high false discovery rates, explaining why linkage peaks have seldom been replicated (see www.bonekey-ibms.org/cgi/content/full/ibmske;20040121v1). The current study represents a major collaborative effort to overcome some of these limitations by performing a meta-analysis of pooled individual data from all of these major linkage studies, including a clever approach to overcome the difficulty of different markers being used across the individual studies. As a result, a limited number of consistent QTLs for BMD has been ascertained, a new QTL for spine has been identified, and some evidence has emerged for different QTLs in males and females. This should help investigators to focus their search for genetic variation underlying the population-based variance for BMD on these chromosomal regions. —SF

Pathophysiology

Diarra D, Stolina M, Polzer K, Zwerina J, Ominsky MS, Dwyer D, Korb A, Smolen J, Hoffmann M, Scheinecker C, van der Heide D, Landewe R, Lacey D, Richards WG, Schett G. Dickkopf-1 is a master regulator of joint remodeling. *Nat Med*. 2007 Feb;13(2):156-63. [Abstract]

Goldring SR, Goldring MB. Eating bone or adding it: the Wnt pathway decides. *Nat Med*. 2007 Feb;13(2):133-4. [Info]

Rheumatoid arthritis (RA) is typified by erosion of periarticular bone, whereas osteoarthritis causes periarticular formation of new bone as osteophytes. The Wnt signaling inhibitor Dickkopf-1 (DKK-1) is induced in a model of arthritis induced by overexpression of TNF-α, and an anti-DKK-1 antibody blocks periarticular bone resorption and allows osteophyte formation to occur. The antiresorptive effect of DKK-1 antibody is abolished by siRNA to OPG, implicating DKK-1 in induction of bone resorption via RANKL by TNF-α. DKK-1 is also expressed in the synovium and blood of patients with RA. DKK-1 may facilitate erosions and prevent compensatory bone formation in RA. —GJS

Ueki Y, Lin CY, Senoo M, Ebihara T, Agata N, Onji M, Saheki Y, Kawai T, Mukherjee PM, Reichenberger E, Olsen BR. Increased myeloid cell responses to M-CSF and RANKL cause bone loss and inflammation in SH3BP2 "cherubism" mice. *Cell*. 2007 Jan 12;128(1):71-83. [Abstract]

Novack DV, Faccio R. Jawing about TNF: new hope for cherubism. *Cell*. 2007 Jan 12;128(1):15-7. [Abstract]

Cherubism is a rare inherited disorder in which the upper and lower jaw are destroyed, with surrounding inflammation and fibrosis. It is caused by point mutations in Sh3bp2, which encodes a scaffold protein. In mice with a cherubism mutation knocked into Sh3bp2, TNF-α is secreted from hyperactive macrophages, leading to increased release of RANKL and M-CSF from stromal cells; osteoclasts also display hyper-responsiveness to RANKL and M-CSF. Pleiotropic effects of a gain-of-function mutation are thus responsible for cherubism, but patients are predicted to respond to biologics directed against TNF-α. — GJS

Treatment and Drug Effects

Lindsay R, Zhou H, Cosman F, Nieves J, Dempster DW, Hodsman AB. Effects of a one-month treatment with parathyroid hormone (1-34) on bone formation on cancellous, endocortical and

periosteal surfaces of the human ilium. *J Bone Miner Res*. 2007 Jan 16; [Epub ahead of print] [Abstract]

> *Anabolic therapy using parathyroid hormone (1-34) for even one month stimulates new bone formation on cancellous, endocortical, and periosteal surfaces.* —ES

Recker RR, Kendler D, Recknor CP, Rooney TW, Lewiecki EM, Utian WH, Cauley JA, Lorraine J, Qu Y, Kulkarni PM, Gaich CL, Wong M, Plouffe L Jr, Stock JL. Comparative effects of raloxifene and alendronate on fracture outcomes in postmenopausal women with low bone mass. *Bone*. 2006 Dec 18; [Epub ahead of print] [Abstract]

> *Demonstrating that two effective agents differ in their anti-fracture efficacy is difficult. In this double-blind, randomized study of 1412 women, after 312+/-254 days (mean+/-SD), 22 women treated with alendronate and 20 treated with raloxifene had new fractures. Four women in the ALN group and none in the RLX group had moderate/severe vertebral fractures (P=0.04). The inadequate recruitment and essentially null result due to few events is difficult to interpret one way or another.* —ES

Samadfam R, Xia Q, Goltzman D. Co-treatment of PTH with osteoprotegerin or alendronate increases its anabolic effect on the skeleton of oophorectomized mice. *J Bone Miner Res*. 2007 Jan;22(1):55-63. [Abstract]

> *The combination of PTH(1-84) and alendronate (10mg/d) in humans did not improve spine or femur BMD better than PTH alone, and actually decreased markedly the anabolic effects of intermittent PTH on trabecular spine. Does this mean that osteoclast activity is required for the net anabolic effects of PTH? Does this represent the end of any attempt to combine anabolic and anti-resorptive agents? In the study by Samadfam et al., combining alendronate or osteoprotegerin (OPG) with PTH administered immediately after OVX in adult mice produced additive effects on BMD and trabecular bone density compared to any treatment alone, whereas the mechanical strength of the femur was not improved compared to PTH alone. Most impressively, the combined effects of OPG + PTH occurred despite complete suppression of bone resorption (sTRAP-5b) and osteoclasts on bone surfaces. In contrast, this study provides some evidence that OPG promotes osteoblast differentiation in vitro. Whether the latter effect is indirectly mediated by suppression of the osteoclast lineage in bone marrow cultures (which would otherwise deliver an inhibitory message to osteoblasts) and/or could result from a direct effect of OPG binding to RANKL on osteoblast membranes remains unclear.*

