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NOT TO BE MISSED

Clinical and Basic Research Papers – September 2011

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Cancer and Bone

Lipton A, Chapman JA, Demers L, Shepherd LE, Han L, Wilson CF, Pritchard KI, Leitzel KE, Ali SM, Pollak M. Elevated bone turnover predicts for bone metastasis in postmenopausal breast cancer: results of NCIC CTG MA.14. *J Clin Oncol*. 2011 Aug 22. [Epub ahead of print] [Abstract]

> *The aim of this study is to determine whether serum levels of a bone resorption marker (the C-terminal telopeptide of type I collagen or CTX) before treatment of 621 patients with primary breast cancer are predictive of relapses. Recurrence-free survival (RFS) is a secondary endpoint in the study; the focus here is bone-only relapse. Results showed that high serum CTX levels before treatment were associated with shorter bone-only RFS (P=.02), indicating that increased bone resorption creates an environment that promotes the growth of breast cancer cells.* —PC

Sathiakumar N, Delzell E, Morrisey MA, Falkson C, Yong M, Chia V, Blackburn J, Arora T, Brill I, Kilgore ML. Mortality following bone metastasis and skeletal-related events among women with breast cancer: a population-based analysis of U.S. Medicare beneficiaries, 1999-2006. *Breast Cancer Res Treat*. 2011 Aug 13. [Epub ahead of print] [Abstract]

> *The purpose of this work is to quantify the impact of bone metastasis and skeletal-related events (SREs) on mortality in older breast cancer patients (65 years of age or older). Among 98,260 women with breast cancer (median follow-up, 3.3 years), 7,189 (7.3%) had bone metastasis either at breast cancer diagnosis (1.5%) or during follow-up (5.8%). SREs occurred in 3,319 (46%) of women with bone metastasis. Having a bone metastasis was strongly associated with mortality among women with breast cancer (HR=4.9; 95% CI, 4.7-5.1) compared with women without bone metastasis. This association was even stronger for bone metastasis complicated by SREs than for bone metastasis without SREs (HR=6.2; 95% CI, 5.9-6.5).* —PC

Wu P, Walker BA, Brewer D, Gregory WM, Ashcroft J, Ross FM, Jackson GH, Child JA, Davies FE, Morgan GJ. A gene expression based predictor for myeloma patients at high risk of developing bone disease on bisphosphonate treatment. *Clin Cancer Res*. 2011 Aug 19. [Epub ahead of print] [Abstract]

> *The goal of this research is to develop a predictive gene signature for patients at high risk of developing SREs despite bisphosphonate treatment. Global gene expression analysis was performed with 261 presenting myeloma samples. A signature comprising 7 genes (including the WNT signaling antagonist DKK1) was identified as a SRE predictor.* —PC

Genetics

Grimes R, Jepsen KJ, Fitch JL, Einhorn TA, Gerstenfeld LC. The transcriptome of fracture healing defines mechanisms of coordination of skeletal and vascular development during endochondral bone formation. *J Bone Miner Res*. 2011 Aug 8. [Epub ahead of print] [Abstract]

Dimitriou R, Carr IM, West RM, Markham AF, Giannoudis PV. Genetic predisposition to fracture non-union: a case control study of a preliminary single nucleotide polymorphisms analysis of the BMP pathway. *BMC Musculoskelet Disord*. 2011 Feb 10;12:44. [Abstract]

> *Here are two papers dealing with the role of bone morphogenetic proteins (BMPs) in fracture healing. In the first study, two mouse strains, C57/B6 (B6) and C3HeJ (C3H), served as a model. It was noted that, during fracture healing, B6 mice initiate chondrogenesis earlier and develop more cartilage than C3H, while C3H develop more bone than cartilage. By comparing the transcriptomes of fracture healing between these strains, the authors identified genes that showed differences in timing and quantitative expression. Thus, significant differences were found in expression of genes associated with the BMP/TGF-β signal transduction pathway.*
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> *In the second study, 15 SNPs within four genes of the BMP pathway (BMP-2, BMP-7, NOGGIN and SMAD6) were examined in humans with long bone fractures. There were 64 patients with atrophic non-union (cases) and 47 with uneventful fracture union (controls). Despite the relatively small sample size of the study, two SNPs — one in NOGGIN and the other in SMAD6 — were associated with a greater risk of fracture non-union. Thus the authors believe that simple genetic testing may contribute to the early identification of non-healing patients and improve understanding of the biologic aspects of fracture healing.* —DK

