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NOT TO BE MISSED

Clinical and Basic Research Papers – August 2005 Selections

Ego Seeman, Clinical Editor
Gordon J. Strewler, Editor

Bone Modeling and Remodeling

Fu L, Patel MS, Bradley A, Wagner EF, Karsenty G. The molecular clock mediates leptin-regulated bone formation. *Cell*. 2005 Sep 9;122(5):803-15. [Abstract]

> *The clock genes* Per *and* Cry *are expressed in osteoblasts and block the osteoblast cell cycle via cyclin D1. Deletion of clock genes leads to a high bone mass phenotype attributed to increased osteoblast activity. Intraventricular leptin, which leads to bone loss in WT mice, increases bone mass in mice with an osteoblast-specific deletion of* Per. *Thus, clock genes mediate the osteoblast effects of leptin, and their deletion uncovers an anabolic effect of leptin that is mediated by stimulation of AP-1 via the sympathetic nervous system. The diurnal rhythm in bone remodeling has been attributed to gut hormones and the role of clock genes is presently unknown. —GJS*

Hong JH, Hwang ES, McManus MT, Amsterdam A, Tian Y, Kalmukova R, Mueller E, Benjamin T, Spiegelman BM, Sharp PA, Hopkins N, Yaffe MB. TAZ, a transcriptional modulator of mesenchymal stem cell differentiation. *Science.* 2005 Aug 12;309(5737):1074-8. [Abstract] [Full Text]

> *Mesenchymal stem cells in bone can differentiate into osteoblasts, chondrocytes or adipocytes, and the control of cell fate is complex. This paper reports that TAZ, a 14-3-3 binding protein, coactivates Runx2-dependent gene expression while repressing PPAR-γ-dependent gene expression. Depletion of TAZ enhances the adipocyte potential of mesenchymal cell lines. TAZ-depleted zebrafish embryos display severe defects in osteogenesis, suggesting a critical role for TAZ in switching cells to an osteoblast cell fate. —GJS*

Koga T, Matsui Y, Asagiri M, Kodama T, de Crombrugghe B, Nakashima K, Takayanagi H. NFAT and Osterix cooperatively regulate bone formation. *Nat Med.* 2005 Aug;11(8):880-5. [Abstract]

> *Post-transplant bone disease has a component of impaired osteoblast function that is attributed to the use of calcineurin inhibitors like cyclosporine A and FK506 for immunosuppression. In the mouse, administration of FK506 reduces bone mass, despite negatively affecting osteoclast differentiation, by severely impairing bone formation. In culture, bone formation is inhibited in* Nfatc1- *and* Nfatc2-*deficient cells as well as in FK506-treated osteoblasts. Thus, NFAT transcription factors, which are important in osteoclast differentiation, also have an important role in the transcriptional program of osteoblasts. —GJS*

Miao D, He B, Jiang Y, Kobayashi T, Soroceanu MA, Zhao J, Su H, Tong X, Amizuka N, Gupta A, Genant HK, Kronenberg HM, Goltzman D, Karaplis AC. Osteoblast-derived PTHrP is a potent endogenous bone anabolic agent that modifies the therapeutic efficacy of administered PTH 1-34. *J Clin Invest.* 2005 Sep 1;115(9):2402-11. [Abstract] [Full Text]

Martin TJ. Osteoblast-derived PTHrP is a physiological regulator of bone formation. *J Clin Invest.* 2005 Sep 1;115(9):2322-2324. [Abstract] [Full Text]

> *PTHrP has a critical feedback role in the control of chondrocyte hypertrophy. Miao,* et al, *reviewed by Martin, show that PTHrP also has a physiological role in bone. Secreted by preosteoblasts, PTHrP regulates both entry of cells into the final osteoblast lineage and apoptosis of mature osteoblasts. Removal of PTHrP from the osteoblast lineage produces severe osteoporosis. Thus, in contrast to its role in cartilage, PTHrP has a "feed-forward" action in bone. This may be the "short loop" that was co-opted by PTH to create an anabolic "long loop", but its physiological role is not yet clear. —GJS*

