

NOT TO BE MISSED

Clinical and Basic Research Papers – May 2011

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Clinical Studies and Drug Effects

◆ Berenson J, Pflugmacher R, Jarzem P, Zonder J, Schechtman K, Tillman JB, Bastian L, Ashraf T, Vrionis F; Cancer Patient Fracture Evaluation (CAFE) Investigators. Balloon kyphoplasty versus non-surgical fracture management for treatment of painful vertebral body compression fractures in patients with cancer: a multicentre, randomised controlled trial. *Lancet Oncol.* 2011 Mar;12(3):225-35. [[Abstract](#)]

◆ Boonen S, Van Meirhaeghe J, Bastian L, Cummings SR, Ranstam J, Tillman JB, Eastell R, Talmadge K, Wardlaw D. Balloon kyphoplasty for the treatment of acute vertebral compression fractures: 2-year results from a randomized trial. *J Bone Miner Res.* 2011 Feb 17. [Epub ahead of print] [[Abstract](#)]

These two recent RCTs examine balloon kyphoplasty in cancer and osteoporosis. In the Berenson et al. study, 134 patients were enrolled and randomly assigned to kyphoplasty (n = 70) or non-surgical management (n = 64). Patients in the control group were offered kyphoplasty after the 1-month assessment. At 1 month, the kyphoplasty treatment effect for Roland-Morris disability questionnaire (RDQ) was -8.4 points (95% CI, -7.6 to -9.2; p < 0.0001). Improvements over those opting for continued conservative care were largely maintained at 1 year.

In the Boonen et al. study, 2-year follow-up results from the FREE study (1-year results published previously by Wardlaw et al.) are presented. Adults with one to three vertebral fractures were randomized within 3 months from onset of pain to undergo kyphoplasty (n = 149) or non-surgical therapy (n = 151). SF-36 PCS scores showed a mean improvement over one year of 3.24 points, (95% CI, 1.47-5.01; p = 0.0004). Although these differences are not large, the kyphoplasty group also had a significantly greater improvement in QOL, as assessed by the 1.0-point EQ-5D scale when averaged over 24 months of follow-up (treatment effect 0.12 points, 95% CI, 0.06-0.18; p = 0.0002). The calculated improved QALY and cost increase are at the border of most thresholds for willingness to pay.

These improvements are in open-label studies. Although kyphoplasty is a different procedure than vertebroplasty where no balloon is used, where open-label studies showed improvements recent sham studies of vertebroplasty failed to show any differences between treated and sham groups ([Kallmes et al.](#) and [Buchbinder et al.](#)). There may be a need for sham/placebo-controlled trials of vertebroplasty for a thorough review of cost-effectiveness. —DGL

- ◆Eslami B, Zhou S, Van Eekeren I, LeBoff MS, Glowacki J. Reduced osteoclastogenesis and RANKL expression in marrow from women taking alendronate. *Calcif Tissue Int.* 2011 Apr;88(4):272-80. [[Abstract](#)]

Previous in vitro studies have shown that bisphosphonates may affect osteoclastogenesis as well as osteoclast function. This study examined bone marrow-derived stem cells (BMCs) acquired during orthopedic surgery from women taking alendronate and those not taking alendronate. There was a 4.7-fold increase in osteoclasts produced from the marrow in culture in those not taking alendronate. RANKL expression in BMCs in the alendronate group was 57% of that in controls, and OPG was increased, giving a RANKL/OPG ratio that was around 50% that of controls. These findings contrast with those from Weinstein et al., who showed increased osteoclast number in biopsies (although suppression of bone resorption was noted, the osteoclasts were not functional). This latter finding may be related to increases in osteoclast longevity. —DGL

Cancer and Bone

- ◆Ouellet V, Tiedemann K, Mourskaia A, Fong JE, Tran-Thanh D, Amir E, Clemons M, Perbal B, Komarova SV, Siegel PM. CCN3 impairs osteoblast and stimulates osteoclast differentiation to favor breast cancer metastasis to bone. *Am J Pathol.* 2011 May;178(5):2377-88. [[Abstract](#)]

