

## **NOT TO BE MISSED**

### **Clinical and Basic Research Papers – December 2005 Selections**

**Serge Ferrari, Associate Editor**  
**Ego Seeman, Clinical Editor**  
**Gordon J. Stewler, Editor**

#### **Bone Modeling and Remodeling**

◆Wang X, Kua HY, Hu Y, Guo K, Zeng Q, Wu Q, Ng HH, Karsenty G, de Crombrugge B, Yeh J, Li B. p53 functions as a negative regulator of osteoblastogenesis, osteoblast-dependent osteoclastogenesis, and bone remodeling. *J Cell Biol.* 2006 Jan 2;172(1):115-25. [[Abstract](#)] [[Full Text](#)]

*A famous tumor suppressor, p53, is shown to inhibit osteoblast differentiation and proliferation by repressing transcription of osterix, itself an osteoblast-specific transcription factor acting downstream of Runx2. Bone analyses of p53 null mice revealed increased periosteal and trabecular bone formation, cortical and trabecular bone volume and a mild increase of BMD in adults. Moreover, osteoclastogenesis and bone turnover were increased in p53 KO mice as a result of an increased expression of M-CSF by osteoblasts. Hence, p53 appears as a novel regulating factor of bone remodeling and might be implicated in osteosarcoma development. —SF*

#### **Diagnosis**

◆Khosla S, Riggs BL, Atkinson EJ, Oberg AL, McDaniel LJ, Holets M, Peterson JM, Melton LJ 3rd. Effects of sex and age on bone microstructure at the ultradistal radius: a population-based noninvasive in vivo assessment. *J Bone Miner Res.* 2006 Jan;21(1):124-31. [[Abstract](#)]

*High-resolution 3-D pQCT is showing us the skeleton in 3D instead of in 2D as densitometry has done. The authors report several new observations and confirm others. They report that men have thicker trabeculae than women at the ultradistal radius with greater trabecular bone volume/tissue volume but similar trabecular number. That's new. The cross sectional decrease in BV/TV were similar by sex. That's not new, but it is different than the perception in the communal 'mind' and it has important implications. Trabecular number decreased in women, and trabecular thickness decreased in men. That's not new. Whether these structural differences explain sex differences in fracture rates is untested experimentally. —ES*

#### **Epidemiology**

◆Qiu S, Rao DS, Palnitkar S, Parfitt AM. Differences in osteocyte and lacunar density between Black and White American women. *Bone.* 2006 Jan;38(1):130-5. [[Abstract](#)]

*Osteocyte deficiency may be an independent risk factor for bone fragility. There is evidence for loss of bone strength associated with apoptosis before any bone loss. Black women have fewer fractures than White women. This is the only study examining osteocyte density in Blacks. The authors report cancellous bone is made with more osteocytes in Blacks, perhaps because of diminished apoptosis of osteoblasts. There are*

*fewer osteocytes in deep bone than in superficial bone, as is the case in White women, and there was moderate age-related loss of osteocytes in deep bone in Black and White women. —ES*

## Pathophysiology

◆Chutipongtanate S, Nakagawa Y, Sritippayawan S, Pittayamateekul J, Parichatikanond P, Westley BR, May FE, Malasit P, Thongboonkerd V. Identification of human urinary trefoil factor 1 as a novel calcium oxalate crystal growth inhibitor. *J Clin Invest*. 2005 Dec 1;115(12):3613-22. [\[Abstract\]](#) [\[Full Text\]](#)

*The pathogenesis of calcium-containing kidney stones is enigmatic, but since urine is typically supersaturated with calcium oxalate, inhibitors of precipitation may be what protect most of us from kidney stones. This paper reports the brute force purification from urine and the identification of urinary trefoil factor 1 as a new member of a small group of anionic proteins that inhibit calcium oxalate crystal growth. Levels of trefoil factor 1 are markedly reduced in the urine of stone formers. —GJS*

◆Kitaura H, Zhou P, Kim HJ, Novack DV, Ross FP, Teitelbaum SL. M-CSF mediates TNF-induced inflammatory osteolysis. *J Clin Invest*. 2005 Dec;115(12):3418-27. [\[Abstract\]](#) [\[Full Text\]](#)

