

NOT TO BE MISSED

Clinical and Basic Research Papers – November-December 2011

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Clinical Studies and Drug Effects

◆Brown JP, Dempster DW, Ding B, Dent-Acosta R, San Martin J, Grauer A, Wagman RB, Zanchetta J. Bone remodeling in postmenopausal women who discontinued denosumab treatment: Off-treatment biopsy study. *J Bone Miner Res.* 2011 Nov;26(11):2737-44. [\[Abstract\]](#)

Reversibility of remodeling suppression is important. Trans-iliac crest bone biopsies in subjects receiving denosumab showed no labeling in up to one-third of subjects. Discontinuation of denosumab has revealed that the effects are reversible. Fifteen subjects discontinued osteoporosis treatment for approximately 25.1 months and had normal histology and bone remodeling. All biopsies had tetracycline labels. —ES

◆Esses SI, McGuire R, Jenkins J, Finkelstein J, Woodard E, Watters WC, Goldberg MJ, Keith M, Turkelson CM, Wies JL, Sluka P, Boyer KM, Hitchcock K, Raymond L. American Academy of Orthopaedic Surgeons Clinical Practice Guideline on: The Treatment of Osteoporotic Spinal Compression Fractures. *J Bone Joint Surg Am.* 2011 Oct 19;93(20):1934-6. [\[Abstract\]](#)

A step in the right direction to have such guidelines. Many comments can be made about guidelines, but at least these are evidence-based. —DGL

◆Fitzpatrick LA, Dabrowski CE, Cicconetti G, Gordon DN, Fuerst T, Engelke KA, Genant HK. Ronacaleret, a calcium-sensing receptor antagonist, increases trabecular but not cortical bone in postmenopausal women. *J Bone Miner Res.* 2011 Nov 2. [Epub ahead of print] [\[Abstract\]](#)

It was a good idea until the data came. Ronacaleret, an oral calcium-sensing receptor antagonist, stimulates endogenous parathyroid hormone (PTH). In 314 women, during 12 months, ronacaleret increased spine (0.49% to 3.9%) and trabecular (1.8% to 13.3%) volumetric BMD, though 2-fold less than in those given teriparatide (14.8% and 24.4%, respectively), and similar or superior to what was observed in those given alendronate (5.0% and 4.9%, respectively). The problem was cortical bone loss consistent with the induction of hyperparathyroidism. In the presence of osteoclasts, PTH does its resorption thing. —ES

◆Ma Y, Zhang P, Wang F, Yang J, Liu Z, Qin H. Association between vitamin D and risk of colorectal cancer: a systematic review of prospective studies. *J Clin Oncol.* 2011 Oct 1;29(28):3775-82. [\[Abstract\]](#)

Nine studies on vitamin D intake and nine studies on blood 25(OH)D levels were included in the meta-analysis. The relative risks (RRs) of colorectal cancer for the

highest versus lowest categories of vitamin D intake and blood 25(OH)D levels were 0.88 (95% CI, 0.80 to 0.96) and 0.67 (95% CI, 0.54 to 0.80), respectively. A 10 ng/mL increment in blood 25(OH)D conferred an RR of 0.74 (95% CI, 0.63 to 0.89). —ES

- ◆Murad MH, Elamin KB, Abu Elnour NO, Elamin MB, Alkatib AA, Fatourechi MM, Almandoz JP, Mullan RJ, Lane MA, Liu H, Erwin PJ, Hensrud DD, Montori VM. Clinical review: The effect of vitamin D on falls: a systematic review and meta-analysis. *J Clin Endocrinol Metab.* 2011 Oct;96(10):2997-3006. [\[Abstract\]](#) [\[Full Text\]](#)

Like much of the literature in this fashionable area, statistics and even meta-analysis cannot overcome problems in study design and execution and so cannot answer the questions posed with any sort of credibility. In this meta-analysis, 26 eligible trials of moderate quality enrolled 45,782 participants. Vitamin D use was associated with a reduction in the risk of falls (odds ratio (OR) = 0.86; 95% CI, 0.77-0.96). This effect was more prominent in patients who were vitamin D-deficient at baseline and in studies in which calcium was administered. The quality of evidence was low because of heterogeneity and publication bias. Vitamin D combined with calcium was associated with fewer falls but not in studies without calcium. —ES