The CCN proteins contain six members, CCN1 to CCN6, which are small, secreted, cysteine-rich proteins. Previous studies reported that CCN1 (Cyr61) and CCN2 (connective tissue growth factor or CTGF) were involved in the formation of osteolytic lesions induced by breast cancer cells. Here, Ouellet and colleagues identified CCN3 as a factor that is highly expressed in bone metastatic breast cancer cells from a xenograft mouse model and in bone metastatic lesions from patients with breast cancer. CCN3 overexpression enhances the ability of weakly bone metastatic breast cancer cells to colonize and grow in the bone without altering their growth in the mammary fat pad. Indeed, CCN3 inhibits osteoblast differentiation and promotes osteoclast differentiation. These results indicate that CCN3 creates a resorptive environment that promotes the formation of osteolytic breast cancer metastases. —PC

- ◆Shiozawa Y, Pedersen EA, Havens AM, Jung Y, Mishra A, Joseph J, Kim JK, Patel LR, Ying C, Ziegler AM, Pienta MJ, Song J, Wang J, Loberg RD, Krebsbach PH, Pienta KJ, Taichman RS. Human prostate cancer metastases target the hematopoietic stem cell niche to establish footholds in mouse bone marrow. *J Clin Invest.* 2011 Apr 1;121(4):1298-312. [[Abstract](#)]

Hematopoietic stem cell (HSC) homing, quiescence and self-renewal in the bone marrow are known to depend on a region termed the HSC niche. Here, Shiozawa and colleagues provide evidence that prostate cancer cells home to the osteoblastic (or endosteal) niche in the bone marrow, where they compete with normal HSCs for niche support. Increasing the niche size promotes metastasis, whereas decreasing the niche size compromises dissemination. Prostate cancer cells target the HSC niche through the CXCL12/CXCR4 pathway. Once in the niche, tumor cells reduce HSC numbers by driving their terminal differentiation. These observations have important implications for the treatment of metastatic prostate cancer in bone. —PC

- ◆Zhang H, Pan Y, Zheng L, Choe C, Lindgren B, Jensen ED, Westendorf JJ, Cheng L, Huang H. FOXO1 inhibits Runx2 transcriptional activity and prostate cancer cell migration and invasion. *Cancer Res.* 2011 May 1;71(9):3257-67. [[Abstract](#)]

The transcription factor Runx2 plays an important role in bone formation and prostate

cancer cell migration, invasion, and metastasis. Here, Zhang and colleagues show that the forkhead box O (FOXO1) protein binds to Runx2, inhibits the transcriptional activity of Runx2 in prostate cancer cells and blocks Runx2-promoted migration of prostate cancer cells. Conversely, silencing of endogenous FOXO1 enhances prostate cancer cell migration in a Runx2-dependent manner. Finally, there is an inverse correlation ($P = 0.059$) between Runx2 and FOXO1 expression in a cohort of prostate cancer specimens from patients with lymph node and bone metastasis. These data reveal FOXO1 as a critical negative regulator of Runx2 in prostate cancer cells. —PC

Genetics

◆Farber CR, Bennett BJ, Orozco L, Zou W, Lira A, Kostem E, Kang HM, Furlotte N, Berberyan A, Ghazalpour A, Suwanwela J, Drake TA, Eskin E, Wang QT, Teitelbaum SL, Lusic AJ. Mouse genome-wide association and systems genetics identify *asxl2* as a regulator of bone mineral density and osteoclastogenesis. *PLoS Genet.* 2011 Apr;7(4):e1002038. [\[Abstract\]](#)

◆Suwanwela J, Farber CR, Haug BL, Song B, Pan C, Lyons KM, Lusic AJ. Systems genetics analysis of mouse chondrocyte differentiation. *J Bone Miner Res.* 2011 Apr;26(4):747-60. [\[Abstract\]](#)