Hwang JY, et al. Genomewide association study identification of a new genetic locus with susceptibility to osteoporotic fracture in the Korean Population. *Genomics & Informatics*. 2011 Jun 30;9(2):52-8. [Full Text]

> *An adequately-powered genome-wide association study (GWAS) of osteoporotic fracture has yet to be performed. Nevertheless, this modest-size GWAS in a population-based cohort from the Korean Association Resource (KARE) with 288 cases (any low-trauma fracture) and 1,139 controls is among the first attempts. The authors identified a suggestive genetic locus in an intergenic region at 10p11.2 (near the FZD8 (frizzled homolog 8) and ANKRD30A (ankyrin repeat domain 30A) genes) and performed a replication study in a hospital-based sample of vertebral fractures (272 cases and 810 controls). It would be nice to see a confirmation of this locus in another cohort(s) with a more refined phenotype definition.* —DK

Bone Modeling, Remodeling, and Repair

Furuya Y, Mori K, Ninomiya T, Tomimori Y, Tanaka S, Takahashi N, Udagawa N, Uchida K, Yasuda H. Increased bone mass in mice after a single injection of an anti-RANKL neutralizing antibody: evidence for a bone anabolic effect of PTH in mice with few osteoclasts. *J Biol Chem*. 2011 Aug 23. [Epub ahead of print] [Abstract]

> *Four days of injection of a new mouse RANKL neutralizing antibody followed by 2 weeks of high-dose intermittent PTH (160 μg/kg/d) exerted temporally additive effects on bone mass, whereas osteoclasts remained undetectable on bone at the end of the experiment. These results are in keeping with the effects of PTH after OPG treatment*

in mice (Samadfam et al.), whereas concomitant administration of denosumab and PTH showed no additive effects on bone (Pierroz et al.). In the latter study, however, PTH increased osteoclast number on bone surfaces despite denosumab treatment. Therefore, whether or not PTH is capable of activating osteoclastogenesis, bone remodeling and bone mass gain in the presence of RANKL inhibition remains unclear. —SF

Holstein JH, Orth M, Scheuer C, Tami A, Becker SC, Garcia P, Histing T, Mörsdorf P, Klein M, Pohlemann T, Menger MD. Erythropoietin stimulates bone formation, cell proliferation, and angiogenesis in a femoral segmental defect model in mice. *Bone*. 2011 Aug 9. [Epub ahead of print] [Abstract]

This is a nice study showing that erythropoietin (EPO), which is already available, increases angiogenesis and bone formation in a mouse defect model. Previous studies have achieved these effects with vascular endothelial growth factor (VEGF), but VEGF is not, and may never be, available. Simpler pro-angiogenic stimuli such as desferroxamine (Shen et al., 2009) may prove more cost-effective than engineered proteins if research can show that the effects are similar. —DGL

Hsu YH, Chen WY, Chan CH, Wu CH, Sun ZJ, Chang MS. Anti-IL-20 monoclonal antibody inhibits the differentiation of osteoclasts and protects against osteoporotic bone loss. *J Exp Med*. 2011 Aug 29;208(9):1849-61. [Abstract]

A neutralizing antibody against the pro-inflammatory cytokine IL-20 has previously been shown to prevent inflammation and bone loss in a rat model of rheumatoid arthritis. This study now demonstrates that IL-20 promotes RANK expression in osteoclast precursors and RANKL expression in osteoblasts. Il-20 KO mice have increased BMD while IL-20 antibodies prevent ovariectomy-induced bone loss. The role of IL-20 and effects of IL-20 antibodies in rheumatoid arthritis and osteoporosis are very similar to those of IL-15 and anti-IL-15 antibody recently reported (Djaafar et al.). —SF

Huang Y, Zhang X, Du K, Yang F, Shi Y, Huang J, Tang T, Chen D, Dai K. Inhibition of β-catenin signaling in chondrocytes induces delayed fracture healing in mice. *J Orthop Res*. 2011 Aug 4. [Epub ahead of print] [Abstract]

Using the Col2a1-ICAT transgenic mouse, where β-catenin signaling is inhibited in chondrocytes, fracture healing was delayed. Delayed cartilage maturation and vascular invasion were features of disordered healing. Wnt signaling needs to increase for endochondral fracture healing to proceed, but in an ever-emerging, complex situation, decreased Wnt signaling may favor early chondrogenesis in long bone fractures. —DGL

Keibl C, Fügl A, Zanoni G, Tangl S, Wolbank S, Redl H, van Griensven M. Human adipose derived stem cells reduce callus volume upon BMP-2 administration in bone regeneration. *Injury*. 2011 Aug;42(8):814-20. [Abstract]