- ◆Sköldenberg OG, Salemyr MO, Bodén HS, Ahl TE, Adolphson PY. The effect of weekly risedronate on periprosthetic bone resorption following total hip arthroplasty: a randomized, double-blind, placebo-controlled trial. *J Bone Joint Surg Am.* 2011 Oct 19;93(20):1857-64. [\[Abstract\]](#)

- ◆Hamilton WG. Risedronate decreases bone loss around hip implants, but how useful is its effect? *J Bone Joint Surg Am.* 2011 Oct 19;93(20):e1201-2. [\[Info\]](#)

A randomized trial of weekly oral risedronate was performed in 73 patients (age 40-70 years) undergoing total hip replacement. BMD in Gruen femoral zone 1 was 9.2% higher at six months postoperatively and 7.2% higher at one year in the risedronate group than in the placebo group, and BMD in Gruen zone 7 was 8.0% higher in the risedronate group than in the placebo group at six months postoperatively and 4.3% higher at 1 year. Prosthesis migration could not be shown to differ, but the technique used had an accuracy limit of only 1 mm. The mean Harris hip score, EQ-5D, and Pain Numerical Rating Scale all improved compared with the preoperative value and did not differ between the groups at any time. Although primary outcome endpoints were met, longer studies would be needed to show differences in clinical outcome or migration.

An editorial by Hamilton on the above paper questions the clinical relevance of maintaining the bone in Gruen zones 1 and 7 in the proximal femur; notes the withdrawal of 11% of patients from the trial because of risedronate side effects; and raises the specter of bisphosphonate-related femoral stress fracture as a possible long-term undesirable consequence of such treatment that would only be revealed with studies over much longer time frames. —DGL

- ◆Tanaka S, Kuroda T, Saito M, Shiraki M. Urinary pentosidine improves risk classification using fracture risk assessment tools for postmenopausal women. *J Bone Miner Res.* 2011 Nov;26(11):2778-84. [\[Abstract\]](#)

We need tools to assess bone qualities, one of which is cross-linking of collagen. Urinary pentosidine, plus a Fracture and Immobilization Score (FRISC), were assessed in 765 postmenopausal Japanese women. A 1 standard deviation (SD) increase in pentosidine gave a hazard ratio (HR) of 1.18 (95% CI, 1.05-1.33; p < 0.01)

for vertebral fracture and 1.20 (95% CI, 1.07-1.33, $p < 0.01$) for both long bone and vertebral fractures. The C statistics were 0.732 (95% CI, 0.686-0.778) for the model with both pentosidine and the 10-year risk, and 0.702 (95% CI, 0.654-0.750) for the 10-year risk alone. Eighty-three subjects (11%) were in the highest quartile of pentosidine, although their 10-year risks were less than 15% and included 17 incident vertebral fracture cases. Urinary pentosidine improves risk classification. —ES

Cancer and Bone

◆D'Souza S, Del Prete D, Jin S, Sun Q, Huston AJ, Kostov FE, Sammut B, Hong CS, Anderson JL, Patrene KD, Yu S, Velu CS, Xiao G, Grimes HL, Roodman GD, Galson DL. Gfi1 expressed in bone marrow stromal cells is a novel osteoblast suppressor in patients with multiple myeloma bone disease. *Blood*. 2011 Oct 31. [Epub ahead of print] [\[Abstract\]](#)

The authors found that bone marrow stromal cells from both multiple myeloma-bearing mice and multiple myeloma patients had increased levels of the transcriptional repressor Gfi1, inhibiting expression of the critical osteoblast transcription factor Runx2 that promotes osteoblast differentiation. Thus, Gfi1 may be a new therapeutic target in multiple myeloma bone disease. —PC

◆Julien S, Ivetic A, Grigoriadis A, Qize D, Burford B, Sproviero D, Picco G, Gillett C, Papp SL, Schaffer L, Tutt A, Taylor-Papadimitriou J, Pinder SE, Burchell JM. Selectin ligand sialyl-Lewis x antigen drives metastasis of hormone-dependent breast cancers. *Cancer Res*. 2011 Oct 24. [Epub ahead of print] [\[Abstract\]](#)

