IBMS BoneKEy. 2010 November;7(11):373-381
http://www.bonekey-ibms.org/cgi/content/full/ibmske;7/11/373
doi: 10.1138/20100471

NOT TO BE MISSED

Clinical and Basic Research Papers – November 2010

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

Clinical Studies and Drug Effects

Bashutski JD, Eber RM, Kinney JS, Benavides E, Maitra S, Braun TM, Giannobile WV, McCauley LK. Teriparatide and osseous regeneration in the oral cavity. *N Engl J Med*. 2010 Oct 16. [Epub ahead of print] [Abstract]

> *40 patients with periodontitis underwent periodontal surgery and received daily teriparatide (20 μg) or placebo for 6 weeks. The patients were followed for 1 year. Compared to placebo, radiographic linear resolution of osseous defects was greater after teriparatide at 6 months, with a reduction in periodontal probing depth of 33% vs. 20% (2.42 mm vs. 1.32 mm) and a gain in clinical attachment level of 22% vs. 7% (1.58 mm vs. 0.42 mm) in target lesions at 1 year (P = 0.02 for both comparisons).* —ES

Burghardt AJ, Kazakia GJ, Sode M, de Papp AE, Link TM, Majumdar S. A longitudinal HR-pQCT study of alendronate treatment in post-menopausal women with low bone density: Relations between density, cortical and trabecular micro-architecture, biomechanics, and bone turnover. *J Bone Miner Res*. 2010 Jun 18. [Epub ahead of print] [Abstract]

Seeman E. Bone morphology in response to alendronate as seen by high resolution computed tomography: Through a glass darkly. *J Bone Miner Res*. 2010 Oct 6. [Epub ahead of print] [Info]

> *Effects of alendronate (ALN) on vBMD and bone microstructure by HR-pQCT have previously been reported against strontium ranelate on one side, and denosumab or placebo on another side (see recent BoneKEy Commentary by S. Ferrari), with somewhat discordant results (increase in cortical thickness from baseline with ALN in one study, but not in the other). This study reports improvements of vBMD and bone structure at the tibia, particularly in cortical thickness and area, but not at the radius, after 2 years of ALN vs. baseline in osteopenic women, and minor improvements vs. placebo at both sites. In a brilliant accompanying editorial, Dr. Seeman explains the mechanisms by which antiresorptive therapy produces some changes in cortical bone microstructure (porosity) and mineralization that may result in detectable changes by HR-microCT.* —SF

Cosman F, Eriksen EF, Recknor C, Miller PD, Guañabens N, Kasperk C, Papanastasiou P, Readie A, Rao H, Gasser JA, Bucci-Rechtweg C, Boonen S. Effects of intravenous zoledronic acid plus subcutaneous teriparatide [(1-34)rhPTH] in postmenopausal osteoporosis. *J Bone Miner Res*. 2010 Sep 2. [Epub ahead of print] [Abstract]

> *It is well-known that oral ALN plus daily sc PTH given simultaneously has no additive effects on BMD gain. Yet once yearly iv zoledronic acid plus daily sc teriparatide (TPT)*

given to post-menopausal women with osteoporosis for 1 year produced greater earlier increases of hip and spine BMD than either treatment alone, and greater one-year increases of hip BMD vs. TPT alone. Although unlikely to result in new clinical practice, these results challenge the notion that bisphosphonates necessarily blunt TPT effects in humans and may pave the way to optimize rapid BMD gain at both the spine and hip simultaneously. —SF

Grey A, Bolland M, Wattie D, Horne A, Gamble G, Reid IR. Prolonged antiresorptive activity of zoledronate: a randomized, controlled trial. *J Bone Miner Res*. 2010 Oct;25(10):2251-5. [Abstract]

In this 3-year, double-blind, randomized, placebo-controlled trial in 50 postmenopausal women with osteopenia taking a single 5-mg dose of zoledronate, mean serum CTX and P1NP were 44% and 40% lower in the zoledronate group ($p < .001$ vs. placebo for each marker). BMD was higher in the zoledronate group than in the placebo group by an average of 6.8% at the lumbar spine, 4.0% at the total hip, and 2.0% at the total body ($p < .001$ for each skeletal site). Between-group differences in bone turnover markers and BMD were stable from 12 to 36 months. —ES

Reid IR, Miller PD, Brown JP, Kendler DL, Fahrleitner-Pammer A, Valter I, Maasalu K, Bolognese MA, Woodson G, Bone H, Ding B, Wagman RB, San Martin J, Ominsky MS, Dempster DW; Denosumab Phase 3 Bone Histology Study Group. Effects of denosumab on bone histomorphometry: the FREEDOM and STAND studies. *J Bone Miner Res*. 2010 Oct;25(10):2256-65. [Abstract]