*Two studies from the same group used a systems genetics approach for new gene discovery. In the first study, Farber et al. performed GWAS in the mouse and network analysis of co-expression to identify and functionally characterize novel BMD genes. The study used the Hybrid Mouse Diversity Panel (HMDP), a collection of ~100 mouse strains that have been genotyped for 108,064 common SNPs. For the eQTL analysis, they generated gene expression microarray profiles using RNA isolated from cortical bone in these HMDP strains. The authors identified the *Asxl2* gene, belonging to polycomb group (PcG) proteins. Notably, mice deficient in *Asxl2* had reduced BMD. *Asxl2* demonstrated a pattern of expression indicative of genes that play a critical role in osteoclasts; shRNA targeting of *Asxl2* in bone marrow macrophages confirmed this gene as a regulator of osteoclastogenesis.*

*The study by Suwanwela et al. integrated microarray gene expression profiles from isolated chondrocytes and bone phenotypic data from two sets of recombinant inbred strains. Microarrays were used to generate co-expression networks. This analysis resulted in the identification of highly coregulated subnetworks (modules) of coexpressed genes that were then further examined by siRNA knockdown in mouse prechondrocyte cells, and 5 of the 28 genes were found to play a role in chondrocyte differentiation. Two of these, *Hspd1* and *Cdkn1a*, are known to function in chondrocyte development, whereas the other three, *Bhlhb9*, *Cugbp1*, and *Spcs3*, are novel genes. —DK*

◆Freudenberg J, Lee HS, Han BG, Shin HD, Kang YM, Sung YK, Shim SC, Choi CB, Lee AT, Gregersen PK, Bae SC. Genome-wide association study of rheumatoid arthritis in Koreans: Population-specific loci as well as overlap with European susceptibility loci. *Arthritis Rheum.* 2011 Apr;63(4):884-93. [\[Abstract\]](#)

This GWAS confirmed the following genes for a role in rheumatoid arthritis: major histocompatibility complex (HLA-DRB1), peptidylarginine deiminase type 4 (PADI4), as well as ARHGEF3 (Rho guanine nucleotide exchange factor 3, on 3p14.3). Interestingly, the latter gene was proposed as a candidate gene for postmenopausal osteoporosis ([Mullin et al. Am J Hum Genet. 2008 Jun;82\(6\):1262-9](#)). —DK

- ◆Rufo A, Del Fattore A, Capulli M, Carvello F, De Pasquale L, Ferrari S, Pierroz D, Morandi L, De Simone M, Rucci N, Bertini E, Bianchi ML, De Benedetti F, Teti A. Mechanisms inducing low bone density in Duchenne muscular dystrophy in mice and humans. *J Bone Miner Res*. 2011 Apr 20. [Epub ahead of print] [\[Abstract\]](#)

Duchenne muscular dystrophy (DMD) is an X-linked disease due to various mutations in the dystrophin gene. In dystrophin-deficient (MDX) mice, which are a model of human DMD, μ CT and histomorphometric analyses showed reduced bone mass and higher osteoclast and bone resorption parameters compared to WT. Human primary osteoblasts from healthy donors incubated with 10% sera from DMD patients showed decreased mineralization. Many osteogenic genes, including osterix and osteocalcin, were downregulated in these cultures. In contrast, the mRNAs of osteoclastogenic cytokines, IL-6, IL-11, Inhibin A β and TGF β 2 were increased. The investigators thus propose that IL-6 may link the muscular and the bone phenotype in muscular dystrophies and, therefore, an antibody for IL-6 might serve as a treatment option for DMD bones. —DK

- ◆Wu DD, Zhang YP. Different level of population differentiation among human genes. *BMC Evol Biol*. 2011 Jan 14;11:16. [\[Abstract\]](#)

In this study of differentiation between human populations based on genetic polymorphism data, the authors follow-up their previous paper ([Hum Mol Genet. 2010 Jun 15;19\(12\):2341-6.](#)) in which they concluded that the observed high levels of population differentiation in skeletal genes are driven by positive selection. Indeed, evidence indicates that the human skeletal system has evolved rapidly since the advent of agriculture, and thus phenotypic variation is prominent in traits such as height, body mass, BMD, and craniofacial features. Interestingly, other genes that showed higher levels of population differentiation (genetic distance) include those involved in reproduction (e.g., sperm motility) and some metabolic pathways (such as triglyceride, cholesterol, and glucose homeostasis), and, obviously, in pigmentation and hair follicle development. —DK