In this study the authors found that high expression of sialyl-Lewis x (sLex) in estrogen receptor-positive breast tumors was correlated with metastasis to the bone where the sLex receptor E-selectin is constitutively expressed. —PC

◆Monsees GM, Malone KE, Tang MT, Newcomb PA, Li CI. Bisphosphonate use after estrogen receptor-positive breast cancer and risk of contralateral breast cancer. *J Natl Cancer Inst*. 2011 Oct 21. [Epub ahead of print] [\[Abstract\]](#)

Nitrogen-containing bisphosphonates (N-BPs) may reduce the risk of developing a first breast cancer. The aim of this study was to assess the effect of N-BPs on the risk of a second primary contralateral breast cancer. The authors found that current use of N-BPs is associated with a reduced risk of contralateral breast cancer compared with never use (OR = 0.41, 95% CI, 0.20 to 0.84; $P = 0.03$). —PC

Genetics

◆Day-Williams AG, Southam L, Panoutsopoulou K, et al. A variant in MCF2L is associated with osteoarthritis. *Am J Hum Genet*. 2011 Sep 9;89(3):446-50. [\[Abstract\]](#)

Although osteoarthritis (OA) is a common, heritable degenerative joint disease, it's genomic discovery has lagged behind that of osteoporosis, primarily because of an unclear phenotypic definition. In this genome-wide association study (GWAS), OA cases from the U.K. were included based on two criteria: (1) radiographic evidence of disease (defined as a Kellgren-Lawrence (KL) grade ≥ 2) and/or (2) clinical evidence of disease requiring joint replacement (TJR). The first is a mix of many traits of different etiologies, while the second may not be applicable to other health care settings. In any case, this study was able to detect a previously unidentified risk locus (as a reminder, two loci (GDF5 on chromosome 20 and a signal on 7q22) have reached genome-wide

significance in previous GWAS of OA). This study found association with single nucleotide polymorphisms (SNPs) in MCF2L, which was then replicated in 19,041 OA cases and 24,504 controls of European descent. Its allelic odds ratio of approximately 1.17 was on par with the previous 2 loci. MCF2L regulates a nerve growth factor (NGF); treatment with a humanized monoclonal antibody against NGF is known to result in a reduction in pain and improvement in function for knee OA patients. —DK

◆Li GH, Cheung CL, Xiao SM, Lau KS, Gao Y, Bow CH, Huang QY, Sham PC, Kung AW. Identification of QTL genes for BMD variation using both linkage and gene-based association approaches. *Hum Genet.* 2011 Oct;130(4):539-46. [[Abstract](#)]

◆Kuipers AL, Gundberg C, Kammerer CM, Dressen AS, Nestlerode CS, Patrick AL, Wheeler VW, Bunker CH, Newman AB, Zmuda JM. Genetic analysis of serum osteocalcin and bone mineral in multigenerational Afro-Caribbean families. *Osteoporos Int.* 2011 Sep 21. [Epub ahead of print] [[Abstract](#)]

Human linkage analysis for complex traits is not dead yet! In the first paper, a quantitative trait locus (QTL) on 5q21 originally identified in Northern Chinese by Annie Kung's group was replicated in Southern Chinese pedigrees. Subsequent QTL-wide gene-based association analysis in 800 Chinese subjects with extreme BMD identified CAST and ERAP1 as novel femoral neck BMD candidate genes. The associations were independently replicated in a Northern European population.

The second study investigated the heritability of serum osteocalcin (OC) measures and performed a genome-wide linkage analysis in African ancestry individuals from Tobago. Heritabilities of total OC, uncarboxylated OC, carboxylated OC, and percent uncarboxylated OC were 0.74, 0.89, 0.46, and 0.41, respectively. Since OC levels were found to genetically correlate with whole body bone mineral content (BMC), the bivariate linkage found a QTL on chromosome 17q, which might be relevant for both bone and energy metabolism. —DK

◆N'Diaye A, Chen GK, Palmer CD, et al. Identification, replication, and fine-mapping of loci associated with adult height in individuals of African ancestry. *PLoS Genet.* 2011 Oct;7(10):e1002298. [[Abstract](#)]