*Cytokines interact in complex ways to induce osteoclastic bone resorption. This paper shows that the inflammatory cytokine TNF- $\alpha$  acts on both osteoclasts and stromal cells to induce bone resorption, but its predominant effect is mediated by induction of M-CSF production in stromal cells, and an antibody to the M-CSF receptor, c-Fms, blocks periarticular bone destruction in a mouse model of inflammatory arthritis. M-CSF is another potential target of drugs to prevent bone destruction in arthritic conditions. —GJS*

## Physiology and Metabolism

◆Li J, Liu D, Ke HZ, Duncan RL, Turner CH. The P2X7 nucleotide receptor mediates skeletal mechanotransduction. *J Biol Chem*. 2005 Dec 30;280(52):42952-9. [\[Abstract\]](#) [\[Full Text\]](#)

*The P2X7 nucleotide receptor is an ATP-gated ion channel. Mice with a null mutation of P2X7R have osteopenia in load bearing bones. Skeletal sensitivity to loading was reduced in P2X7R null mice. Release of ATP in calvarial osteoblasts occurred within one minute of shear stress, and pore formation failed to occur while prostaglandin (PG) E2 release failed to occur. ATP signaling through P2X7R is necessary for mechanically-induced release of prostaglandins and osteogenesis. —ES*

## Reviews, Perspectives and Editorials

◆Balooch G, Balooch M, Nalla RK, Schilling S, Filvaroff EH, Marshall GW, Marshall SJ, Ritchie RO, Derynck R, Alliston T. TGF-beta regulates the mechanical properties and composition of bone matrix. *Proc Natl Acad Sci U S A*. 2005 Dec 27;102(52):18813-8. [\[Abstract\]](#) [\[Full Text\]](#)

◆Clowes JA, Riggs BL, Khosla S. The role of the immune system in the pathophysiology of osteoporosis. *Immunol Rev*. 2005 Dec;208:207-27. [\[Abstract\]](#)

◆Kannus P, Sievanen H, Palvanen M, Jarvinen T, Parkkari J. Prevention of falls and consequent injuries in elderly people. *Lancet*. 2005 Nov 26;366(9500):1885-93. [\[Abstract\]](#)

- ◆Khosla S, Riggs BL. Pathophysiology of age-related bone loss and osteoporosis. *Endocrinol Metab Clin North Am*. 2005 Dec;34(4):1015-30, xi. [\[Info\]](#)
- ◆Raisz LG. Pathogenesis of osteoporosis: concepts, conflicts, and prospects. *J Clin Invest*. 2005 Dec;115(12):3318-25. [\[Abstract\]](#) [\[Full Text\]](#)
- ◆Weitzmann MN, Pacifici R. The role of T lymphocytes in bone metabolism. *Immunol Rev*. 2005 Dec;208:154-68. [\[Abstract\]](#)

