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NOT TO BE MISSED

Clinical and Basic Research Papers – March 2007 Selections

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

Bone Modeling and Remodeling

Eswarakumar VP, Schlessinger J. Skeletal overgrowth is mediated by deficiency in a specific isoform of fibroblast growth factor receptor 3. *Proc Natl Acad Sci U S A*. 2007 Mar 6;104(10):3937-42. [Abstract] [Full Text]

> *Inactivation of the FGF receptor 1 and 2 isoform c, normally expressed in mesenchymal cells, prevents normal development of the embryo due to a gastrulation defect (FGFR1c) and causes delayed ossification (FGFR2c) respectively. In this piece of molecular art, the authors selectively inactivated the mesenchymal (c) or epithelial (b) isoforms of FGF receptor 3, resulting in increased longitudinal growth by an increase in proliferating chondrocytes, which was accompanied by decreased cortical and trabecular bone thickness. It is therefore suggested that FGFR3c primarily regulates chondrocytic proliferation and thereby osteogenesis*. —SF

Lopez-Granados E, Temmerman ST, Wu L, Reynolds JC, Follmann D, Liu S, Nelson DL, Rauch F, Jain A. Osteopenia in X-linked hyper-IgM syndrome reveals a regulatory role for CD40 ligand in osteoclastogenesis. *Proc Natl Acad Sci U S A*. 2007 Mar 20;104(12):5056-61. [Abstract] [Full Text]

> *The X-linked hyper-IgM syndrome is caused by loss-of-function mutations in CD40 ligand and is characterized by consequent failures to switch immunoglobulin production from IgM to IgG/IgA and to produce T_H1 cells that produce interferon-γ (IFN-γ). Patients are osteopenic, and have increased urinary N-telopeptide excretion and fracture. Their CD4+ T cells express normal levels of RANKL but induce markedly increased osteoclast numbers in coculture. This exuberant osteoclastogenesis can be blocked by addition of IFN-γ, suggesting that defective production of the cytokine underlies excessive bone resorption.* —GJS

Nordstrom P, Neovius M, Nordstrom A. Early and rapid bone mineral density loss of the proximal femur in men. *J Clin Endocrinol Metab*. 2007 Feb 20; [Epub ahead of print]

> *This study demonstrates that between 17 and 25 years healthy males' peak BMD was achieved at 19y of age at the proximal femur, followed by losses of 25% of peak BMD by the age of 50*. —ES

Sampath TK, Simic P, Sendak R, Draca N, Bowe AE, O'brien S, Schiavi SC, McPherson JM, Vukicevic S. Thyroid stimulating hormone (TSH) restores bone volume, microarchitecture and strength in aged ovariectomized rats. *J Bone Miner Res*. 2007 Mar 12; [Epub ahead of print] [Abstract]

Systemic administration of TSH increases bone volume and improves bone microarchitecture and strength in aged ovariectomized rats. TSH's actions are mediated by its inhibitory effects on RANKL-induced osteoclast formation and bone resorption coupled with stimulatory effects on osteoblast differentiation and bone formation, suggesting TSH directly affects bone remodeling in vivo. —ES

Genetics

Gajendran VK, Lin JR, Fyhrie DP. An application of bioinformatics and text mining to the discovery of novel genes related to bone biology. *Bone*. 2007 May;40(5):1378-88. [Abstract]

Finding potentially new bone genes is the dream and the nightmare of all those working on osteoporosis genetics. How to best use the enormous reservoir of knowledge accumulating every day in various web-based sources remains a challenge. These authors developed a text-mining tool to dig and link genetic and published article databases, leading to the identification of a list of potentially interesting genes related to the function of osteocytes, bisphosphonates, apoptosis and osteoporosis. —SF

Van Wesenbeeck L, Odgren PR, Coxon FP, Frattini A, Moens P, Perdu B, Mackay CA, Van Hul E, Timmermans JP, Vanhoenacker F, Jacobs R, Peruzzi B, Teti A, Helfrich MH, Rogers MJ, Villa A, Van Hul W. Involvement of PLEKHM1 in osteoclastic vesicular transport and osteopetrosis in incisors absent rats and humans. *J Clin Invest*. 2007 Apr 2;117(4):919-30. [Abstract] [Full Text]

A beautiful paper reports the identification of loss-of-function mutations in PLEKHM1, a pleckstrin homology domain protein, in incisors absent rats and in a single human family with a mild autosomal recessive form of osteopetrosis. Osteoclasts from affected family members adhere to dentine but do not resorb it. They have large numbers of intracytoplasmic vesicles, no ruffled border, and an abnormal actin ring. PLEKHM1 colocalizes with Rab7 on the surface of late lysosomal vesicles in a fashion that is blocked by inhibitors of prenylation. It seems likely, therefore, that PLEKHM1 functions in the trafficking of vesicles to form the ruffled border. —GJS