Adult height is a highly heritable, complex phenotype, a classic polygenic trait, with a pronounced skeletal component. A meta-analysis of GWAS for adult height in 20,427 individuals of African ancestry with replication in up to 16,436 African Americans produced two novel height loci—on chromosomes Xp22 and 2p14. Unsurprisingly, these 2 loci are relevant for our field too: thus, on Xp22, it was the arylsulfatase E (ARSE) gene; mutations in this gene cause X-linked brachytelephalangic chondrodysplasia punctata (OMIM #302950), a congenital disorder of bone and cartilage development. On 2p14, the top SNP is 189 kb upstream of the bone morphogenetic protein 10 (BMP10) gene, a member of the TGF- β signaling pathway. These results highlight (a) the utility of genetic studies in non-European populations to further understanding of complex human traits and (b) potentially pleiotropic effects of biologically relevant genes on normal skeletal growth and adult stature. —DK

◆Nielson CM, Zmuda JM, Carlos AS, Wagoner WJ, Larson EA, Orwoll ES, Klein RF. Rare coding variants in ALPL are associated with low serum alkaline phosphatase and low bone mineral density. *J Bone Miner Res.* 2011 Sep 28. [Epub ahead of print] [[Abstract](#)]

◆Beamer WG, Shultz KL, Coombs HF 3rd, Horton LG, Donahue LR, Rosen CJ. Multiple quantitative trait loci for cortical and trabecular bone regulation map to mid-distal mouse

chromosome 4 that shares linkage homology to human chromosome 1p36. *J Bone Miner Res.* 2011 Sep 28. [Epub ahead of print] [\[Abstract\]](#)

Here are two studies appearing in JBMR, both of which deal with a mouse QTL on chr. 4, which is homologous with human chr. 1p36. In the first one, by Nielson et al., the mouse chr. 4 region was identified in experimental intercrosses using strains divergent for the Alpl haplotype—B6 x C3H/HeJ and B6 x D2. Alpl coding variations (Gln318Arg and Leu324Pro) exist between B6 and D2 or C3H/HeJ mouse strains. The authors sequenced the coding regions of the ALP gene in MrOS men with low (<40 U/L) and normal (70-74 U/L) serum ALP levels. Of the 25 sequence variants in ALPL identified, 7 had not been reported previously. 19 rare (frequency <1%) nonsynonymous variants were much more frequent among the low ALP men. They also had 6.7% lower BMD ($p = 0.03$) and 11.1% higher serum phosphate ($p = 0.002$) than those without multiple rare ALPL coding variants.

The study by Beamer et al. utilized 18 nested congenic strains to decompose the complexity of the gene-rich mid-distal region of mouse chr. 4. Adult females and males from the congenic strains carrying discrete C3H sequences were phenotyped by pQCT and Micro-CT 40. The authors showed that the region consists of at least 10 regulatory QTL regions that affected either or both pQCT and Micro-CT phenotypes. The QTL sub-regions contained from 1 to 102 known genes. The authors identified 13 candidate genes that can be linked to bone: 6 were linked to osteoblasts (Cnr2, Wnt4, Alpl, Ece1, EphA2 and Plod1), three to osteoclasts (Lck, Pla2g2a and EphA2), and two to skeletal development (Phc2 and Col16a1). This list merits further experimental evaluation in vitro and confirmation with bone phenotypes in humans. —DK

◆Takahashi Y, Kou I, Takahashi A, Johnson TA, Kono K, Kawakami N, Uno K, Ito M, Minami S, Yanagida H, Taneichi H, Tsuji T, Suzuki T, Sudo H, Kotani T, Watanabe K, Chiba K, Hosono N, Kamatani N, Tsunoda T, Toyama Y, Kubo M, Matsumoto M, Ikegawa S. A genome-wide association study identifies common variants near LBX1 associated with adolescent idiopathic scoliosis. *Nat Genet.* 2011 Oct 23. [Epub ahead of print] [\[Abstract\]](#)

◆Lei SF, Shen H, Yang TL, Guo Y, Dong SS, Xu XH, Deng FY, Tian Q, Liu YJ, Liu YZ, Li J, Deng HW. Genome-wide association study identifies HMGN3 locus for spine bone size variation in Chinese. *Hum Genet.* 2011 Sep 25. [Epub ahead of print] [\[Abstract\]](#)

GWAS continue to provide new insights into the pathogenesis of complex conditions of the musculoskeletal system. Thus, adolescent idiopathic scoliosis (AIS) was studied in 1,376 affected Japanese females and 11,297 female controls. The authors identified a locus at chromosome 10q24.31 associated with AIS susceptibility. The most significant SNP was located near the LBX1 gene, which was first identified as a homeobox gene with homology to the “ladybird late” gene in Drosophila. In vertebrates, high expression levels of LBX1 were detectable in both adult and fetal skeletal muscle, especially in muscle precursor cells.