### Other Studies of Potential Interest

- ◆Bendre MS, Margulies AG, Walser B, Akel NS, Bhattacharya S, Skinner RA, Swain F, Ramani V, Mohammad KS, Wessner LL, Martinez A, Guise TA, Chirgwin JM, Gaddy D, Suva LJ. Tumor-derived interleukin-8 stimulates osteolysis independent of the receptor activator of nuclear factor-kappaB ligand pathway. *Cancer Res*. 2005 Dec 1;65(23):11001-9. [\[Abstract\]](#)
- ◆Bergwitz C, Roslin NM, Tieder M, Loredó-Osti JC, Bastepe M, Abu-Zahra H, Frappier D, Burkett K, Carpenter TO, Anderson D, Garabedian M, Sermet I, Fujiwara TM, Morgan K, Tenenhouse HS, Juppner H. SLC34A3 mutations in patients with hereditary hypophosphatemic rickets with hypercalciuria predict a key role for the sodium-phosphate cotransporter NaPi-IIc in maintaining phosphate homeostasis. *Am J Hum Genet*. 2006 Feb;78(2):179-92. [\[Abstract\]](#)
- ◆Deckelbaum RA, Majithia A, Booker T, Henderson JE, Loomis CA. The homeoprotein engrailed 1 has pleiotropic functions in calvarial intramembranous bone formation and remodeling. *Development*. 2006 Jan;133(1):63-74. [\[Abstract\]](#)
- ◆Gardner JC, van Bezooijen RL, Mervis B, Hamdy NA, Lowik CW, Hamersma H, Beighton P, Papapoulos SE. Bone mineral density in sclerosteosis; affected individuals and gene carriers. *J Clin Endocrinol Metab*. 2005 Dec;90(12):6392-5. [\[Abstract\]](#) [\[Full Text\]](#)
- ◆Hughes S, Magnay J, Foreman M, Publicover SJ, Dobson JP, El Haj AJ. Expression of the mechanosensitive 2PK+ channel TREK-1 in human osteoblasts. *J Cell Physiol*. 2006 Mar;206(3):738-48. [\[Abstract\]](#)
- ◆Kobayashi T, Lyons KM, McMahon AP, Kronenberg HM. BMP signaling stimulates cellular differentiation at multiple steps during cartilage development. *Proc Natl Acad Sci U S A*. 2005 Dec 13;102(50):18023-7. [\[Abstract\]](#) [\[Full Text\]](#)
- ◆Liu W, Wang S, Wei S, Sun L, Feng X. Receptor activator of NF-kappaB (RANK) cytoplasmic motif, 369PFQEP373, plays a predominant role in osteoclast survival in part by activating Akt/PKB and its downstream effector AFX/FOXO4. *J Biol Chem*. 2005 Dec 30;280(52):43064-72. [\[Abstract\]](#) [\[Full Text\]](#)
- ◆Macdonald HM, McGuigan FE, Stewart A, Black AJ, Fraser WD, Ralston S, Reid DM. Large-scale population-based study shows no evidence of association between common polymorphism of the VDR gene and BMD in British women. *J Bone Miner Res*. 2006 Jan;21(1):151-62. [\[Abstract\]](#)
- ◆Mahon MJ, Bonacci TM, Divieti P, Smrcka AV. A docking site for G protein betagamma subunits on the parathyroid hormone 1 receptor supports signaling through multiple pathways. *Mol Endocrinol*. 2006 Jan;20(1):136-46. [\[Abstract\]](#) [\[Full Text\]](#)

◆ van Meurs JB, Rivadeneira F, Jhamai M, Hagens W, Hofman A, van Leeuwen JP, Pols HA, Uitterlinden AG. Common genetic variation of the low-density lipoprotein receptor-related protein 5 and 6 genes determines fracture risk in elderly white men. *J Bone Miner Res*. 2006 Jan;21(1):141-50. [[Abstract](#)]

◆ Wermers RA, Khosla S, Atkinson EJ, Achenbach SJ, Oberg AL, Grant CS, Melton LJ 3rd. Incidence of primary hyperparathyroidism in Rochester, Minnesota, 1993-2001: an update on the changing epidemiology of the disease. *J Bone Miner Res*. 2006 Jan;21(1):171-7. [[Abstract](#)]

◆ Xi R, Xie T. Stem cell self-renewal controlled by chromatin remodeling factors. *Science*. 2005 Dec 2;310(5753):1487-9. [[Abstract](#)] [[Full Text](#)]

◆ Yasmin R, Williams RM, Xu M, Noy N. Nuclear import of the retinoid X receptor, the vitamin D receptor, and their mutual heterodimer. *J Biol Chem*. 2005 Dec 2;280(48):40152-60. [[Abstract](#)] [[Full Text](#)]

◆ Young N, Mikhalkevich N, Yan Y, Chen D, Zheng WP. Differential regulation of osteoblast activity by Th cell subsets mediated by parathyroid hormone and IFN-gamma. *J Immunol*. 2005 Dec 15;175(12):8287-95. [[Abstract](#)]

**Conflict of Interest:** Dr. Ferrari and Dr. Strewler report that no conflicts of interest exist. 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.