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NOT TO BE MISSED

Clinical and Basic Research Papers – March 2008

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Bone Modeling, Remodeling and Repair

Behonick DJ, Xing Z, Lieu S, Buckley JM, Lotz JC, Marucucio RS, Werb Z, Miclau T, Colnot C. Role of matrix metalloproteinase 13 in both endochondral and intramembranous ossification during skeletal regeneration. *PLoS ONE*. 2007 Nov 7;2(11):e1150. [Abstract]

> *Endochondral repair was significantly delayed in MMP-13 KO mice, with excessive retention of the early cartilaginous callus. Bone marrow transplantation from WT controls did not rescue this defect in healing, confirming that MMP-13 competent cells derived from hemopoeitic origin (including osteoclasts) are insufficient to restore normal endochondral repair. Hence, MMP-13 produced by hypertrophic chondrocytes and osteoblasts may be directly involved in cartilage degradation, independent of MMP-9 and the invading vasculature. Delayed remodeling was also noted, with impaired resorption of spongy bone. Since MMP-13 competent osteoclasts were unable to restore normal resorption of the spongy bone, the defect in its removal is therefore in the local bone matrix or mesenchymal origin cell population. This paper is further evidence of the evolving understanding of the critical role of MMPs in bone repair.* —DGL

Grimston SK, Brodt MD, Silva MJ, Civitelli R. Attenuated response to in vivo mechanical loading in mice with conditional osteoblast ablation of the connexin43 gene (Gja1). *J Bone Miner Res*. 2008 Feb 18; [Epub ahead of print] [Abstract]

> *Mechanotrasduction is mediated via osteocyte processes to the flattened osteoblast lining cells on periosteal and endosteal surfaces. The connection between the processes and the flattened lining cells is by gap junctions that allow transportation of molecules signaling the need for an anabolic response to loading. Connexins are proteins that form part of this relay and in their absence mechanotransduction fails. 4-month-old female mice with genetic deficiency of the Cx43 gene (Gja1) had thinner cortices, but larger marrow area and total cross-sectional area in the tibial diaphysis. The mice required 40% more force to generate endocortical strain, and mineral apposition rate and bone formation rate were lower in mutants. It is not clear to me why the authors concentrated on the endocortical surface. Periosteal apposition was certainly vigorous and indeed compensated so strength was not reduced and bone area was also normal as the thinner cortex was distributed around a large tibial perimeter.* —ES

Li X, Ominsky MS, Niu QT, Sun N, Daugherty B, D'Agostin D, Kurahara C, Gao Y, Cao J, Gong J, Asuncion F, Barrero M, Warmington K, Dwyer D, Stolina M, Morony S, Sarosi I, Kostenuik PJ, Lacey DL, Simonet WS, Ke HZ, Paszty C. Targeted deletion of the sclerostin gene in mice results in increased bone formation and bone strength. *J Bone Miner Res*. 2008 Feb 12; [Epub ahead of print] [Abstract]

The osteocyte is in fashion. It's having its 15 minutes of fame but this may only be the beginning. The osteocyte functions in two important ways, in damage prevention and damage removal. The former is the function of adaptation; bone adapts to its loading circumstances by depositing or removing bone depending on the signal, and this signal comes from the osteocyte that modulates sclerostin output, decreasing it with loading, increasing it with unloading. The second important function is death. Elvis is dead and lives on. The osteocyte is at its best when it dies. Osteocytes die to signal the location of damage and initiate reparative remodeling activity to remove the damage and replace it with new bone. Li et al. demonstrate that sclerostin knockout mice have increased bone formation, high bone mass and increased bone strength. This is a lovely paper. —ES

Mizoguchi F, Mizuno A, Hayata T, Nakashima K, Heller S, Ushida T, Sokabe M, Miyasaka N, Suzuki M, Ezura Y, Noda M. Transient receptor potential vanilloid 4 deficiency suppresses unloading-induced bone loss. *J Cell Physiol*. 2008 Feb 8; [Epub ahead of print] [Abstract]

TRPV4 in unloading induces bone loss by reducing bone formation in wild-type mice. TRPV4 deficiency suppressed unloading-induced bone loss. TRPV4 deficiency suppressed the unloading-induced reduction in the levels of mineral apposition rate and bone formation rate. In these mice, the unloading-induced increase in the number of osteoclasts in the primary trabecular bone was suppressed by TRPV4 deficiency. The unloading-induced reduction in the longitudinal length of primary trabecular bone was also suppressed by TRPV4 deficiency. TRPV4 protein is expressed in both osteoblasts and osteoclasts. These results indicated that TRPV4 plays a critical role in unloading-induced bone loss. —ES