The second study investigated bone size (BS) of the spine by GWAS in 1,627 Han Chinese. SNPs upstream of the high-mobility group nucleosomal binding domain 3 (HMGN3) gene were followed-up for replication in 1,728 unrelated Caucasian women. The associations were “suggestively replicated.” Indeed, beyond well-known differences between Caucasians and Chinese in genetic background (allele frequencies and linkage disequilibrium), the age between the discovery and replication cohorts was quite different (34.5 in Chinese vs. 51.6 in Caucasians). The sex composition was different, with both men and women in Chinese, but only women in Caucasians. Therefore, larger and better-matched replication samples should be

sought. —DK

- ◆Wang J, Stern PH. Sex-specific effects of estrogen and androgen on gene expression in human monocyte-derived osteoclasts. *J Cell Biochem*. 2011 Dec;112(12):3714-21. [[Abstract](#)]

Estrogen and androgen are both critical for the maintenance of bone, however, it is still unclear whether men do require estrogen or testosterone (or both) for normal bone functioning. To compare sex-specific actions of estrogen and androgen on bone-resorbing cells, human peripheral blood mononuclear precursors from adult Caucasian males (n = 3) and females (n = 3) were differentiated into osteoclasts and then treated for 24 hours with 17 β -estradiol (10 nM) or testosterone (10 nM). Gene expression was studied with a custom designed qPCR-based array containing 94 target genes related to bone or hormone metabolism. The study found that 17 β -estradiol and testosterone largely affected different genes. For example, genes that were affected by testosterone in female-derived cells—TGF β 3, PTEN, ICAM 1, and TNF—were not affected by 17 β -estradiol in either male or female-derived cells, and thus it seems likely that these effects of testosterone were not due to its conversion to 17 β -estradiol. —DK

Molecular and Cell Biology

- ◆Courtial N, Smink JJ, Kuvardina ON, Leutz A, Göthert JR, Lausen J. Tal1 regulates osteoclast differentiation through suppression of the master regulator of cell fusion DC-STAMP. *FASEB J*. 2011 Oct 11. [E-pub ahead of print] [[Abstract](#)]

The transcription factor Tal1 is involved in the establishment of hematopoietic stem cells in the embryo and is a master regulator of hematopoietic gene expression in the adult. The authors demonstrate that Tal1 is expressed in osteoclasts and the expression increases during osteoclast differentiation, that loss of Tal1 in osteoclast progenitors modulates the expression of 1,273 genes, and that DC-STAMP, a key regulator of osteoclast cell fusion, is a direct target gene of Tal1. Tal1 represses the DC-STAMP gene promoter by counteracting the transcriptional activation by PU.1 and MITF. Further elucidation of the relationship between Tal1 and DC-STAMP may contribute to the understanding of disorders with excess osteoclastic bone resorption. —TM

- ◆Ferron M, Boudiffa M, Arsenault M, Rached M, Pata M, Giroux S, Elfassihi L, Kisseleva M, Majerus PW, Rousseau F, Vacher J. Inositol polyphosphate 4-phosphatase B as a regulator of bone mass in mice and humans. *Cell Metab*. 2011 Oct 5;14(4):466-77. [[Abstract](#)]

The authors identified the murine homolog of inositol polyphosphate 4-phosphatase type IIa (Inpp4ba) as a negative regulator of osteoclastogenesis. Inpp4ba is expressed from early osteoclast differentiation to the activation stage. Phosphatase activity of Inpp4ba regulates intracellular calcium levels that modulate NFATc1 nuclear translocation and activation. Mice deficient in Inpp4b displayed an increased rate and potential of osteoclast differentiation resulting in decreased bone mass and osteoporosis. INPP4B in humans was identified as a susceptibility locus for osteoporosis. This study defines Inpp4b as an important modulator of osteoclast differentiation and bone mass in mice and humans. —TM