Bone Modeling, Remodeling, and Repair

- ◆Kim DG, Shertok D, Ching Tee B, Yeni YN. Variability of tissue mineral density can determine physiological creep of human vertebral cancellous bone. *J Biomech*. 2011 Apr 7. [Epub ahead of print] [\[Abstract\]](#)

Creep and residual strains of specimens cored out of human vertebrae were measured after a two-hour physiological compressive constant static loading and unloading cycle. Creep developed ($3877 \pm 2158\mu\epsilon$) resulting in substantial levels of non-recoverable post-creep residual strain ($1797 \pm 1391\mu\epsilon$). A strong positive linear correlation was found between creep and residual strain ($r = 0.94$, $p < 0.001$). The current results showed that smaller thickness, larger surface area, greater connectivity of trabeculae, less mean tissue mineral density (TMD, represented by gray levels) and higher variability of TMD are associated with increasing logarithmic creep rate. TMD variability was the strongest correlate of creep rate ($r = 0.79$, $p < 0.001$). TMD variability may be a useful parameter for estimating the long-term deformation of a whole vertebral body. —ES

- ◆Kostenuik PJ, Smith SY, Jollette J, Schroeder J, Pyrah I, Ominsky MS. Decreased bone remodeling and porosity are associated with improved bone strength in ovariectomized cynomolgus monkeys treated with denosumab, a fully human RANKL antibody. *Bone*. 2011 Mar

30. [Epub ahead of print] [\[Abstract\]](#)

Ovariectomized (OVX) cynomolgus monkeys were treated with subcutaneous vehicle (OVX-Veh) or denosumab (25 or 50 mg/kg/month) for 16 months. Both doses of denosumab inhibited remodeling at all sites with reductions in trabecular eroded surfaces (48-86% lower than OVX-Veh controls), cortical porosity (28-72% lower), and dynamic parameters of bone formation (81-100% lower). Decreased fluorochrome labeling with denosumab was related to reductions in cortical porosity and trabecular eroded surfaces. Denosumab-treated animals with the lowest levels of fluorescent labeling exhibited the greatest structural bone strength. —ES

- ◆Marenzana M, Greenslade K, Eddleston A, Okoye R, Marshall D, Moore A, Robinson M. Sclerostin antibody treatment enhances bone strength but does not prevent growth retardation in young mice treated with dexamethasone. *Arthritis Rheum.* 2011 Apr 11. [Epub ahead of print] [\[Abstract\]](#)

In dexamethasone (DEX)-treated mice, sclerostin antibody (Scl-Abl) had no significant effect on linear growth but increases in trabecular bone at the femoral metaphysis (BV/TV: Scl-Abl + 117% compared to control antibody) and cortical bone width and volume at the femoral diaphysis (Ct.Wi: Scl-Abl +24%; Ct.V: Scl-Abl +20% compared to control antibody) were noted. Scl-Abl improved mechanical strength at the femoral diaphysis (maximum load +60%; ultimate strength +47% compared to control antibody). Elevated osteocalcin levels were not detected although TRAP5b levels were lower. —ES

- ◆McGee-Lawrence ME, Stoll DM, Mantila ER, Fahrner BK, Carey HV, Donahue SW. Thirteen-lined ground squirrels (*Ictidomys tridecemlineatus*) show microstructural bone loss during hibernation but preserve bone macrostructural geometry and strength. *J Exp Biol.* 2011 Apr 15;214(Pt 8):1240-7. [\[Abstract\]](#)

Cortical bone geometry, strength and mineral content are similar in hibernating and active squirrels. Osteocyte lacunar size increased and osteocyte lacunar density and porosity were greater (+44 and +59%) in hibernating than active squirrels, reflecting a decrease in osteoblastic activity during hibernation. Trabecular bone volume in the proximal tibia was decreased (-20%) in hibernating compared with physically active adult squirrels, but was not different between hibernating and active juvenile squirrels. 13-lined ground squirrels may be unable to prevent microstructural losses of cortical and trabecular bone during hibernation, but may possess a mechanism to preserve cortical bone macrostructure and strength. —ES