Adult human adipose-derived stem cells (hASCs) can differentiate into osteoblasts in an osteogenic environment. hASCs were added with or without BMP-2 to drill hole defects into Sprague Dawley rats. No bone formed in the hASC group and less bone formed in the BMP-2 hASC group than the BMP-2-alone group. hASCs inhibited bone formation. Although not investigated here, since BMP-2 is a PPAR-γ stimulator, fat production may have overridden bone production. These cells are not promising candidates for bone repair. —DGL

Kondo H, Ezura Y, Nakamoto T, Hayata T, Notomi T, Sorimachi H, Takeda S, Noda M. MURF1 deficiency suppresses unloading-induced effects on osteoblasts and osteoclasts to lead to bone loss. *J Cell Biochem*. 2011 Aug 22. [Epub ahead of print] [Abstract]

> *MURF1 is a RING finger protein that is expressed in striated muscle tissue. MURF1 has been suggested to act as a ubiquitin ligase, thereby controlling proteasome-dependent degradation of muscle proteins. MURF1 expression increases whereas MURF1 KO mice are protected from muscle loss in response to denervation (disuse). In this study, MURF1 KO mice are shown to have lower trabecular, but not cortical, bone mass, and to be protected against bone loss induced by hind limb suspension. MURF1 was implicated in both the increased bone resorption and decreased bone formation that occurs with disuse. Whether these effects are mediated by MURF1 in muscle and/or whether this molecule is also expressed in bone remains to be clarified.* —SF

Li R, Atesok K, Nauth A, Wright D, Qamirani E, Whyne CM, Schemitsch EH. Endothelial progenitor cells for fracture healing: a microcomputed tomography and biomechanical analysis. *J Orthop Trauma*. 2011 Aug;25(8):467-71. [Abstract]

> *Endothelial progenitor cells (EPCs) were cultured ex vivo from the marrow and implanted in a critical defect model. Successful bony union occurred in the EPC group, but not in controls. In a subsequent but as yet unpublished study, EPCs and mesenchymal stem cells (MSCs) were compared (derived from the same marrow) and EPCs proved superior. Other studies (Lounev et al., 2009) suggest that Tie-2-positive cells (mostly EPCs) can trans-differentiate into cartilage and bone cells in heterotopic ossification. The role of EPCs may be not only to coordinate revascularization but also to supply some of the cellular elements in bone repair.* —DGL

Okamoto M, Murai J, Imai Y, Ikegami D, Kamiya N, Kato S, Mishina Y, Yoshikawa H, Tsumaki N. Conditional deletion of Bmpr1a in differentiated osteoclasts increases osteoblastic bone formation, increasing volume of remodeling bone in mice. *J Bone Miner Res*. 2011 Jul 22. [Epub ahead of print] [Abstract]

> *In order to clarify the function of BMP signals in osteoclasts during bone remodeling, the authors deleted BMP receptor type IA (BMPR1A) specifically in osteoclasts using Cathepsin K-Cre mice. In vitro experiments revealed that the Bmpr1a gene was deleted after osteoclasts were formed from bone marrow macrophages of Bmpr1a conditional KO mice. TRAP staining was increased in osteoclasts of these mice, suggesting that BMPRIA signaling negatively regulates osteoclast differentiation. Bone histomorphometry revealed increased bone volume and trabecular thickness with increased bone formation rates in the secondary spongiosa. Thus, BMPR1A signaling in osteoclasts negatively regulates coupling to osteoblastic bone formation during bone remodeling.* —TM

Molecular and Cell Biology

Barrow AD, Raynal N, Andersen TL, Slatter DA, Bihan D, Pugh N, Cella M, Kim T, Rho J, Negishi-Koga T, Delaisse JM, Takayanagi H, Lorenzo J, Colonna M, Farndale RW, Choi Y, Trowsdale J. OSCAR is a collagen receptor that costimulates osteoclastogenesis in DAP12-deficient humans and mice. *J Clin Invest*. 2011 Sept 1;121(9):3505-16. [Abstract]

> *Osteoclast-associated receptor (OSCAR) was shown to be a potent Fc receptor common γ (FcRγ)-associated co-stimulatory receptor expressed by preosteoclasts in vitro, but a ligand to OSCAR is unknown and OSCAR's role in vivo has been unclear.*