Pathophysiology

Coelho LF, Magno de Freitas Almeida G, Mennechet FJ, Blangy A, Uze G. Interferon-alpha and -beta differentially regulate osteoclastogenesis: role of differential induction of chemokine CXCL11 expression. *Proc Natl Acad Sci U S A.* 2005 Aug 16;102(33):11917-22. [Abstract] [Full Text]

> *Interferon-β (IFN-β) is one hundred fold more potent than IFN-α as an inhibitor of osteoclastogenesis. Gene profiling shows that CXCL11 responds to IFN-β but not IFN-α. While addition of CXCL11 inhibits osteoclast formation in vitro, the responsible receptor has not been identified. Possible CXCL11 receptors include CCR2 and DC-STAMP, which was recently shown to be required for fusion of osteoclast precursors (Yagi M,* et al. J Exp Med 2005 *Aug 1;202(3):345-51.) —GJS*

Kondo H, Nifuji A, Takeda S, Ezura Y, Rittling SR, Denhardt DT, Nakashima K, Karsenty G, Noda M. Unloading induces osteoblastic cell suppression and osteoclastic cell activation to lead to bone loss via sympathetic nervous system. *J Biol Chem.* 2005 Aug 26;280(34):30192-200. [Abstract] [Full Text]

> *Osteoporosis seems to be a neurological disorder. Once again, we have work demonstrating the role of the sympathetic nervous system in the control of bone mass. Treatment with propranolol suppressed the unloading-induced reduction in bone mass. Conversely, isoproterenol reduced bone mass in loaded mice. Reduction in mineral apposition rate, mineralizing surface, and bone formation rate by unloading was suppressed by propranolol. Unloading-induced increases in osteoclast number and surface, as well as urinary deoxypyridinoline, were all suppressed by propranolol. —ES*

Lotinun S, Sibonga JD, Turner RT. Evidence that the cells responsible for marrow fibrosis in a rat model for hyperparathyroidism are preosteoblasts. *Endocrinology.* 2005 Sep;146(9):4074-81. [Abstract] [Full Text]

> *Marrow fibrosis is an important element of severe hyperparathyroidism. This paper explores the fate of marrow fibroblasts in rats infused with continuous PTH. The fibroblasts express osteoblast genes and, at the conclusion of the PTH infusion, they differentiate into osteoblasts on the bone surface. Explosive new bone formation by such cells is the probable basis for hypocalcemia in the "hungry bones syndrome" following successful parathyroidectomy. —GJS*

Physiology and Metabolism

Wang L, Wang Y, Han Y, Henderson SC, Majeska RJ, Weinbaum S, Schaffler MB. In situ measurement of solute transport in the bone lacunar-canalicular system. *Proc Natl Acad Sci U S A*. 2005 Aug 16;102(33):11911-6. [Abstract] [Full Text]

Direct measurement of solute movement in intact bone was achieved by visualizing the movement of sodium fluorescein among lacunae in situ beneath the periosteal surface of mouse cortical bone at depths up to 50 μm with laser scanning confocal microscopy. The diffusion of fluorescein in bone is consistent with the presence of an osteocyte pericellular matrix whose structure resembles that proposed for the endothelial glycocalyx. —ES

Treatment and Drug Effects

Black DM, Bilezikian JP, Ensrud KE, Greenspan SL, Palermo L, Hue T, Lang TF, McGowan JA, Rosen CJ; PaTH Study Investigators. One year of alendronate after one year of parathyroid hormone (1-84) for osteoporosis. *N Engl J Med.* 2005 Aug 11;353(6):555-65. [Abstract] [Full Text]

Women receiving PTH (1-84, 100 μg/d) for 1 year received placebo or alendronate. Subject receiving both PTH and alendronate in year 1, received alendronate only in year 2. Those taking alendronate only in year 1, continued it in year 2. Over 2 years, alendronate after PTH increased BMD relative to placebo after PTH (an increase of 31% in the PTH-alendronate group compared to 14% in the PTH-placebo group). During year 2, subjects receiving placebo lost BMD. After one year of PTH (1-84), gains in BMD appear to be maintained or increased with alendronate but lost if not followed by an antiresorptive agent. —ES