- ◆Rhee Y, Allen MR, Condon K, Lezcano V, Ronda AC, Galli C, Olivos N, Passeri G, O'Brien CA, Bivi N, Plotkin LI, Bellido T. PTH receptor signaling in osteocytes governs periosteal bone formation and intra-cortical remodeling. *J Bone Miner Res.* 2011 May; 26(5):1035-46. [\[Abstract\]](#)

PTH stimulates periosteal expansion and accelerates intracortical bone remodeling. Here, the authors demonstrate that transgenic mice expressing a constitutively active PTH receptor in osteocytes (DMP1-caPTH1R mice) exhibit increased cortical bone area and elevated periosteal and endocortical bone formation rates. These mice also display a marked increase in intracortical remodeling and cortical porosity. Crossing DMP1-caPTH1R mice with LRP5-null or osteocyte-specific Sost transgenic mice (DMP1-Sost mice) reduces or abolishes the phenotypes of the DMP1-caPTH1R mice, with exacerbation of intracortical remodeling and markedly decreased OPG expression. Thus, the increase in intracortical remodeling is independent of Sost down-regulation and is driven by a reduction in OPG. —TM

Molecular and Cell Biology

◆Börjesson AE, Windahl SH, Lagerquist MK, Engdahl C, Frenkel B, Movérare-Skrtic S, Sjögren K, Kindblom JM, Stubelius A, Islander U, Antal MC, Krust A, Chambon P, Ohlsson C. Roles of transactivating functions 1 and 2 of estrogen receptor- α in bone. *Proc Natl Acad Sci U S A*. 2011 Apr 12;108(15):6288-93. [[Abstract](#)] [[Full Text](#)]

◆Ikeda K, Tsukui T, Horie-Inoue K, Inoue S. Conditional expression of constitutively active estrogen receptor α in osteoblasts increases bone mineral density in mice. *FEBS Lett*. 2011 Apr 11. [Epub ahead of print] [[Abstract](#)]

These two studies provide further evidence for the role of estrogen receptor (ER) signaling in bone. The first study establishes that ER activation function (AF)-2 in the ligand-binding domain is responsible for estradiol effects on bone and other target tissues, such as the uterus and the liver, whereas AF-1 in the N-terminal domain of ER mediates estradiol effects more restrictively on trabecular bone and the uterus. The second study shows that osteoblast-targeted expression of a constitutively active ER increases BMD without changes in the mineral apposition rate (MAR), but with an increase of OPG and decrease of IL-6, hence emphasizing that estrogen regulates bone mass at least partially through osteoblasts but not necessarily through a bone-forming effect. —SF

◆Kajimura D, Hinoi E, Ferron M, Kode A, Riley KJ, Zhou B, Guo XE, Karsenty G. Genetic determination of the cellular basis of the sympathetic regulation of bone mass accrual. *J Exp Med*. 2011 Apr 11;208(4):841-51. [[Abstract](#)]

Further genetic dissection of the signaling pathways by which β 2 adrenergic receptor (Adrb2) signaling regulates osteoblastic functions in response to central leptin shows that Adrb2 inhibits bone formation through CREB and stimulates RANKL through ATF4. Neither bone mass nor bone formation indices were increased in osteoblast-targeted Adrb2 KO until at least 12 weeks of age, arguing against a major role for this pathway during bone mass growth. —SF

◆Leupin O, Piters E, Halleux C, Hu S, Kramer I, Morvan F, Bouwmeester T, Schirle M, Bueno-Lozano M, Ramos Fuentes FJ, Itin PH, Boudin E, De Freitas F, Jennes K, Brannetti B, Charara N, Ebersbach H, Geisse S, Lu CX, Bauer A, Van Hul W, Kneissel M. Bone overgrowth-associated mutations in LRP4 impair sclerostin-facilitator function. *J Biol Chem*. 2011 Apr 6. [Epub ahead of print] [[Abstract](#)]