Pathophysiology

Luo JL, Tan W, Ricono JM, Korchynskyi O, Zhang M, Gonias SL, Cheresh DA, Karin M. Nuclear cytokine-activated IKKalpha controls prostate cancer metastasis by repressing Maspin. *Nature*. 2007 Apr 5;446(7136):690-4. [Abstract]

The expression of an inactive form of IKKα (IKKα$^{AA/AA}$), a kinase in the NFκB pathway, blocks metastasis in the TRAMP model of prostate cancer. Phosphorylated IKKα is localized in the nucleus of prostate cancer cells, where it binds the promoter of Maspin, a serpin with antimetatastatic activity, and inhibits Maspin gene transcription. Maspin levels are high in tumors from TRAMP/IKKα$^{AA/AA}$ mice. Restoration of Maspin to prostate cancer cells blocks and knockdown of Maspin enhances their metastatic ability. The authors propose that RANKL-dependent phosphorylation of IKKα promotes metastasis via effects on Maspin, supporting a possible role of RANKL in the osteotropism of prostate cancer. Although the paper shows that the TRAMP model is useful for experimental prostate cancer metastasis, bone metastasis is rare in TRAMP mice. —GJS

Treatment and Drug Effects

Choudhary S, Halbout P, Alander C, Raisz L, Pilbeam C. Strontium ranelate promotes osteoblastic differentiation and mineralization of murine bone marrow stromal cells: involvement of prostaglandins. *J Bone Miner Res*. 2007 Mar 19; [Epub ahead of print] [Abstract]

> *Whether and how strontium ranelate exerts anabolic properties on bone remains a matter of debate. This study shows that Sr-ranelate stimulates osteoblast differentiation (ALP)/ mineralization) in vitro through PGE2 production and that this effect is weaker in cells from COX-2 KO mice. The beginning of a proof-of-concept, but what then about Sr ranelate in the context of COX-2 overactivation, such as in RA?* —SF

Delmas PD, Vrijens B, Eastell R, Roux C, Pols HA, Ringe JD, Grauer A, Cahall D, Watts NB. Effect of monitoring bone turnover markers on persistence with risedronate treatment of postmenopausal osteoporosis. *J Clin Endocrinol Metab*. 2007 Apr;92(4):1296-304. [Abstract] [Full Text]

> *Poor persistence with therapy is an important challenge. About 50% of patients given a prescription for the prevention of fractures stop the medication within 12 months. In this study, positive reinforcement improved persistence and was associated with fewer fractures but, oddly, negative reinforcement — being told the response with markers was not good — did not help with persistence or made it worse.* —ES

Lyytinen H, Pukkala E, Ylikorkala O. Breast cancer risk in postmenopausal women using estrogen-only therapy. *Obstet Gynecol*. 2006 Dec;108(6):1354–60. [Abstract]

Collins J. Hormones and breast cancer: should practice be changed? *Obstet Gynecol*. 2006 Dec;108(6):1352-3. [Info]

> *There is some notion, derived from the WHI, that estrogen alone may be safe. Forget it. In 84,729 women oral estriol (n=7,941), or vaginal estrogens (n=18,314) for at least 6 months were identified, 2,171 women had breast cancer. For estradiol use for 5 years or more the risk was increased by 44%. Oral and transdermal estradiol was accompanied by a similar risk. Oral estradiol use for less than 5 years was not associated with a risk of breast cancer.* —ES

Reviews, Perspectives and Editorials

Balemans W, Van Hul W. The genetics of LRP5 in bone - A story of extremes. *Endocrinology*. 2007 Mar 29; [Epub ahead of print]

Baron R, Rawadi G. Targeting the Wnt/beta-catenin pathway to regulate bone formation in the adult skeleton. *Endocrinology*. 2007 Mar 29; [Epub ahead of print]

Bolos V, Grego-Bessa J, de la Pompa JL. Notch signaling in development and cancer. *Endocr Rev*. 2007 Apr 4; [Epub ahead of print]

Boonen S. Bisphosphonate efficacy and clinical trials for postmenopausal osteoporosis: Similarities and differences. *Bone*. 2007 Mar 28; [Epub ahead of print] [Abstract]

Gao W, Dalton JT. Expanding the therapeutic use of androgens via selective androgen receptor modulators (SARMs). *Drug Discov Today*. 2007 Mar;12(5-6):241-8. [Abstract]

Glass DA 2nd, Karsenty G. In vivo analysis of Wnt signaling in bone. *Endocrinology*. 2007 Mar 29; [Epub ahead of print]

Lindsay R. Are all bisphosphonates the same? *Bone*. 2007 Mar 27; [Epub ahead of print] [Info]

Lindsay R. Beyond clinical trials: The importance of large databases in evaluating differences in the effectiveness of bisphosphonate therapy in postmenopausal osteoporosis. *Bone*. 2007 Mar 27; [Epub ahead of print] [Abstract]