Sackstein R, Merzaban JS, Cain DW, Dagia NM, Spencer JA, Lin CP, Wohlgemuth R. Ex vivo glycan engineering of CD44 programs human multipotent mesenchymal stromal cell trafficking to bone. *Nat Med*. 2008 Feb;14(2):181-7. [Abstract]

Because direct homing of mesenchymal stromal (stem) cells (MSCs) to skeletal sites does not occur, infusion of MSCs does not show osteotropism and has been clinically ineffective. Cellular recruitment to bone occurs via the interaction of marrow vessel-specific vascular E-selectin and its sialofucosylated ligands. Because MSCs do not express E-selectin ligands but express α-2,3-sialyl CD44, the authors converted the native sialylated CD44 into sialofucosylated CD44 using an α-1,3-fucosyltransferase preparation to form hematopoietic cell E-selectin/L-selectin ligand (HCELL) on live cells. Intravenously infused HCELL-positive MSCs infiltrated marrow and successfully formed osteogenic foci. These observations demonstrate that the HCELL form of CD44 confers osteotropism of infused MSCs, and suggest that chemical engineering of CD44 to form HCELL on viable MSCs may become useful for tissue engineering of bone. —TM

Diagnosis

Kanis JA, Burlet N, Cooper C, Delmas PD, Reginster JY, Borgstrom F, Rizzoli R; on behalf of the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO). European guidance for the diagnosis and management of osteoporosis in postmenopausal women. *Osteoporos Int*. 2008 Apr;19(4):399-428. [Abstract]

For those who do not have time to read the hot-off-the-press "WHO scientific group technical report on the assessment of osteoporosis at the primary health care level," this paper will provide the essential information on how to evaluate fracture probability using T-scores and clinical risk factors, as well as the background to understand the logic behind the FRAX® calculator (see link on BoneKEy), and also a review of the efficacy of

all osteoporosis drugs regarding incidental fractures. Some interesting algorithms based on cost-utility analyses are also presented in this review, showing for instance that women below 65 years of age with T-scores just below -1 may deserve treatment...if they have a strong heredity for bone fragility (a mother with hip fracture). —SF

Pathophysiology

Asagiri M, Hirai T, Kunigami T, Kamano S, Gober HJ, Okamoto K, Nishikawa K, Latz E, Golenbock DT, Aoki K, Ohya K, Imai Y, Morishita Y, Miyazono K, Kato S, Saftig P, Takayanagi H. Cathepsin K-dependent toll-like receptor 9 signaling revealed in experimental arthritis. *Science*. 2008 Feb 1;319(5863):624-7. [Abstract] [Full Text]

Cathepsin K was thought to be an osteoclast-specific lysosomal protease. However, this report demonstrates that inhibition of cathepsin K activity can suppress not only osteoclastic bone resorption but also autoimmune inflammation in autoimmune arthritis. A cathepsin K inhibitor, NC-2300, inhibited toll-like receptor 9 signaling in dendritic cells in response to unmethylated CpG DNA, leading to attenuated induction of T helper 17 cells without affecting antigen presentation by dendritic cells. Although inhibitors of cathepsin K might also inhibit other cathepsins involved in immune reactions, targeted disruption of the cathepsin K gene produced the same results. These results are consistent with the notion that cathepsin K plays an important role in the immune system and may serve as a valid therapeutic target in autoimmune diseases. —TM

Treatment and Drug Effects

Chavassieux P, Asser Karsdal M, Segovia-Silvestre T, Neutzsky-Wulff AV, Chapurlat R, Boivin G, Delmas PD. Mechanisms of the anabolic effects of teriparatide on bone: insight from the treatment of a patient with pycnodysostosis. *J Bone Miner Res*. 2008 Feb 26; [Epub ahead of print] [Abstract]

Whether PTH anabolic effects on the skeleton require the presence of pre-osteoclasts, mature osteoclasts and/or their resorbing activity has gained interest recently. Animal studies have given controversial results (see IBMS BoneKey. 2007 Oct;4(10):278-81), and human studies have not directly adressed the question so far. This is the first study to use an experiment of nature, i.e., a patient with a cathepsin K mutation, to test the activity of intermittent teriparatide in the context of missing osteoclast bone-resorbing activity. Results after 6 months suggest a complete lack of PTH response. However, iliac crest bone histomorphometry showed severely reduced osteoblastic activity and bone formation prior to therapy, suggesting that failure of PTH treatment could also be due to deficient osteoblasts. —SF