LRP4 is a sclerostin interaction partner that facilitates the inhibitory action of sclerostin on Wnt1/ β -catenin signaling. The extracellular β -propeller structured domain of LRP4 was required for this sclerostin-facilitator activity. LRP4 protein is present in human and rodent osteoblasts and osteocytes. Silencing of LRP4 by lentiviral-mediated shRNA delivery blocked sclerostin-inhibitory action on in vitro bone mineralization. Two mutations in LRP4 (R1170W, W1186S) in patients suffering from bone overgrowth impaired LRP4 interaction with sclerostin and its concomitant sclerostin-facilitator effect. —ES

◆Ogata N, Shinoda Y, Wettschureck N, Offermanns S, Takeda S, Nakamura K, Segre GV, Chung UI, Kawaguchi H. $G\alpha_q$ signal in osteoblasts is inhibitory to the osteoanabolic action of parathyroid hormone. *J Biol Chem*. 2011 Apr 15;286(15):13733-40. [[Abstract](#)] [[Full Text](#)]

Although Gs-cAMP signaling has long been recognized as necessary to PTH-

stimulated bone formation, the role of Gq signaling in osteoblasts on PTH anabolic activity remains unclear. By generating both osteoblast-targeted transgenic mice overexpressing Gq, and single and double KO mice with deletions of Gq and G11, this work demonstrates the inhibitory role of the Gq-PKC pathway on PTH anabolic effects in vivo and in vitro. Moreover, overexpression of RGS2, a physiological inhibitor of the Gq signal, enhanced PTH osteoanabolic action in cultured osteoblasts. These findings are consistent with previous evidence that PKC activation leads to PTH receptor phosphorylation, β -arrestin-mediated internalization and desensitization of PTH signaling (see [BoneKEy Perspective by Ferrari and Bouxsein](#)). —SF

- ◆ Shimono K, Tung WE, Macolino C, Chi AH, Didizian JH, Mundy C, Chandraratna RA, Mishina Y, Enomoto-Iwamoto M, Pacifici M, Iwamoto M. Potent inhibition of heterotopic ossification by nuclear retinoic acid receptor- γ agonists. *Nat Med.* 2011 Apr;17(4):454-60. [[Abstract](#)]

When mesenchymal stem cells were treated with an RAR- γ agonist and transplanted into nude mice, these cells did not form ectopic bone masses, while control cells did. These cells became unresponsive to rBMP-2 treatment and showed decreased phosphorylation and protein levels of Smad1, 5 and 8. In addition, an RAR- γ agonist blocked heterotopic ossification in transgenic mice expressing activin receptor-like kinase-2 (ALK2) Q207D, a constitutively active form of the receptor that is related to the human ALK2 R206H mutation found in individuals with fibrodysplasia ossificans progressiva (FOP). The data indicate that RAR- γ agonists are potent inhibitors of heterotopic ossification in mouse models and may also be effective against FOP. —TM

- ◆ Tu Q, Zhang J, Dong LQ, Saunders E, Luo E, Tang J, Chen J. Adiponectin inhibits osteoclastogenesis and bone resorption via APPL1-mediated suppression of Akt1. *J Biol Chem.* 2011 Apr 8;286(14):12542-53. [[Abstract](#)] [[Full Text](#)]

Femurs were isolated from genetically double-labeled mBSP9.0Luc/ β -ACT-EGFP transgenic mice and were transplanted into adiponectin knock-out mice or wild-type mice. Growth of bone explants in adiponectin knock-out mice was retarded with reduced trabecular bone volume, decreased cortical bone, and increased osteoclast number. Adiponectin inhibited RANKL-induced osteoclastogenesis from RAW264.7 cells and down-regulated RANKL-enhanced expression of osteoclastogenic regulators including NFAT2, TRAF6, cathepsin K, and tartrate-resistant acid phosphatase. Adiponectin also increased osteoclast apoptosis and decreased survival/proliferation of osteoclast precursor cells. Using siRNA specifically targeting APPL1, the first identified adaptor protein of adiponectin signaling, the inhibitory effect of adiponectin on osteoclasts was induced by APPL1-mediated down-regulation of Akt1 activity. In addition, overexpression of Akt1 reversed adiponectin-induced inhibition in RANKL-stimulated osteoclast differentiation. —ES

