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NOT TO BE MISSED

Clinical and Basic Research Papers – October 2006 Selections

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

Bone Modeling and Remodeling

Baldock PA, Allison S, McDonald MM, Sainsbury A, Enriquez RF, Little DG, Eisman JA, Gardiner EM, Herzog H. Hypothalamic regulation of cortical bone mass: opposing activity of Y2 receptor and leptin pathways. *J Bone Miner Res*. 2006 Oct;21(10):1600-7. [Abstract]

> *NeuropeptideY-, Y2 receptor (Y2)-, and leptin-deficient mice have high cancellous bone density. Ablation of Y2 receptors increases osteoblast activity on endosteal and periosteal surfaces, resulting in increased cortical bone mass. Leptin-deficient models display reduced cortical mass. The Y2-mediated anabolic pathway stimulates cortical and cancellous bone formation, and the leptin-mediated pathway has opposing effects in cortical and cancellous bone.* —ES

Hassenkam T, Jorgensen HL, Lauritzen JB. Mapping the imprint of bone remodeling by atomic force microscopy. *Anat Rec A Discov Mol Cell Evol Biol*. 2006 Oct;288(10):1087-94. [Abstract]

> *Detailed atomic force microscope (AFM) images from the edge, the front end, and the bottom of a resorption pit in a human trabecular bone sample reveal a scalloped surface left by the osteoclasts and the surface morphology of preexisting bone and new bone tissue. Bone formation front in the pit show anchor points between the new and existing bone. Microcracking in the front of the pit suggests that this was the initiator of resorption.* —ES

Mao D, Epple H, Uthgenannt B, Novack DV, Faccio R. PLCgamma2 regulates osteoclastogenesis via its interaction with ITAM proteins and GAB2. *J Clin Invest*. 2006 Nov;116(11):2869-79. [Abstract] [Full Text]

> *A phospholipase Cγ inhibitor blocks osteoclast formation, and PLCγ2(-/-) mice have mild osteopetrosis. Studies of cell signaling indicate that the defect is in osteoclasts rather than osteoblasts. PLCγ2 is downstream of both RANKL and ITAM proteins, and is required for efficient activation of NFκB, cJUN and NFAT. Different functions of PLCγ2 are necessary in individual pathways: whereas PLCγ works mainly as an adaptor protein in the NFκB and Jun/AP-1 pathways, its catalytic activity is necessary for activation of NFATc1*. —GJS

Semenov MV, He X. LRP5 mutations linked to high bone mass diseases cause reduced LRP5 binding and inhibition by SOST. *J Biol Chem*. 2006 Oct 19; [Epub ahead of print]

> *How LRP5 mutations affect Wnt signaling to produce the high bone mass phenotype is controversial. Evidence has been presented that the G171V mutation increases LRP5 binding to the chaperone MESD, thereby making it an autonomous intracellular signaling molecule, or that it makes LRP5 less sensitive to inhibition by DKK1. This paper finds, in*

contrast, that expression of a number of HBM mutations consistently impairs the ability of sclerostin to inhibit Wnt signaling. The authors propose that the first propeller domain of LRP5 is a sclerostin binding motif. A similar result with regard to the G171V mutation was just published by another group (Ellies et al. J Bone Miner Res. 2006 Nov;21(11):1738-49). —GJS

Szulc P, Seeman E, Duboeuf F, Sornay-Rendu E, Delmas PD. Bone fragility: failure of periosteal apposition to compensate for increased endocortical resorption in postmenopausal women. *J Bone Miner Res*. 2006 Sep 18; [Epub ahead of print] [Abstract]

The authors report that periosteal apposition decreases as age advances, and decreases rather than increases as endocortical resorption increases, challenging the notion that periosteal apposition compensates for endocortical bone loss during menopause. —ES

Xiao Z, Zhang S, Mahlios J, Zhou G, Magenheimer BS, Guo D, Dallas SL, Maser R, Calvet JP, Bonewald L, Quarles LD. Cilia-like structures and polycystin-1 in osteoblasts/osteocytes and associated abnormalities in skeletogenesis and Runx2 expression. *J Biol Chem*. 2006 Oct 13;281(41):30884-95. [Abstract] [Full Text]

Most vertebrate cells possess a single cilium; the ciliary complex (polycystin-1, polycystin-2 and associated proteins) is involved in olfactory and visual sensation, in mechanotransduction and in cell-cell interactions (see Singla V, Reiter JF. Science. 2006 Aug 4;313(5787):629-33). Both osteocytes and osteoblasts possess ciliary components. Removal of a functional Pkd1 gene delays bone formation and impairs Runx2 activity; heterozygotes have impaired osteoblast function, which can be restored by expression of the C-terminal tail of polycystin-1. Cilia may function in osteocyte mechanotransduction (see Bonewald LF. Mechanosensation and Transduction in Osteocytes. BoneKEy-Osteovision. 2006 October;3(10):7-15) and osteoblast function. This landmark paper, together with related work presented at the 2006 ASBMR meeting (see Bellido T. BoneKEy-Osteovision. 2006 November;3(11):14-50), will change the way we think about bone. —GJS

