IBMS BoneKEy. 2009 August;6(8):265-267
http://www.bonekey-ibms.org/cgi/content/full/ibmske;6/8/265
doi: 10.1138/20090389

NOT TO BE MISSED

Clinical and Basic Research Papers – August 2009

Serge Ferrari, Editor-in-Chief
Ego Seeman, Clinical Editor
Hong-Wen Deng, Associate Editor
David G. Little, Associate Editor
Toshio Matsumoto, Associate Editor

Bone Modeling, Remodeling, and Repair

Nikolaou VS, Efstathopoulos N, Kontakis G, Kanakaris NK, Giannoudis PV. The influence of osteoporosis in femoral fracture healing time. *Injury*. 2009 Jun;40(6):663-8. [Abstract]

McCann RM, Colleary G, Geddis C, Clarke SA, Jordan GR, Dickson GR, Marsh D. Effect of osteoporosis on bone mineral density and fracture repair in a rat femoral fracture model. *J Orthop Res*. 2008 Mar;26(3):384-93. [Abstract]

> *In the first study, 165 patients with femoral shaft fractures that were treated with locked-reamed intramedullary nailing were retrospectively reviewed to assess the effect of osteoporosis on healing time. The Singh-index score for osteoporosis and the canal bone ratio (CBR) were used as surrogates for the presence of osteoporosis. 29 patients >65 years of age had evidence of osteoporosis whereas 37 aged 18-40 had no evidence of osteoporosis. Fractures in the older age group healed in 19.38+/-5.9 weeks (12-30) and in young patients 16.19+/-5.07 weeks (10-28). Although this represents a difference of 20% mean healing (P=0.02), the impact is not large, with similar ranges in the two groups.*
>
> *The second paper is an animal study on the same issue. Externally fixated, mid-diaphyseal femoral osteotomy at 6 months in ovariectomy (OVX) and control rats. Animals were sacrificed at multiple time points to allow assessment of rate of healing histologically and mechanical testing at later time points. OVX animals had significantly lower BMD, slower fracture repair, and reduced stiffness in the fractured femora (8 weeks) and strength in the contralateral femora (6 and 8 weeks). Mobility was decreased in OVX rats, and body weight increased. OVX delayed fracture healing in this experiment.*
>
> *OVX and age do seem to be associated with delays in healing. More evidence on this point and whether this can be reversed by OVX treatment is warranted.* —DGL

Liu JT, Liao WJ, Tan WC, Lee JK, Liu CH, Chen YH, Lin TB. Balloon kyphoplasty versus vertebroplasty for treatment of osteoporotic vertebral compression fracture: a prospective, comparative, and randomized clinical study. *Osteoporos Int*. 2009 Jun 10. [Epub ahead of print] [Abstract]

> *This randomized study of 100 patients with acute vertebral compression fractures showed no difference in outcome between balloon kyphoplasty (expensive) and vertebroplasty (cheap). Vertebral body height and kyphotic wedge angle of the T-L spine were improved. Visual analog scale (VAS) pain scores did not differ significantly between the treatment groups over 6 months. Two patients in the kyphoplasty group*

had an adjacent segment fracture. In terms of clinical outcome there was little difference between the treatment groups. —DGL

Clinical Studies and Drug Effects

Bell KJ, Hayen A, Macaskill P, Irwig L, Craig JC, Ensrud K, Bauer DC. Value of routine monitoring of bone mineral density after starting bisphosphonate treatment: secondary analysis of trial data. *BMJ*. 2009 Jun 23;338:b2266. [Abstract] [Full Text]

Not easy reading but the message is important. There is no scientific justification for repeating BMD measurement to monitor response. In 6,459 postmenopausal women, alendronate increases hip bone density in 97.5% of patients during three years. —ES

Molecular and Cell Biology

Jansen ID, Mardones P, Lecanda F, de Vries TJ, Recalde S, Hoeben KA, Schoenmaker T, Ravesloot JH, van Borren MM, van Eijden TM, Bronckers AL, Kellokumpu S, Medina JF, Everts V, Oude Elferink RP. $Ae2_{a,b}$-Deficient mice exhibit osteopetrosis of long bones but not of calvaria. *FASEB J*. 2009 Jun 29. [E-pub ahead of print]

During proton pumping at the ruffled border of osteoclasts, intracellular pH is kept virtually constant by chloride/bicarbonate exchange at the apical membrane. This study, using Na^+-independent chloride/bicarbonate anion exchanger 2 (Ae2)(-/-) mice (deficient in the main isoforms Ae2a, $Ae2b_1$, and $Ae2b_2$), showed that multinucleated osteoclasts in the long bones lacked a ruffled border and displayed impaired bone resorption activity, resulting in an osteopetrotic phenotype. In contrast, the skulls of $Ae2_{a,b}$(-/-) mice showed no alterations, with normal resorptive activity of calvaria osteoclasts. Because calvaria osteoclasts, but not long-bone osteoclasts, possessed a sodium-dependent bicarbonate transporting activity with expression of Slc4a4 in addition to Ae2, this might compensate for the absence of Ae2 in calvaria osteoclasts of $Ae2_{a,b}$(-/-) mice. This study provides evidence of functional diversity between different osteoclast populations at different skeletal sites. —TM