The authors show that OSCAR binds to specific motifs within fibrillar collagens in the extracellular matrix on bone surfaces in which osteoclasts undergo terminal differentiation in vivo. OSCAR promoted osteoclastogenesis in vivo, and OSCAR binding to its collagen motif led to increased numbers of osteoclasts in culture. These results suggest that immunoreceptor tyrosine-based activation motif (ITAM)-containing receptors can respond to exposed ligand in collagen, leading to the functional differentiation of preosteoclasts. —TM

Wu JY, Aarnisalo P, Bastepe M, Sinha P, Fulzele K, Selig MK, Chen M, Poulton IJ, Purton LE, Sims NA, Weinstein LS, Kronenberg HM. Gsα enhances commitment of mesenchymal progenitors to the osteoblast lineage but restrains osteoblast differentiation in mice. *J Clin Invest*. 2011 Aug 1. [Epub ahead of print] [Abstract]

Conditional deletion of Gsα from osterix-expressing cells led to severe osteoporosis with fractures at birth due to impaired bone formation. Rapid differentiation of mature osteoblasts into osteocytes appeared to cause a marked decrease in osteoblast number, resulting in the formation of woven bone. The number of committed osteoblast progenitors was also diminished in mutant mice. Expression of sclerostin and DKK1 was markedly increased with reduced Wnt signaling in the osteoblast lineage. These results demonstrate that Gsα regulates bone formation in two ways: by facilitating the commitment of mesenchymal progenitors to the osteoblast lineage via enhanced Wnt signaling, and by restraining the differentiation of committed osteoblasts to enable formation of normal bone. —TM

Yamaguchi M, Neale Weitzmann M. The intact strontium ranelate complex stimulates osteoblastogenesis and suppresses osteoclastogenesis by antagonizing NF-κB activation. *Mol Cell Biochem*. 2011 Aug 27. [Epub ahead of print] [Abstract]

When strontium ranelate (SR) is administered orally, strontium is absorbed while ranelate is not and is excreted in the feces. At the cellular level, strontium has been shown to inhibit osteoclast development and activity and to promote osteoblast differentiation, through multiple mechanisms, including binding and activation of the calcium-sensing receptor, activation of FGF receptors, and inhibition of NF-κB . This new in vitro study compared the effects of SR, sodium ranelate and strontium chloride on MC3T3 and RAW264 cells. Inhibition of NF-κB was achieved in both cell lines with 10 to 100 μM of SR, but not with only strontium or ranelate. This work suggests that ranelate is an essential component of SR effects on NF-κB inactivation, osteoclastogenesis and osteoblastogenesis. —SF

Physiology and Metabolism

López I, Rodríguez-Ortiz ME, Almadén Y, Guerrero F, Oca AM, Pineda C, Shalhoub V, Rodríguez M, Aguilera-Tejero E. Direct and indirect effects of parathyroid hormone on circulating levels of fibroblast growth factor 23 in vivo. *Kidney Int*. 2011 Sep;80(5):475-82. [Abstract]

Parathyroidectomized (PTX) rats have lower serum calcium and calcitriol levels, and higher phosphate, while PTH infusion restores normal mineral and hormone levels. Surprisingly, FGF23 declined in PTX rats, despite high phosphate levels, and increased with PTH infusion. Calcitriol administration also increased FGF23 levels. These results indicate that PTH is an essential regulator of FGF23. They suggest that FGF23 elevation in chronic renal disease is not merely due to phosphate retention, but to the subsequent increase in PTH levels. —SF

Bone Acquisition/Pediatric Bone

Bhola S, Chen J, Fusco J, Duarte GF, Andarawis-Puri N, Ghillani R, Jepsen KJ. Variation in childhood skeletal robustness is an important determinant of cortical area in young adults. *Bone*. 2011 Jul 23. [Epub ahead of print] [Abstract]

> *Longitudinally-acquired hand radiographs of a modest sample of boys and girls were obtained from the Bolton-Brush study for 6 time points spanning 8 to 18 years of age. Second and third metacarpals were measured for robustness (bone width relative to length). Cortical area for slender bones was as much as 19.7% to 32.2% lower than for robust metacarpals, respectively, indicating that robustness was a major determinant of adult cortical area, an important determinant of bone mass. Interestingly, the inter-individual variation in cortical area was evident as early as 8 years of age.* —DK

Reviews, Perspectives and Editorials

Ackert-Bicknell CL. HDL cholesterol and bone mineral density: Is there a genetic link? *Bone*. 2011 Aug 10. [Epub ahead of print] [Abstract]

Del Buono A, Denaro V, Maffulli N. Genetic susceptibility to aseptic loosening following total hip arthroplasty: a systematic review. *Br Med Bull*. 2011 Jun 7. [Epub ahead of print] [Abstract]