Idris AI, Rojas J, Greig IR, Van't Hof RJ, Ralston SH. Aminobisphosphonates cause osteoblast apoptosis and inhibit bone nodule formation in vitro. *Calcif Tissue Int*. 2008 Mar;82(3):191-201. [Abstract]

The aminobisphosphonates pamidronate and alendronate inhibited osteoblast growth, caused osteoblast apoptosis, and inhibited protein prenylation in osteoblasts. Alendronate inhibited protein prenylation in calvarial osteoblasts in vivo. Pamidronate and alendronate inhibited bone nodule formation. These effects were not observed with non-nitrogen-containing bisphosphonates or with other inhibitors of protein prenylation and were only partially reversed by cotreatment with a fourfold molar excess of ss-glycerol phosphate. —ES

MacLean C, Newberry S, Maglione M, McMahon M, Ranganath V, Suttorp M, Mojica W, Timmer M, Alexander A, McNamara M, Desai SB, Zhou A, Chen S, Carter J, Tringale C, Valentine D, Johnsen B, Grossman J. Systematic review: comparative effectiveness of treatments to prevent fractures in men and women with low bone density or osteoporosis. *Ann Intern Med*. 2008 Feb 5;148(3):197-213. [Abstract]

> If you want to be definitely uncertain about the actual efficacy of osteoporosis drugs in reducing fractures, you should check this systematic review: it mixes up prior meta-analyses and genuine RCTs to generate figures stimulating the comparison of drug efficacy, thereby adding confusion to an already confused field. The only good thing here is that the tables provided in the appendix clearly demonstrate that, depending on the meta-analysis, the relative risk reduction of fracture by a certain drug may vary by a factor of 3 (min.). Who said systematic reviews/meta-analyses provided the highest level of evidence for clinical practice? —SF

Nam KW, Kim YL, Yoo JJ, Koo K, Yoon KS, Kim HJ. Fate of untreated asymptomatic osteonecrosis of the femoral head. *J Bone Joint Surg Am*. 2008 Mar;90(3):477-84. [Abstract] [Full Text]

> *This study followed patients with asymptomatic osteonecrosis of the hip to determine what extent of involvement predicted progression of symptoms or deterioration of osteonecrosis stage. A policy of offering surgical treatment to patients under age 50 was followed. Some of the group studied declined such surgery, while others had asymptomatic contralateral involvement and a symptomatic operated or replaced hip. The series establishes that <30% femoral head involvement is not associated with progression or symptoms over 5-year follow-up. Intermediate patients (30-50%) progressed, while rapid progression occurred in severely involved hips (>50%). The study concludes that no treatment is required for asymptomatic stage 1 hips with <30% involvement of the femoral heads. Further, such hips should be excluded from clinical trials as they are unlikely to progress and effects of treatment will not be detectable.*
> —DGL

Reid IR, Bolland MJ, Grey A. Effect of calcium supplementation on hip fractures. *Osteoporos Int*. 2008 Feb 20; [Epub ahead of print] [Abstract]

> *Reid et al. report that a meta-analysis, involving 5,500 women, examinining the effect of calcium on hip fractures suggests adverse trends in numbers of hip fractures (relative risk 1.50, 95% CI 1.06-2.12). This is interesting but is it right? The pendulum will always swing widely to the left or right when trials used in meta-analyses are poorly designed and executed. Have a close look at the trials included here. Many are flawed and include problems such as subjects being replete in calcium – why should supplementation be beneficial when there is no deficiency? In many of the trials there was poor compliance – indeed, in several studies compliance was 50% and a claim was made that there was a benefit in those that complied with calcium. Well, that observation is open to interpretation because violation of randomization means that the lower fracture rate in those taking calcium may be due to factors other than the calcium supplement. So, although meta-analyses look impressive with large sample sizes, I remain skeptical and would prefer one well-designed and well-executed study over a meta-analysis of problematic studies. Does calcium increase or decrease hip fracture rates – I have no idea.* —ES

Syed FA, Oursler MJ, Hefferanm TE, Peterson JM, Riggs BL, Khosla S. Effects of estrogen therapy on bone marrow adipocytes in postmenopausal osteoporotic women. *Osteoporos Int*. 2008 Feb 15; [Epub ahead of print] [Abstract]

> *One-year transdermal estrogen resulted in decreases in marrow adipocyte volume and prevented increases in adipocyte number compared to placebo. Estrogen also prevented increases in mean adipocyte size over 1 year. There is an obvious question, isn't there: what might that do to BMD changes? Heaven forbid that we should acknowledge the nonsense bone densitometry it spits out.* —ES