Roux C. Antifracture efficacy of strontium ranelate in postmenopausal osteoporosis. *Bone*. 2007 Feb 17; [Epub ahead of print] [Abstract]

Russell RG. Determinants of structure-function relationships among bisphosphonates. *Bone*. 2007 Apr 3; [Epub ahead of print] [Abstract]

Torres PU, Prie D, Molina-Bletry V, Beck L, Silve C, Friedlander G. Klotho: An antiaging protein involved in mineral and vitamin D metabolism. *Kidney Int*. 2007 Apr;71(8):730-7. [Abstract]

Other Studies of Potential Interest

Demissie S, Dupuis J, Cupples LA, Beck TJ, Kiel DP, Karasik D. Proximal hip geometry is linked to several chromosomal regions: genome-wide linkage results from the Framingham Osteoporosis Study. *Bone*. 2007 Mar;40(3):743-50. [Abstract]

Dvorak MM, Chen TH, Orwoll B, Garvey C, Chang W, Bikle DD, Shoback DM. Constitutive activity of the osteoblast Ca2+-sensing receptor promotes loss of cancellous bone. *Endocrinology*. 2007 Apr 5; [Epub ahead of print]

Greenspan SL, Bone HG, Ettinger MP, Hanley DA, Lindsay R, Zanchetta JR, Blosch CM, Mathisen AL, Morris SA, Marriott TB; Treatment of Osteoporosis with Parathyroid Hormone Study Group. Effect of recombinant human parathyroid hormone (1-84) on vertebral fracture and bone mineral density in postmenopausal women with osteoporosis: a randomized trial. *Ann Intern Med*. 2007 Mar 6;146(5):326-39. [Abstract]

Greenspan SL, Nelson JB, Trump DL, Resnick NM. Effect of once-weekly oral alendronate on bone loss in men receiving androgen deprivation therapy for prostate cancer: a randomized trial. *Ann Intern Med*. 2007 Mar 20;146(6):416-24. [Abstract]

Land C, Rauch F, Travers R, Glorieux FH. Osteogenesis imperfecta type VI in childhood and adolescence: effects of cyclical intravenous pamidronate treatment. *Bone*. 2007 Mar;40(3):638-44. [Abstract]

Makita N, Sato J, Manaka K, Shoji Y, Oishi A, Hashimoto M, Fujita T, Iiri T. An acquired hypocalciuric hypercalcemia autoantibody induces allosteric transition among active human Ca-sensing receptor conformations. *Proc Natl Acad Sci U S A*. 2007 Mar 27;104(13):5443-8. [Abstract] [Full Text]

Martin RB. Targeted bone remodeling involves BMU steering as well as activation. *Bone*. 2007 Mar 1; [Epub ahead of print] [Abstract]

Mau E, Whetstone H, Yu C, Hopyan S, Wunder JS, Alman BA. PTHrP regulates growth plate chondrocyte differentiation and proliferation in a Gli3 dependent manner utilizing hedgehog ligand dependent and independent mechanisms. *Dev Biol*. 2007 Jan 27; [Epub ahead of print] [Abstract]

Mosig RA, Dowling O, Difeo A, Ramirez MC, Parker IC, Abe E, Diouri J, Aqeel AA, Wylie JD, Oblander SA, Madri J, Bianco P, Apte SS, Zaidi M, Doty SB, Majeska RJ, Schaffler MB, Martignetti JA. Loss of MMP-2 disrupts skeletal and craniofacial development, and results in decreased bone mineralization, joint erosion, and defects in osteoblast and osteoclast growth. *Hum Mol Genet*. 2007 Mar 30; [Epub ahead of print] [Abstract]

Rauch F, Cornibert S, Cheung M, Glorieux FH. Long-bone changes after pamidronate discontinuation in children and adolescents with osteogenesis imperfecta. *Bone*. 2007 Apr;40(4):821-7. [Abstract]

Song B, Haycraft CJ, Seo HS, Yoder BK, Serra R. Development of the post-natal growth plate requires intraflagellar transport proteins. *Dev Biol*. 2007 Feb 12; [Epub ahead of print] [Abstract]

Vistoropsky Y, Keter M, Malkin I, Trofimov S, Kobyliansky E, Livshits G. Contribution of the putative genetic factors and ANKH gene polymorphisms to variation of circulating calciotropic molecules, PTH, and BGP. *Hum Mol Genet*. 2007 Apr 2; [Epub ahead of print] [Abstract]

Zhou X, Tian F, Sandzen J, Cao R, Flaberg E, Szekely L, Cao Y, Ohlsson C, Bergo MO, Boren J, Akyurek LM. Filamin B deficiency in mice results in skeletal malformations and impaired microvascular development. *Proc Natl Acad Sci U S A*. 2007 Mar 6;104(10):3919-24. [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.