Cosman F, Nieves J, Zion M, Woelfert L, Luckey M, Lindsay R. Daily and cyclic parathyroid hormone in women receiving alendronate. *N Engl J Med.* 2005 Aug 11;353(6):566-75. [Abstract] [Full Text]

Of 126 women with osteoporosis who had been taking alendronate for 1 year, one group continued alendronate, another took PTH (1-34) daily, and a third group took PTH daily for 3 months on and 3 months off. During the subsequent 15 months, markers of bone formation increased in PTH-treated subjects and cycled up in the PTH "on" cycles and down in the PTH "off" cycles. Bone resorption markers increased more in the daily-treatment group than in the cyclic-therapy group. Spinal BMD rose similarly (~5-6%) for each parathyroid hormone group compared with the alendronate group. The authors infer there is an early stage of "pure stimulation of bone formation" by PTH. —ES

Reviews, Perspectives, and Editorials

Bachrach LK. Osteoporosis and measurement of bone mass in children and adolescents. *Endocrinol Metab Clin North Am.* 2005 Sep;34(3):521-35. [Abstract]

Baum M, Schiavi S, Dwarakanath V, Quigley R. Effect of fibroblast growth factor-23 on phosphate transport in proximal tubules. *Kidney Int.* 2005 Sep;68(3):1148-53. [Abstract]

Bonnelye E, Aubin JE. Estrogen receptor-related receptor α: a mediator of estrogen response in bone. *J Clin Endocrinol Metab* 2005;May 90(5):3115–21. [Abstract] [Full Text]

Brinton LA, Lacey JV Jr, Trimble EL. Hormones and endometrial cancer—new data from the Million Women Study. *Lancet.* 2005 Apr 30-May 6;365(9470):1517-8. [Abstract]

Davies JH, Evans BA, Gregory JW. Bone mass acquisition in healthy children. *Arch Dis Child.* 2005 Apr;90(4):373-8. [Abstract]

DiCaprio MR, Enneking WF. Fibrous dysplasia. Pathophysiology, evaluation, and treatment. *J Bone Joint Surg Am.* 2005 Aug;87(8):1848-64. [Abstract] [Full Text]

Diffey B. Do white British children and adolescents get enough sunlight? *BMJ.* 2005 Jul 2;331(7507):3-4. [Full Text]

Hamerman D. Osteoporosis and atherosclerosis: biological linkages and the emergence of dual-purpose therapies. *QJM.* 2005 Jul;98(7):467-84. [Abstract]

Hubner RA, Houston SJ. Bisphosphonates' use in metastatic bone disease. *Hosp Med.* 2005 Jul;66(7):414-9. [Abstract]

Järvinen TLN, Sievänen H, Jokihaara J, Einhorn TA. Revival of bone strength: the bottom line. *J Bone Miner Res.* 2005 May;20(5):717-20. [Info]

Kalaitzidis D, Gilmore TD. Transcription factor cross-talk: the estrogen receptor and NF-κB *Trends Endocrinol Metab.* 2005 Mar;16(2):46-52. [Abstract]

Pettifor JM. Rickets and vitamin d deficiency in children and adolescents. *Endocrinol Metab Clin North Am.* 2005 Sep;34(3):537-53. [Abstract]

Rubin CD. Emerging concepts in osteoporosis and bone strength. *Curr Med Res Opin.* 2005 Jul;21(7):1049-56. [Abstract]

Shaw NJ, Bishop NJ. Bisphosphonate treatment of bone disease. *Arch Dis Child.* 2005 May;90(5):494-9. [Abstract]

Termaat MF, Den Boer FC, Bakker FC, Patka P, Haarman HJ. Bone morphogenetic proteins. Development and clinical efficacy in the treatment of fractures and bone defects. *J Bone Joint Surg Am.* 2005 Jun;87(6):1367-78. [Abstract] [Full Text]

Weinstein RS, Manolagas SC. Apoptosis in glucocorticoid-induced bone disease. *Curr Opin Endocrinol Diabetes.* 2005 June;12(3):219–23.