- ◆Frisch BJ, Ashton JM, Xing L, Becker MW, Jordan CT, Calvi LM. Functional inhibition of osteoblastic cells in an in vivo mouse model of myeloid leukemia. *Blood*. 2011 Sep 28. [Epub ahead of print] [[Abstract](#)]

Osteoblasts (OBs) play an important role in supporting hematopoiesis. The authors employed an immunocompetent murine model of acute myeloid leukemia (AML) to clarify effects of AML on OB development and function. In AML mice, osteoprogenitor cells and endosteal-lining osteopontin+ cells were reduced, and osteocalcin mRNA in CD45- marrow cells was diminished, resulting in severe loss of mineralized bone. Bone resorption was not increased. Expression of CCL-3, a chemokine with an inhibitory effect on OB function, was increased in leukemic cells from the bone marrow of AML mice as well as from AML patients. Thus, suppression of OB function by CCL-3 may play a role in the suppression of normal hematopoiesis in AML patients. —TM

- ◆Liu J, Lv F, Sun W, Tao C, Ding G, Karaplis A, Brown E, Goltzman D, Miao D. The abnormal phenotypes of cartilage and bone in calcium-sensing receptor deficient mice are dependent on the actions of calcium, phosphorus, and PTH. *PLoS Genet.* 2011 Sep;7(9):e1002294. [[Abstract](#)]

To determine effects of calcium-sensing receptor (CaR) deficiency on skeletal development and interactions between CaR and 1,25(OH)₂D₃ or PTH on calcium and skeletal homeostasis, the authors compared the skeletal phenotypes of CaR(-/-) mice to those of double homozygous CaR- and 1 α (OH)ase-deficient [CaR(-/-)1 α (OH)ase(-/-)] mice or those of double homozygous CaR- and PTH-deficient [CaR(-/-)PTH(-/-)] mice. The results indicate that reductions in hypercalcemia play a critical role in preventing the early lethality of CaR(-/-) mice and that defects in endochondral bone formation in CaR(-/-) mice result from the marked elevation in serum calcium and the decreases in serum phosphorus and skeletal PTHrP, whereas the increased osteoblastic bone formation results from direct effects of PTH. —TM

- ◆Negishi-Koga T, Shinohara M, Komatsu N, Bito H, Kodama T, Friedel RH, Takayanagi H. Suppression of bone formation by osteoclastic expression of semaphorin 4D. *Nat Med.* 2011 Oct 23;17(11):1473-80. [[Abstract](#)]

The authors found that osteoclasts express semaphorin 4D (Sema4D), an axon guidance molecule, which potently inhibits bone formation. The binding of Sema4D to its receptor Plexin-B1 on osteoblasts activated the small GTPase RhoA, which inhibits bone formation by suppressing IGF-1 signaling and by modulating osteoblast motility. Sema4d(-/-) mice, Plxnb1(-/-) mice and mice expressing a dominant-negative RhoA specifically in osteoblasts showed a cluster of osteoblasts in close proximity to osteoclasts, and an osteosclerotic phenotype due to augmented bone formation. Sema4D-specific antibody markedly prevented bone loss in ovariectomized mice. Thus, Sema4D inhibits osteoblast differentiation in the proximity of osteoclasts and repels osteoblasts by increasing their motility. Sema4D may become a new therapeutic target for the development of bone anabolic agents. —TM

- ◆Williams SA, Maecker HL, French DM, Liu J, Gregg A, Silverstein LB, Cao TC, Carano RA, Dixit VM. USP1 deubiquitinates ID proteins to preserve a mesenchymal stem cell program in osteosarcoma. *Cell.* 2011 Sep 16;146(6):918-30. [[Abstract](#)]