- ◆ Zaiss MM, Kurowska-Stolarska M, Böhm C, Gary R, Scholtyssek C, Stolarski B, Reilly J, Kerr S, Millar NL, Kamradt T, McInnes IB, Fallon PG, David JP, Liew FY, Schett G. IL-33 shifts the balance from osteoclast to alternatively activated macrophage differentiation and protects from TNF-alpha-mediated bone loss. *J Immunol.* 2011 Apr 22. [Epub ahead of print] [[Abstract](#)]

- ◆ Schulze J, Bickert T, Beil FT, Zaiss MM, Albers J, Wintges K, Streichert T, Klaetschke K, Keller J, Hissnauer TN, Spiro AS, Gessner A, Schett G, Amling M, McKenzie AJ, Horst AK, Schinke T. Interleukin-33 is expressed in differentiated osteoblasts and blocks osteoclast formation from bone marrow precursor cells. *J Bone Miner Res.* 2011 Apr;26(4):704-17. [[Abstract](#)]

IL-33, a member of the IL-1 family, was first recognized as an “alarmin” in endothelial

and epithelial cells, then as an inflammatory cytokine in rheumatoid arthritis. These two complementary studies identify IL-33 as an inhibitor of RANKL-mediated osteoclastogenesis, hence ST2 – the IL-33 receptor – KO mice have increased bone mass. In contrast, IL-33 diverts osteoclast precursor differentiation towards the macrophage lineage. —SF

- ◆ Yasui T, Kadono Y, Nakamura M, Oshima Y, Matsumoto T, Masuda H, Hirose J, Omata Y, Yasuda H, Imamura T, Nakamura K, Tanaka S. Regulation of RANKL-induced osteoclastogenesis by TGF- β through molecular interaction between Smad3 and TRAF6. *J Bone Miner Res.* 2011 Feb 8. [Epub ahead of print] [\[Abstract\]](#)

The authors show that blockade of TGF- β signals either by a specific inhibitor of TGF- β type I receptor kinase, SB431542, or by introducing a dominant negative mutant of the TGF- β type II receptor almost completely suppressed RANKL-induced osteoclastogenesis. Blockade of Smad signaling in osteoclast precursors by Smad7 or c-Ski overexpression, or gene silencing of Smad3 markedly suppressed RANKL-induced osteoclastogenesis. Smad2/3 directly associated via the MH2 domain with the TRAF6-TAB1-TAK1 molecular complex that is essential for RANKL-induced osteoclast differentiation. These results demonstrate that TGF- β is indispensable in RANKL-induced osteoclastogenesis, and the binding of Smad3 to the TRAF6-TAB1-TAK1 complex is crucial for RANKL-induced osteoclastogenic signaling. —TM

Physiology and Metabolism

- ◆ Foresta C, Strapazzon G, De Toni L, Perilli L, Di Mambro A, Muciaccia B, Sartori L, Selice R. Bone mineral density and testicular failure: evidence for a role of vitamin D 25-hydroxylase in human testis. *J Clin Endocrinol Metab.* 2011 Apr;96(4):E646-52.

The topic of interactions between bone and the reproductive system, which may be due to hormonal factors other than sex hormones, and which was re-invigorated by the Karsenty group ([Cell. 2011 Mar 4;144\(5\):796-809](#)) is also a focus of this paper. In patients with testiculopathy (Sertoli-cell-only syndrome and severe hypospermatogenesis, thus altered spermatogenesis), there was higher osteopenia and osteoporosis despite normal testosterone (and estrogen) levels compared with controls; also, 25-hydroxyvitamin D levels were significantly lower in testiculopathic patients. Vitamin D reduction might be another etiological link between osteopenia and male reproductive health. —DK