Yirmiya R, Goshen I, Bajayo A, Kreisel T, Feldman S, Tam J, Trembovler V, Csernus V, Shohami E, Bab I. Depression induces bone loss through stimulation of the sympathetic nervous system. *Proc Natl Acad Sci U S A*. 2006 Nov 7;103(45):16876-81. [Abstract] [Full Text]

Two apparently separate findings, namely, the association of major depression with osteoporosis on one side, and the possible decrease in fracture risk among users of β-blockers on another side, may find here a common mechanism. Mice exposed to a (dis)stressful environment for some time develop a decreased interest in drinking and exploring their cage mates, a depression model in rodents. In parallel, these mice lose trabecular bone volume due to decreased bone formation rates. Imipramine, an anti-depressant, as well as propranolol, a β-adrenergic receptor antagonist, prevent these effects. Hence, stress and/or depression may directly affect bone loss by activating the adrenergic pathway. —SF

Epidemiology

Johnell O, Kanis JA. An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. *Osteoporos Int*. 2006 Dec;17(12):1726-33. [Abstract]

At the beginning of this century, there were an estimated 9 million osteoporotic fractures, 1.6 million hip, 1.7 million forearm, and 1.4 million clinical vertebral fractures, 34.8% in Europe. 5.8 million disability-adjusted life-years (DALYs) were lost, 51% accounted for by fractures in Europe and the Americas. Fractures accounted for 0.83% of the global burden of non-communicable disease. In Europe, osteoporotic fractures accounted for more DALYs lost than common cancers, except lung cancer. For chronic musculo-skeletal disorders, the DALYs lost in Europe due to osteoporosis (2.0 million) were less than for osteoarthrosis (3.1 million) but greater than for rheumatoid arthritis (1.0 million). —ES

Pathophysiology

Pellegata NS, Quintanilla-Martinez L, Siggelkow H, Samson E, Bink K, Hofler H, Fend F, Graw J, Atkinson MJ. Germ-line mutations in p27Kip1 cause a multiple endocrine neoplasia syndrome in rats and humans. *Proc Natl Acad Sci U S A*. 2006 Oct 17;103(42):15558-63. [Abstract] [Full Text]

A recessive multiple endocrine neoplasia (MEN) syndrome in rats (bilateral pheochromocytoma, parathyroid tumors, thyroid C-cell hyperplasia and endocrine pancreas hyperplasia, associated with bilateral cataracts) was traced to a hypomorphic allele of the Cdkn1b gene, which encodes the cell cycle regulator $p27^{kip1}$. Cdkn1b(-/-) mice develop pituitary intermediate lobe hyperplasia without a true MEN syndrome, but they also do not develop cataracts, indicating there are species differences in gene expression. A patient with MEN1 and no identifiable mutation in the MEN1 gene was shown to have a germline mutation that truncated the $p27^{kip1}$ protein; not yet convincing are family studies to confirm that the mutation is associated with a familial MEN syndrome in humans. —GJS

Reviews, Perspectives and Editorials

Compston JE. Skeletal actions of intermittent parathyroid hormone: Effects on bone remodelling and structure. *Bone*. 2006 Oct 11; [Epub ahead of print] [Abstract]

Eng-Wong J, Reynolds JC, Venzon D, Liewehr D, Gantz S, Danforth D, Liu ET, Chow C, Zujewski J. Effect of raloxifene on bone mineral density in premenopausal women at increased risk of breast cancer. *J Clin Endocrinol Metab*. 2006 Oct;91(10):3941-6. [Abstract] [Full Text]

Franz-Odendaal TA, Hall BK, Witten PE. Buried alive: how osteoblasts become osteocytes. *Dev Dyn*. 2006 Jan;235(1):176-90. [Abstract]

Johnson KA. The SERM of My Dreams. *J Clin Endocrinol Metab*. 2006 Oct;91(10):3754-6. [Info] [Full Text]

Lanou AJ. Bone health in children. *BMJ*. 2006 Oct 14;333(7572):763-4. [Info] [Full Text]

Liu YJ, Shen H, Xiao P, Xiong DH, Li LH, Recker RR, Deng HW. Molecular genetic studies of gene identification for osteoporosis: a 2004 update. *J Bone Miner Res*. 2006 Oct;21(10):1511-35. [Abstract]

Moe SM. Vascular calcification: Hardening of the evidence. *Kidney Int*. 2006 Nov;70(9):1535-7. [Abstract]