The authors show that the deubiquitinating enzyme USP1 promotes inhibitor of DNA binding (ID) protein stability and stem cell-like characteristics in osteosarcoma. USP1 bound, deubiquitinated, and stabilized ID1, ID2, and ID3. Primary human osteosarcomas coordinately overexpressed USP1 and ID proteins. USP1 knockdown in osteosarcoma cells caused ID protein destabilization, cell-cycle arrest, and osteogenic differentiation. Conversely, ectopic USP1 expression in mesenchymal stem cells stabilized ID proteins, inhibited osteoblastic differentiation, and enhanced proliferation. These results demonstrate that USP1 preserves the stem cell state that characterizes osteosarcoma and suggest that USP1 can be a target for differentiation

therapy. —TM

Bone Modeling, Remodeling, and Repair

- ◆Bivi N, Condon KW, Allen MR, Farlow N, Passeri G, Brun LR, Rhee Y, Bellido T, Plotkin LI. Cell autonomous requirement of connexin 43 for osteocyte survival: consequences for endocortical resorption and periosteal bone formation. *J Bone Miner Res*. 2011 Oct 25. [Epub ahead of print] [\[Abstract\]](#)

Connexin 43 (Cx43) is essential in osteocyte survival and expression of osteocytic genes affecting osteoclast and osteoblast function. Mice lacking Cx43 in osteoblasts/osteocytes or only in osteocytes (Cx43(Δ Ot) mice) have increased osteocyte apoptosis, endocortical resorption and periosteal bone formation at the femoral mid-diaphysis. Blocking resorption prevented marrow cavity expansion but not total tissue area. Cx43 controls osteoclast activity by osteoprotegerin (OPG) and osteoblast activity by regulating sclerostin in osteocytes. Empty lacunae and living osteocytes lacking OPG were found throughout cortical bone and apoptotic osteocytes were located in areas containing osteoclasts. Also, Cx43 deletion in cultured osteocytic cells increased apoptosis and decreased OPG expression. —ES

- ◆Fukui T, Matsumoto T, Mifune Y, Shoji T, Kuroda T, Kawakami Y, Kawamoto A, Ii M, Kawamata S, Kurosaka M, Asahara T, Kuroda R. Local transplantation of granulocyte colony stimulating factor-mobilized human peripheral blood mononuclear cells for unhealing bone fractures. *Cell Transplant*. 2011 Sep 16. [Epub ahead of print] [\[Abstract\]](#)

Granulocyte colony stimulating factor-mobilized (GM) human peripheral blood (hPB) mononuclear cell (MNC) transplantation was examined for its effect on fracture healing via vasculogenesis/angiogenesis and osteogenesis. Nude rats with unhealing fractures received local delivery in collagen of either low or high doses of GM hPB MNCs or phosphate-buffered saline (PBS). Immunohistochemistry and real-time reverse transcriptase-polymerase chain reaction (RT-PCR) demonstrated human cell-derived vasculogenesis and osteogenesis in the Hi and Lo groups, but not in the PBS group at week 1. Angiogenesis and osteogenesis assessed by rat capillary, osteoblast density, and real time RT-PCR analysis was significantly enhanced in the Hi group compared to the other groups. Blood flow assessment by laser doppler perfusion imaging showed a significantly higher blood flow ratio at week 1 in the Hi group compared with the other groups. Fracture healing was radiographically and histologically confirmed in about 30% of animals in the Hi group at week 8, whereas all animals in the other groups resulted in non-union. GM hPB MNCs may improve fracture healing, and this could be performed in an autologous fashion in humans. —DGL

- ◆Nagao M, Feinstein TN, Ezura Y, Hayata T, Notomi T, Saita Y, Hanyu R, Hemmi H, Izu Y, Takeda S, Wang K, Rittling S, Nakamoto T, Kaneko K, Kurosawa H, Karsenty G, Denhardt DT, Vilardaga JP, Noda M. Sympathetic control of bone mass regulated by osteopontin. *Proc Natl Acad Sci U S A*. 2011 Oct 25;108(43):17767-72. [\[Abstract\]](#) [\[Full Text\]](#)

The sympathetic nervous system suppresses bone mass through osteopontin (OPN) and stimulation of the sympathetic tone. Isoproterenol increased OPN expression in the plasma and bone and mice lacking OPN (OPN-KO) suppressed the isoproterenol-induced bone loss by preventing reduced osteoblastic and enhanced osteoclastic activities. OPN is necessary for changes in the expression of genes related to resorption and formation induced by activation of the sympathetic tone. Intracellular OPN modulated the capacity of the β 2-adrenergic receptor to generate cyclic AMP