Tang Y, Wu X, Lei W, Pang L, Wan C, Shi Z, Zhao L, Nagy TR, Peng X, Hu J, Feng X, Van Hul W, Wan M, Cao X. TGF-beta1-induced migration of bone mesenchymal stem cells couples bone resorption with formation. *Nat Med*. 2009 Jul;15(7):757-65. [Abstract]

The mechanism whereby bone formation is initiated at newly resorbed sites remains unclear. This study demonstrates that active TGF-β1 released during bone resorption coordinates bone formation by inducing migration of bone mesenchymal stem cells to bone resorptive sites, and that this process is mediated through a SMAD signaling pathway. Camurati-Engelmann disease (CED) is caused by mutations in the latency-associated protein region of the TGF-β1 gene, causing release of greater amounts of active TGF-β1. Mice carrying a CED-derived mutant TGF-β1 displayed uncoupled bone remodeling with typical progressive diaphyseal dysplasia seen in the human disease. These results demonstrate that TGF-β1 functions to couple bone resorption and formation. Modulation of TGF-β1 activity in bone could become a new modality of therapy by modulating the balance between bone resorption and formation. —TM

Pathophysiology

Korpal M, Yan J, Lu X, Xu S, Lerit DA, Kang Y. Imaging transforming growth factor-beta signaling dynamics and therapeutic response in breast cancer bone metastasis. *Nat Med*. 2009

July 13. [E-pub ahead of print] [Abstract]

> *This study examined spatio-temporal involvement and the role of transforming growth factor-β (TGF-β) in the establishment of breast cancer metastasis to bone. The authors engineered a sophisticated xenograft model system using a breast cancer cell line, SCP28, with a dual-luciferase reporter system for tracing both metastatic burden by renila luciferase and TGF-β signaling activity by firefly luciferase in vivo. TGF-β-SMAD signaling was conditionally controlled directly by doxocycline-dependent control of SMAD4 expression or a TGF-β receptor I kinase inhibitor, LY2109761, and indirectly by inhibition of osteoclast function with bisphosphonates. The results demonstrate that TGF-β signaling is upregulated in osteolytic bone lesions, and plays an important role in the early phase of bone metastasis, but that disruption of TGF-β signaling becomes less effective after establishment of bone lesions. Real-time manipulation and detection of metastasis-associated signaling pathways can provide a powerful platform to expedite the development of therapeutic agents.* —TM

Other Studies of Potential Interest

Houde N, Chamoux E, Bisson M, Roux S. TGF-beta1 induces human osteoclast apoptosis by uregulating bim. *J Biol Chem*. 2009 Jul 1. [Epub ahead of print]

Huang HH, Brennan TC, Muir MM, Mason RS. Functional alpha1- and beta2-adrenergic receptors in human osteoblasts. *J Cell Physiol*. 2009 Jul;220(1):267-75. [Abstract]

Kalak R, Zhou H, Street J, Day RE, Modzelewski JR, Spies CM, Liu PY, Li G, Dunstan CR, Seibel MJ. Endogenous glucocorticoid signalling in osteoblasts is necessary to maintain normal bone structure in mice. *Bone*. 2009 Jul;45(1):61-7. [Abstract]

Mead TJ, Yutzey KE. Notch pathway regulation of chondrocyte differentiation and proliferation during appendicular and axial skeleton development. *Proc Natl Acad Sci U S A*. 2009 Jul 9. [Epub ahead of print]

Orriss IR, Knight GE, Utting JC, Taylor SE, Burnstock G, Arnett TR. Hypoxia stimulates vesicular ATP release from rat osteoblasts. *J Cell Physiol*. 2009 Jul;220(1):155-62. [Abstract]

Zhang F, Qiu T, Wu X, Wan C, Shi W, Wang Y, Chen JG, Wan M, Clemens TL, Cao X. Sustained BMP signaling in osteoblasts stimulates bone formation by promoting angiogenesis and osteoblast differentiation. *J Bone Miner Res*. 2009 Jul;24(7):1224-33. [Abstract]

Zhang X, Dowd DR, Moore MC, Kranenburg TA, Meester-Smoor MA, Zwarthoff EC, Macdonald PN. Meningioma 1 is required for appropriate osteoblast proliferation, motility, differentiation, and function. *J Biol Chem*. 2009 Jul 3;284(27):18174-83. [Abstract] [Full Text]

Zou W, Reeve JL, Zhao H, Ross FP, Teitelbaum SL. Syk tyrosine 317 negatively regulates osteoclast function via the ubiquitin-protein isopeptide ligase activity of Cbl. *J Biol Chem*. 2009 Jul 10;284(28):18833-9. [Abstract] [Full Text]

Conflict of Interest: Dr. Ferrari reports that he receives research support from Amgen and is an advisory committee member and lectures occasionally at conference symposia for Merck Sharp & Dohme, the Alliance for Better Bone Health (sanofi aventis/P&G), Amgen, Eli Lilly (Switzerland), Servier (Switzerland), and Novartis (Switzerland). Dr. Little reports that he receives royalties, research funds and consultancy fees from Novartis Pharma, as well as research support from Stryker Biotech. 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. Matsumoto and Dr. Deng report no conflicts of interest.