Other Studies of Potential Interests

Bi Y, Stuelten CH, Kilts T, Wadhwa S, Iozzo RV, Robey PG, Chen XD, Young MF. Extracellular matrix proteoglycans control the fate of bone marrow stromal cells. *J Biol Chem.* 2005 Aug 26;280(34):30481-9. [Abstract] [Full Text]

Celil AB, Campbell PG. BMP-2 and insulin-like growth factor-I mediate Osterix (Osx) expression in human mesenchymal stem cells via the MAPK and protein kinase D signaling pathways. *J Biol Chem.* 2005 Sep 9;280(36):31353-9. [Abstract] [Full Text]

Grech AP, Gardam S, Chan T, Quinn R, Gonzales R, Basten A, Brink R. Tumor necrosis factor receptor 2 (TNFR2) signaling is negatively regulated by a novel, carboxyl-terminal TNFR-associated factor 2 (TRAF2)-binding site. *J Biol Chem.* 2005 Sep 9;280(36):31572-81. [Abstract] [Full Text]

Koga S, Yogo K, Yoshikawa K, Samori H, Goto M, Uchida T, Ishida N, Takeya T. Physical and functional association of c-Src and adhesion and degranulation promoting adaptor protein (ADAP) in osteoclastogenesis in vitro. *J Biol Chem.* 2005 Sep 9;280(36):31564-71. [Abstract] [Full Text]

Li X, Liu P, Liu W, Maye P, Zhang J, Zhang Y, Hurley M, Guo C, Boskey A, Sun L, Harris SE, Rowe DW, Ke HZ, Wu D. Dkk2 has a role in terminal osteoblast differentiation and mineralized matrix formation. *Nat Genet.* 2005;37(9): 945-52. [Abstract]

Matsuoka T, Ahlberg PE, Kessaris N, Iannarelli P, Dennehy U, Richardson WD, McMahon AP, Koentges G. Neural crest origins of the neck and shoulder. *Nature.* 2005 Jul 21;436(7049):347-55. [Abstract]

Roca H, Phimphilai M, Gopalakrishnan R, Xiao G, Franceschi RT. Cooperative interactions between RUNX2 and homeodomain protein-binding sites are critical for the osteoblast-specific expression of the bone sialoprotein gene. *J Biol Chem.* 2005 Sep 2;280(35):30845-55. [Abstract] [Full Text]

Stevens MM, Marini RP, Schaefer D, Aronson J, Langer R, Shastri VP. In vivo engineering of organs: The bone bioreactor. *Proc Natl Acad Sci U S A.* 2005 Aug 9;102(32):11450-5. [Abstract] [Full Text]

Xiao G, Jiang D, Ge C, Zhao Z, Lai Y, Boules H, Phimphilai M, Yang X, Karsenty G, Franceschi RT. Cooperative interactions between activating transcription factor 4 and Runx2/Cbfa1 stimulate osteoblast-specific osteocalcin gene expression. *J Biol Chem.* 2005 Sep 2;280(35):30689-96. [Abstract] [Full Text]

Yagi R, McBurney D, Horton WE Jr. Bcl-2 positively regulates Sox9-dependent chondrocyte gene expression by suppressing the MEK-ERK1/2 signaling pathway. *J Biol Chem.* 2005 Aug 26;280(34):30517-25. [Abstract] [Full Text]

Yamamoto K, Uchida E, Urushino N, Sakaki T, Kagawa N, Sawada N, Kamakura M, Kato S, Inouye K, Yamada S. Identification of the amino acid residue of CYP27B1 responsible for binding of 25-hydroxyvitamin D3 whose mutation causes vitamin D-dependent rickets type 1. *J Biol Chem.* 2005 Aug 26;280(34):30511-6. [Abstract] [Full Text]

Yang L, Carlson SG, McBurney D, Horton WE Jr. Multiple signals induce endoplasmic reticulum stress in both primary and immortalized chondrocytes resulting in loss of differentiation, impaired cell growth, and apoptosis. *J Biol Chem.* 2005 Sep 2;280(35):31156-65. [Abstract] [Full Text]

Zhang YW, Su Y, Lanning N, Swiatek PJ, Bronson RT, Sigler R, Martin RW, Vande Woude GF. Targeted disruption of Mig-6 in the mouse genome leads to early onset degenerative joint disease. *Proc Natl Acad Sci U S A.* 2005 Aug 16;102(33):11740-5. [Abstract] [Full Text]