Bone biopsies were collected at 24 and/or 36 months from osteoporotic postmenopausal women in the FREEDOM study (45 receiving placebo, 47 denosumab) and at 12 months from women previously treated with alendronate in the STAND study (21 continuing alendronate, 15 changed to denosumab). In FREEDOM, median eroded surface was reduced by > 80% and osteoclasts were absent from > 50% of biopsies. Double labeling in trabecular bone was observed in 94% of placebo bones and 19% of those treated with denosumab. Median bone formation rate was reduced by 97%. In STAND, double labeling in trabecular bone was seen in 20% of the denosumab biopsies and in 90% of the alendronate samples. —ES

Wilkinson GS, Baillargeon J, Kuo YF, Freeman JL, Goodwin JS. Atrial fibrillation and stroke associated with intravenous bisphosphonate therapy in older patients with cancer. *J Clin Oncol*. 2010 Oct 12. [Epub ahead of print] [Abstract]

13,714 bisphosphonate nonusers were matched to 6,857 bisphosphonate users, at a 2:1 ratio, on cancer type, age, sex, presence of bone metastases, and SEER geographic region. Results suggested that intravenous bisphosphonate use was associated with an increased risk for atrial fibrillation (HR = 1.30; 95% CI: 1.18-1.43), all supraventricular tachycardia (SVT) (HR = 1.28; 95% CI: 1.19-1.38), and stroke (HR = 1.30; 95% CI: 1.09-1.54). The risk for all SVT increased 7% for each increase of five bisphosphonate dose equivalents (HR = 1.07; 95% CI: 1.02-1.12). —ES

Public Health – Epidemiology

Cawthon PM, Parimi N, Barrett-Connor E, Laughlin GA, Ensrud KE, Hoffman AR, Shikany JM, Cauley JA, Lane NE, Bauer DC, Orwoll ES, Cummings SR; Osteoporotic Fractures in Men (MrOS) Research Group. Serum 25-hydroxyvitamin D, parathyroid hormone, and mortality in older men. *J Clin Endocrinol Metab*. 2010 Oct;95(10):4625-34. [Abstract] [Full Text]

1,490 community-dwelling men at least 65 years of age were followed for 7.3 years.

330 (22.2%) died: 97 from cancer, 110 from cardiovascular disease, and 106 from other causes. The adjusted HR per SD decrease in 25(OH)D for all-cause mortality was 1.01 (95% CI: 0.89-1.14); no association between 25(OH)D and cardiovascular or other-cause mortality was seen. Lower 25(OH)D levels were associated with a decreased risk of cancer mortality (HR per SD decrease = 0.80; 95% CI: 0.64- 0.99). Higher PTH was associated with an increased risk of all-cause mortality (HR per SD increase = 1.15; 95% CI: 1.03-1.29) and cardiovascular mortality (HR per SD increase in PTH = 1.21; 95% CI: 1.00-1.45). —ES

Jassal SK, Chonchol M, Mühlen DV, Smits G, Barrett-Connor E. Vitamin D, parathyroid hormone, and cardiovascular mortality in older adults: The Rancho Bernardo Study. *Am J Med*. 2010 Sep 24. [Epub ahead of print] [Abstract]

1,073 community-dwelling older adults were followed to 10.4 (mean 6.4) years with 111 cardiovascular deaths. After adjusting for age alone or multiple covariates, there was no association between 25(OH)D, 1,25(OH)$_2$D, or intact PTH and cardiovascular mortality. —ES

Michaëlsson K, Baron JA, Snellman G, Gedeborg R, Byberg L, Sundström J, Berglund L, Arnlöv J, Hellman P, Blomhoff R, Wolk A, Garmo H, Holmberg L, Melhus H. Plasma vitamin D and mortality in older men: a community-based prospective cohort study. *Am J Clin Nutr*. 2010 Oct;92(4):841-8. [Abstract]

Among 1,194 men (mean age 71) followed for 12.7 years, 584 (49%) died. A 50% higher total mortality was observed among men in the lowest 10% (< 46 nmol/L) and the highest 5% (> 98 nmol/L) of plasma 25(OH)D concentrations compared with intermediate concentrations. Cancer mortality was also higher at low plasma concentrations (HR = 2.20; 95% CI: 1.44-3.38) and at high concentrations (HR = 2.64; 95% CI: 1.46-4.78). For cardiovascular death, only low (HR = 1.89; 95% CI: 1.21-2.96), not high (HR = 1.33; 95% CI: 0.69-2.54) concentrations suggested higher risk. Both high and low concentrations of plasma 25(OH)D are associated with elevated risks of overall and cancer mortality. Low concentrations are associated with cardiovascular mortality. —ES

Genetics

Farber CR. Identification of a gene module associated with BMD through the integration of network analysis and genome-wide association data. *J Bone Miner Res*. 2010 Nov;25(11):2359-67. [Abstract]