Yang YX, Lewis JD, Epstein S, Metz DC. Long-term proton pump inhibitor therapy and risk of hip fracture. *JAMA*. 2006 Dec 27;296(24):2947-53. [Abstract]

> *Proton pump inhibitors (PPIs) induce hypochlorhydria and reduce bone resorption through inhibition of osteoclastic vacuolar proton pumps. In 13,556 hip fracture cases and 135,386 controls, the adjusted odds ratio (AOR) for hip fracture with more than 1 year of PPI was 1.44 (1.30-1.59), and 2.65 (1.80-3.90) for long-term high-dose usage, with the strength of the association increasing with years of use.* —ES

Reviews, Perspectives and Editorials

Asagiri M, Takayanagi H. The molecular understanding of osteoclast differentiation. *Bone*. 2007 Feb;40(2):251-64. [Abstract]

Briggs AM, Greig AM, Wark JD. The vertebral fracture cascade in osteoporosis: a review of aetiopathogenesis. *Osteoporos Int*. 2007 Jan 6; [Epub ahead of print] [Abstract]

Eriksen EF, Eghbali-Fatourechi GZ, Khosla S. Remodeling and vascular spaces in bone. *J Bone Miner Res*. 2007 Jan;22(1):1-6. [Abstract]

Karsdal MA, Martin TJ, Bollersev J, Christiansen C, Henriksen K. Are non-resorbing osteoclasts sources of bone anabolic activity? *J Bone Miner Res*. 2007 Jan 16; [Epub ahead of print] [Abstract]

> *By reviewing the status of bone formation in human diseases and mouse models where osteoclastogenesis or the activity of differentiated osteoclasts is defective, Karsdal et al. arrive at the same conclusion (see Samadfam et al., above) that pharmacological attenuation of bone resorption may be possible without necessitating a concomitant reduction in bone formation.* —SF

Liu H, Bravata DM, Olkin I, Nayak S, Roberts B, Garber AM, Hoffman AR. Systematic review: the safety and efficacy of growth hormone in the healthy elderly. *Ann Intern Med*. 2007 Jan 16;146(2):104-15. [Abstract]

Lucas GJ, Daroszewska A, Ralston SH. Contribution of genetic factors to the pathogenesis of Paget's disease of bone and related disorders. *J Bone Miner Res*. 2006 Dec;21 Suppl 2:P31-7. [Abstract]

Morissette J, Laurin N, Brown JP. Sequestosome 1: mutation frequencies, haplotypes, and phenotypes in familial Paget's disease of bone. *J Bone Miner Res*. 2006 Dec;21 Suppl 2:P38-44. [Abstract]

Remuzzi A. Vitamin D, insulin resistance, and renal disease. *Kidney Int*. 2007 Jan;71(2):96-8. [Abstract]

Other Studies of Potential Interest

Dwyer JR, Sever N, Carlson M, Nelson SF, Beachy PA, Parhami F. Oxysterols are novel activators of the hedgehog signaling pathway in pluripotent mesenchymal cells. *J Biol Chem*. 2007 Jan 2; [Epub ahead of print]

Grady EF. Cell signaling. Beta-arrestin, a two-fisted terminator. *Science*. 2007 Feb 2;315 (5812):605-6. [Summary] [Full Text]

Liu Z, Lavine KJ, Hung IH, Ornitz DM. FGF18 is required for early chondrocyte proliferation, hypertrophy and vascular invasion of the growth plate. *Dev Biol*. 2007 Feb 1;302(1):80-91. [Abstract]

Nelson CD, Perry SJ, Regier DS, Prescott SM, Topham MK, Lefkowitz RJ. Targeting of diacylglycerol degradation to M1 muscarinic receptors by beta-arrestins. *Science*. 2007 Feb 2;315(5812):663-6. [Abstract] [Full Text]

Rauch F, Travers R, Glorieux FH. Intracortical remodeling during human bone development--a histomorphometric study. *Bone*. 2007 Feb;40(2):274-80. [Abstract]

Speirs AD, Heller MO, Duda GN, Taylor WR. Physiologically based boundary conditions in finite element modelling. *J Biomech*. 2006 Dec 11; [Epub ahead of print]

Wang Q, Wei X, Zhu T, Zhang M, Shen R, Xing L, O'keefe RJ, Chen D. BMP-2 activates Smad6 gene transcription through bone-specific transcription factor Runx2. *J Biol Chem*. 2007 Jan 10; [Epub ahead of print]

Wettschureck N, Lee E, Libutti SK, Offermanns S, Robey PG, Spiegel AM. Parathyroid-specific double knockout of Gq and G11 alpha-subunits leads to a phenotype resembling germline knockout of the extracellular Ca2+ -sensing receptor. *Mol Endocrinol*. 2007 Jan;21(1):274-80. [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.