Other Studies of Potential Interest

Brunner M, Millon-Frémillon A, Chevalier G, Nakchbandi IA, Mosher D, Block MR, Albigès-Rizo C, Bouvard D. Osteoblast mineralization requires beta1 integrin/ICAP-1-dependent fibronectin deposition. *J Cell Biol*. 2011 Jul 25;194(2):307-22. [Abstract] [Full Text]

Dishowitz MI, Terkhorn SP, Bostic SA, Hankenson KD. Notch signaling components are upregulated during both endochondral and intramembranous bone regeneration. *J Orthop Res*. 2011 Aug 4. [Epub ahead of print] [Abstract]

Lagerholm S, Park HB, Luthman H, Grynpas M, McGuigan F, Swanberg M, Akesson K. Identification of candidate gene regions in the rat by co-localization of QTLs for bone density, size, structure and strength. *PLoS One*. 2011;6(7):e22462. [Abstract]

Morrison C, Mancini S, Cipollone J, Kappelhoff R, Roskelley C, Overall C. Microarray and proteomic analysis of breast cancer cell and osteoblast co-cultures: the role of osteoblast matrix metalloproteinase (MMP)-13 in bone metastasis. *J Biol Chem*. 2011 Jul 22. [Epub ahead of print] [Abstract]

Perrien DS, Nicks KM, Liu L, Akel NS, Bacon AW, Skinner RA, Swain FL, Aronson J, Suva LJ, Gaddy D. Inhibin A enhances bone formation during distraction osteogenesis. *J Orthop Res*. 2011 Aug 1. [Epub ahead of print] [Abstract]

Romeo F, Falbo L, Di Sanzo M, Misaggi R, Faniello MC, Barni T, Cuda G, Viglietto G, Santoro C, Quaresima B, Costanzo F. Negative transcriptional regulation of the human periostin gene by YingYang-1 transcription factor. *Gene*. 2011 Aug 3. [Epub ahead of print] [Abstract]

Takahata Y, Takarada T, Hinoi E, Nakamura Y, Fujita H, Yoneda Y. Osteoblastic $GABA_B$ receptors negatively regulate osteoblastogenesis toward disturbance of osteoclastogenesis mediated by receptor activator of nuclear factor-kappaB ligand in mouse bone. *J Biol Chem*. 2011 Aug 2. [Epub ahead of print] [Abstract]

Tang W, Li Y, Orsini L, Zhang C. Osteoblast-specific transcription factor osterix (Osx) is an upstream regulator of Satb2 during bone formation. *J Biol Chem*. 2011 Aug 2. [Epub ahead of print] [Abstract]

Wang XX, Allen RJ Jr, Tutela JP, Sailon A, Allori AC, Davidson EH, Paek GK, Saadeh PB, McCarthy JG, Warren SM. Progenitor cell mobilization enhances bone healing by means of improved neovascularization and osteogenesis. *Plast Reconstr Surg*. 2011 Aug;128(2):395-405. [Abstract]

Wong KE, Kong J, Zhang W, Szeto FL, Ye H, Deb DK, Brady MJ, Li YC. Targeted expression of human vitamin D receptor in adipocytes decreases energy expenditure and induces obesity in mice. *J Biol Chem*. 2011 Aug 12. [Epub ahead of print] [Abstract]

Yao Y, Jumabay M, Wang A, Boström KI. Matrix Gla protein deficiency causes arteriovenous malformations in mice. *J Clin Invest*. 2011 Aug 1;121(8):2993-3004. [Abstract]

Zhu W, Liang G, Huang Z, Doty SB, Boskey AL. Conditional inactivation of the CXCR4 receptor in osteoprecursors reduces postnatal bone formation due to impaired osteoblast development. *J Biol Chem*. 2011 Jul 29;286(30):26794-805. [Abstract] [Full Text]

Conflict of Interest: Dr. Clézardin reports receiving research support from Novartis (Basel, Switzerland) and honoraria for advisory work and speaking engagements from Novartis and Amgen. Dr. Ferrari reports that he receives research support from Amgen and Merck Sharp & Dohme, and is an advisory committee member and lectures occasionally at conference symposia for the Alliance for Better Bone Health (sanofi aventis/P&G), Amgen, Merck Sharp & Dohme, Eli Lilly, Servier, and Novartis. 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 reports that he is a member of the advisory board for Eli Lilly, and receives consultancy fees from Chugai, Astellas, Teijin, JT, and Daiichi-Sankyo. Dr. Karasik reports no conflicts of interest.