Reviews, Perspectives and Editorials

- ◆ Baron R, Ferrari S, Russell RG. Denosumab and bisphosphonates: Different mechanisms of action and effects. *Bone.* 2011 Apr 1;48(4):677-92. [\[Abstract\]](#)
- ◆ Bukata SV. Systemic administration of pharmacological agents and bone repair: What can we expect. *Injury.* 2011 Apr 18. [Epub ahead of print] [\[Abstract\]](#)
- ◆ Manson JE, Mayne ST, Clinton SK. Vitamin D and prevention of cancer--ready for prime time? *N Engl J Med.* 2011 Apr 14;364(15):1385-7. [\[Abstract\]](#)
- ◆ Rachner TD, Khosla S, Hofbauer LC. Osteoporosis: now and the future. *Lancet.* 2011 Apr 9;377(9773):1276-87. [\[Abstract\]](#)

Other Studies of Potential Interest

- ◆ Bishop KA, Coy HM, Nerenz RD, Meyer MB, Pike JW. Mouse Rankl expression is regulated in T cells by c-Fos through a cluster of distal regulatory enhancers designated the T cell control region. *J Biol Chem*. 2011 Apr 12. [Epub ahead of print] [\[Abstract\]](#)
- ◆ Eskildsen T, Taipaleenmäki H, Stenvang J, Abdallah BM, Ditzel N, Nossent AY, Bak M, Kauppinen S, Kassem M. MicroRNA-138 regulates osteogenic differentiation of human stromal (mesenchymal) stem cells in vivo. *Proc Natl Acad Sci U S A*. 2011 Apr 12;108(15):6139-44. [\[Abstract\]](#) [\[Full Text\]](#)
- ◆ Grassi F, Manfredini C, Cattini L, Piacentini A, Gabusi E, Facchini A, Lisignoli G. T cell suppression by osteoclasts in vitro. *J Cell Physiol*. 2011 Apr;226(4):982-90. [\[Abstract\]](#)
- ◆ Kanno Y, Ishisaki A, Kawashita E, Chosa N, Nakajima K, Nishihara T, Toyoshima K, Okada K, Ueshima S, Matsushita K, Matsuo O, Matsuno H. Plasminogen/plasmin modulates bone metabolism by regulating the osteoblast and osteoclast function. *J Biol Chem*. 2011 Mar 18;286(11):8952-60. [\[Abstract\]](#) [\[Full Text\]](#)
- ◆ Kim BJ, Kim SY, Cho YS, Kim BJ, Han BG, Park EK, Lee SH, Kim HY, Kim GS, Lee JY, Koh JM. Association of Paraoxonase 1 (PON1) polymorphisms with osteoporotic fracture risk in postmenopausal Korean women. *Exp Mol Med*. 2011 Feb 28;43(2):71-81. [\[Abstract\]](#)
- ◆ Luderer HF, Gori F, Demay MB. Lymphoid enhancer-binding factor-1 (LEF1) interacts with the DNA binding domain of the vitamin D receptor. *J Biol Chem*. 2011 Apr 6. [Epub ahead of print] [\[Abstract\]](#)
- ◆ Marom B, Heining E, Knaus P, Henis YI. Formation of stable homomeric and transient heteromeric BMP receptor complexes regulates Smad signaling. *J Biol Chem*. 2011 Apr 6. [Epub ahead of print] [\[Abstract\]](#)
- ◆ Melton LJ 3rd, Lieber MM, Atkinson EJ, Achenbach SJ, Zincke H, Therneau TM, Khosla S. Fracture risk in men with prostate cancer: A population-based study. *J Bone Miner Res*. 2011 Apr 21. [Epub ahead of print] [\[Abstract\]](#)
- ◆ Mórocz M, Czibula A, Grózer ZB, Szécsényi A, Almos PZ, Raskó I, Illés T. Association study of BMP4, IL6, leptin, MMP3, and MTNR1B gene promoter polymorphisms and adolescent idiopathic scoliosis. *Spine (Phila Pa 1976)*. 2011 Jan 15;36(2):E123-30. [\[Abstract\]](#)
- ◆ Osborne DL, Weaver CM, McAbe LD, McCabe GM, Novotny R, Boushey C, Savaiano DA. Tanning predicts bone mass but not structure in adolescent females living in Hawaii. *Am J Hum Biol*. 2011 Apr 14. [Epub ahead of print] [\[Abstract\]](#)
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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.