O'Riordan JL. Rickets in the 17th century. *J Bone Miner Res*. 2006 Oct;21(10):1506-10. [Abstract]

Schiavi SC. Bone talk. *Nat Genet*. 2006 Nov;38(11):1230-1. [Abstract]

Shane E, Goldring S, Christakos S, Drezner M, Eisman J, Silverman S, Pendrys D. Osteonecrosis of the jaw: more research needed. *J Bone Miner Res*. 2006 Oct;21(10):1503-5. [Info]

Plaza-Menacho I, Burzynski GM, Groot JW, Eggen BJ, Hofstra RM. Current concepts in RET-related genetics, signaling and therapeutics. *Trends Genet*. 2006 Nov;22(11):627-36. [Abstract]

Other Studies of Potential Interest

Clines GA, Mohammad KS, Bao Y, Stephens OW, Suva LJ, Shaughnessy JD Jr, Fox JW, Chirgwin JM, Guise TA. Dickkopf homolog 1 mediates endothelin-1-stimulated new bone formation. *Mol Endocrinol*. 2006 Oct 26; [Epub ahead of print]

Ellies DL, Viviano B, McCarthy J, Rey JP, Itasaki N, Saunders S, Krumlauf R. Bone density ligand, Sclerostin, directly interacts with LRP5 but not LRP5G171V to modulate Wnt activity. *J Bone Miner Res*. 2006 Nov;21(11):1738-49. [Abstract]

Frank NY, Kho AT, Schatton T, Murphy GF, Molloy MJ, Zhan Q, Ramoni MF, Frank MH, Kohane IS, Gussoni E. Regulation of myogenic progenitor proliferation in human fetal skeletal muscle by BMP4 and its antagonist Gremlin. *J Cell Biol*. 2006 Oct 9;175(1):99-110. [Abstract] [Full Text]

Hassan MQ, Tare RS, Lee SH, Mandeville M, Morasso MI, Javed A, van Wijnen AJ, Stein JL, Stein GS, Lian JB. BMP2 commitment to the osteogenic lineage involves activation of Runx2 by Dlx3 and a homeodomain transcriptional network. *J Biol Chem*. 2006 Oct 23; [Epub ahead of print]

Hikita A, Yana I, Wakeyama H, Nakamura M, Kadono Y, Oshima Y, Nakamura K, Seiki M, Tanaka S. Negative regulation of osteoclastogenesis by ectodomain shedding of receptor activator of NF-kappa B ligand. *J Biol Chem*. 2006 Oct 3; [Epub ahead of print]

Iqbal J, Sun L, Kumar TR, Blair HC, Zaidi M. Follicle-stimulating hormone stimulates TNF production from immune cells to enhance osteoblast and osteoclast formation. *Proc Natl Acad Sci U S A*. 2006 Oct 3;103(40):14925-30. [Abstract] [Full Text]

Jiao X, Billings PC, O'connell MP, Kaplan FS, Shore EM, Glaser DL. Heparan sulfate proteoglycans (HSPGS) modulate BMP2 osteogenic bioactivity in C2C12 cells. *J Biol Chem*. 2006 Oct 3; [Epub ahead of print]

Julien M, Magne D, Masson M, Rolli-Derkinderen M, Chassande O, Cario-Toumaniantz C, Cherel Y, Weiss P, Guicheux J. Phosphate stimulates matrix Gla protein expression in chondrocytes through the ERK signaling pathway. *Endocrinology*. 2006 Oct 26; [Epub ahead of print]

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Singhatanadgit W, Salih V, Olsen I. Up-regulation of bone morphogenetic protein receptor IB by growth factors enhances BMP-2-induced human bone cell functions. *J Cell Physiol*. 2006 Dec;209(3):912-22. [Abstract]

Tew SR, Hardingham TE. Regulation of SOX9 mRNA in human articular chondrocytes involving p38 MAPK activation and mRNA stabilisation. *J Biol Chem*. 2006 Oct 18; [Epub ahead of print]

Yang FC, Chen S, Robling AG, Yu X, Nebesio TD, Yan J, Morgan T, Li X, Yuan J, Hock J, Ingram DA, Clapp DW. Hyperactivation of p21 and PI3K cooperate to alter murine and human neurofibromatosis type 1-haploinsufficient osteoclast functions. *J Clin Invest*. 2006 Nov 1;116(11):2880-91. [Abstract] [Full Text]

Yoon BS, Pogue R, Ovchinnikov DA, Yoshii I, Mishina Y, Behringer RR, Lyons KM. BMPs regulate multiple aspects of growth-plate chondrogenesis through opposing actions on FGF pathways. *Development*. 2006 Dec;133(23):4667-78. [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.