Reviews, Perspectives and Editorials

Cochrane Reviews

Wells G, Cranney A, Peterson J, Boucher M, Shea B, Robinson V, Coyle D, Tugwell P. Alendronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. *Cochrane Database Syst Rev*. 2008 Jan 23;(1):CD001155. [Abstract]

Wells G, Cranney A, Peterson J, Boucher M, Shea B, Robinson V, Coyle D, Tugwell P. Risedronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. *Cochrane Database Syst Rev*. 2008 Jan 23;(1):CD004523. [Abstract]

Wells G, Cranney A, Peterson J, Boucher M, Shea B, Robinson V, Coyle D, Tugwell P. Etidronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. *Cochrane Database Syst Rev*. Jan 2008;(1):CD003376. [Abstract]

Bonewald LF, Johnson ML. Osteocytes, mechanosensing and Wnt signaling. *Bone*. 2008 Jan 12; [Epub ahead of print] [Abstract]

Khosla S, Westendorf JJ, Oursler MJ. Building bone to reverse osteoporosis and repair fractures. *J Clin Invest*. 2008 Feb;118(2):421-8. [Abstract]

Macsai CE, Foster BK, Xian CJ. Roles of Wnt signalling in bone growth, remodelling, skeletal disorders and fracture repair. *J Cell Physiol*. 2008 Feb 4; [Epub ahead of print] [Abstract]

Roodman GD. Bone building with bortezomib. *J Clin Invest*. 2008 Feb;118(2):462-4. [Abstract]

Russell RG, Watts NB, Ebetino FH, Rogers MJ. Mechanisms of action of bisphosphonates: similarities and differences and their potential influence on clinical efficacy. *Osteoporos Int*. 2008 Jan 24; [Epub ahead of print] [Abstract]

Schindeler A, Little DG. Recent insights into bone development, homeostasis, and repair in type 1 neurofibromatosis (NF1). *Bone*. 2007 Nov 28; [Epub ahead of print] [Abstract]

Shaikh A, Berndt T, Kumar R. Regulation of phosphate homeostasis by the phosphatonins and other novel mediators. *Pediatr Nephrol*. 2008 Feb 21; [Epub ahead of print] [Abstract]

Zhang J, Li L. Stem cell niche - Microenvironment and beyond. *J Biol Chem*. 2008 Feb 13; [Epub ahead of print]

Zuscik MJ, Hilton MJ, Zhang X, Chen D, O'Keefe RJ. Regulation of chondrogenesis and chondrocyte differentiation by stress. *J Clin Invest*. 2008 Feb;118(2):429-38. [Abstract]

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Other Studies of Potential Interest

Crotti TN, Sharma SM, Fleming JD, Flannery MR, Ostrowski MC, Goldring SR, McHugh KP. PU.1 and NFATc1 mediate osteoclastic induction of the mouse beta(3) integrin promoter. *J Cell Physiol*. 2008 Feb 20; [Epub ahead of print] [Abstract]

Ignat M, Teletin M, Tisserand J, Khetchoumian K, Dennefeld C, Chambon P, Losson R, Mark M. Arterial calcifications and increased expression of vitamin D receptor targets in mice lacking TIF1alpha. *Proc Natl Acad Sci U S A*. 2008 Feb 19;105(7):2598-603. [Abstract] [Full Text]

Javed A, Bae JS, Afzal F, Gutierrez S, Pratap J, Zaidi SK, Lou Y, van Wijnen AJ, Stein JL, Stein GS, Lian JB. Structural coupling of Smad and Runx2 for execution of the BMP2 osteogenic signal. *J Biol Chem*. 2008 Feb 1; [Epub ahead of print]

Lambertini E, Tavanti E, Torreggiani E, Penolazzi L, Gambari R, Piva R. ERalpha and AP-1 interact in vivo with a specific sequence of the F promoter of the human ERalpha gene in osteoblasts. *J Cell Physiol*. 2008 Feb 4; [Epub ahead of print] [Abstract]

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Méndez-Ferrer S, Lucas D, Battista M, Frenette PS. Haematopoietic stem cell release is regulated by circadian oscillations. *Nature*. 2008 Feb 6; [Epub ahead of print] [Abstract]

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Yao Z, Xing L, Qin C, Schwarz EM, Boyce BF. Osteoclast precursor interaction with bone matrix induces osteoclast formation directly by an IL-1-mediated autocrine mechanism. *J Biol Chem*. 2008 Feb 4; [Epub ahead of print]

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. 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 no conflict of interest.