(cAMP) with a corresponding modulation of cAMP-response element binding (CREB) phosphorylation and associated transcriptional events inside the cell. —ES

- ◆Slyfield CR, Tkachenko EV, Wilson DL, Hernandez CJ. Three-dimensional dynamic bone histomorphometry. *J Bone Miner Res.* 2011 Oct 25. [Epub ahead of print] [\[Abstract\]](#)

A three-dimensional fluorescence imaging method measured individual resorption cavities and formation events in the ovariectomized rat. The three-dimensional images demonstrate that ovariectomy was associated with increases in the number of resorption cavities per unit bone surface and total volume occupied by cavities per unit bone volume, but not surface area per resorption cavity, maximum cavity depth, or cavity volume. Estrogen depletion is associated with an increased number of remodeling events but not remodeling event size, suggesting that estrogens may have their primary effect on the origination of new basic multicellular units (BMUs), with little effect on the progression and termination of active remodeling events. This is interesting work in a rat model that is contrary to current notions concerning the effects of longevity of cells controlled by estrogen. —ES

Physiology and Metabolism

- ◆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 Sep 30;286(39):33804-10. [\[Abstract\]](#) [\[Full Text\]](#)

A high fat diet-resistant lean phenotype of vitamin D receptor (VDR)-null mutant mice is due to increased energy expenditure. Using the α 2 gene promoter to target the expression of the human (h)VDR in adipocytes in mice, the investigators found that the animals developed obesity without changes in food intake. This was the result of reduced energy expenditure, which correlated with decreased locomotive activity and reduced fatty acid oxidation and lipolysis in the adipose tissue. Consistently, the expression of genes involved in the regulation of fatty acid transport, thermogenesis, and lipolysis were suppressed in the transgenic mice. The VDR participates in energy metabolism. —ES

Public Health—Risk Assessment

- ◆Moayyeri A, Adams JE, Adler RA, Krieg MA, Hans D, Compston J, Lewiecki EM. Quantitative ultrasound of the heel and fracture risk assessment: an updated meta-analysis. *Osteoporos Int.* 2011 Oct 27. [Epub ahead of print] [\[Abstract\]](#)

Meta-analysis of prospective studies shows that heel quantitative ultrasound (QUS) using validated devices from different manufacturers predicts the risk of different types of fracture. Here, 21 prospective studies including 55,164 elderly women and 13,742 elderly men were included in a meta-analysis of heel QUS measures at baseline predicting various fracture outcomes in the follow-up. QUS parameters included broadband ultrasound attenuation (BUA), speed of sound (SOS), stiffness index (SI), and quantitative ultrasound index (QUI). The relative risk (RR) of hip fracture for 1 SD decrease in BUA was 1.69 (95% CI, 1.43-2.00), SOS was 1.96 (95% CI, 1.64-2.34), SI was 2.26 (95% CI, 1.71-2.99) and QUI was 1.99 (95% CI, 1.49-2.67). Notably, meta-analysis of studies with QUS measures adjusted for hip BMD showed an independent association with fracture risk. —DK

Muscle and Bone

◆Tong J, Li W, Vidal C, Yeo LS, Fatkin D, Duque G. Lamin A/C deficiency is associated with fat infiltration of muscle and bone. *Mech Ageing Dev.* 2011 Oct 1. [Epub ahead of print] [[Abstract](#)]

Since frailty has been associated with increased fat infiltration in muscle and bone, the authors hypothesized that lamin A/C, a protein of the nuclear envelope that regulates adipose differentiation, could be associated with the pathophysiology of both sarco- and osteopenia in the frailty syndrome. They used a lamin A/C null [Lmna(-/-)] mouse model, which closely mimics sarco- and osteopenia in frail human subjects. Even at age 4 weeks, Lmna(-/-) mice showed a significant increase in inter- (~4-fold) and intra-myofiber (~2.5-fold) fat and marrow fat infiltration (~40-fold), with a significant decrease in muscle volume (~42%) and bone volume (~22%), as compared with wildtype controls. This fat infiltration occurred concomitantly with a significant decline in muscle and bone strength in Lmna(-/-) mice. The authors have not yet investigated lamin A/C expression in human frail patients suffering from sarco- and osteopenia. —DK

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.