Suwanwela J, Farber CR, Haung BL, Song B, Pan C, Lyons KM, Lusis AJ. Systems genetics analysis of mouse chondrocyte differentiation. *J Bone Miner Res*. 2010 Oct 15. [Epub ahead of print] [Abstract]

These 2 papers illustrate the interest in systems genetics to identify new genes (pathways) that regulate bone mass/turnover. By systems genetics, we mean the combination of gene variant association with a phenotypic trait on one side with gene expression data on another side. Hence C. Farber first identified 11 transcribed gene modules (networks) in silico (i.e., using previously published monocyte microarray expression profiles from young Chinese adults with extremely low or high BMD), and then validated his findings by using two publicly available GWAS data sets to perform an in silico association study testing for association of genes in module 9 (immune process viral response!) with aBMD, thereby identifying 6 novel potential

determinants of bone mass. Suwanwela et al. used a similar approach, but in mice, to link chondrocyte gene expression data with femur bone geometry, and subsequently tested the functionality of the newly discovered genes by inhibiting their expression with siRNAs. Both approaches point to new genes potentially involved in bone strength. —SF

Jee SH, Sull JW, Lee JE, Shin C, Park J, Kimm H, Cho EY, Shin ES, Yun JE, Park JW, Kim SY, Lee SJ, Jee EJ, Baik I, Kao L, Yoon SK, Jang Y, Beaty TH. Adiponectin concentrations: a genome-wide association study. *Am J Hum Genet*. 2010 Oct 8;87(4):545-52. [Abstract]

Wu Y, Li Y, Lange EM, Croteau-Chonka DC, Kuzawa CW, McDade TW, Qin L, Curocichin G, Borja JB, Lange LA, Adair LS, Mohlke KL. Genome-wide association study for adiponectin levels in Filipino women identifies CDH13 and a novel uncommon haplotype at KNG1-ADIPOQ. *Hum Mol Genet*. 2010 Oct 11. [Epub ahead of print] [Abstract]

Although the exact effect of adiponectin on bone is incompletely understood, adiponectin was hypothesized to contribute to the pathogenesis of osteoporosis. Recently, several GWAS for adiponectin in Caucasians have identified ADIPOQ and ARL15 as possible causal genes. To date, there have been no GWAS of adiponectin levels in Asians; here are two recent GWAS in two Asian populations. In the first study, 4,001 subjects were genotyped by using a genome-wide marker panel; another 2,304 subjects were used for follow-up replication studies with selected markers. The top SNP associated with mean log adiponectin was rs3865188 in CDH13 on chromosome 16. The meta-analysis p value for this SNP in all 6,305 individuals was 2.82×10^{-83}. This gene encodes a receptor for high-molecular-weight forms of adiponectin.

In the second study of 1,776 unrelated Filipino women, the strongest signal for adiponectin was again shown with the gene CDH13 (same SNP, rs3865188, $P = 7.2 \times 10^{-16}$). Strong association was also detected near the ADIPOQ gene (rs864265, $P = 3.8 \times 10^{-9}$). These signals were also observed in 1,774 young adult offspring of these women. —DK

Styrkarsdottir U, Halldorsson BV, Gudbjartsson DF, Tang NL, Koh JM, Xiao SM, Kwok TC, Kim GS, Chan JC, Cherny S, Lee SH, Kwok A, Ho S, Gretarsdottir S, Kostic JP, Palsson ST, Sigurdsson G, Sham PC, Kim BJ, Kung AW, Kim SY, Woo J, Leung PC, Kong A, Thorsteinsdottir U, Stefansson K. European bone mineral density loci are also associated with BMD in East-Asian populations. *PLoS One*. 2010 Oct 7;5(10):e13217. [Abstract]

To replicate recent GWAS of BMD in populations of European ancestry, the authors genotyped 50 markers from 23 genomic loci in samples from Korea (n = 1,397, women, age 59.06 [SD 7.36] yrs.) and two Chinese Hong Kong samples (n = 3,869 and n = 785, men and women, respectively). 14 loci were associated with BMD in East-Asian samples, including: ZBTB40, GPR177, CTNNB1, MEPE, MEF2C, ESR1, STARD3NL, FLJ42280, TNFRSF11B, SOX6, LRP5, TNFSF11, FOXL1, and SOST, but not TNFRSF11A (RANK). The effect of BMD association in each of these loci is very similar to that observed in the European samples; the same alleles were associated with a BMD decrease in both ethnicities. —DK

Suh KT, Eun IS, Lee JS. Polymorphism in vitamin D receptor is associated with bone mineral density in patients with adolescent idiopathic scoliosis. *Eur Spine J*. 2010 Sep;19(9):1545-50. [Abstract]

Lee JS, Suh KT, Eun IS. Polymorphism in interleukin-6 gene is associated with bone mineral

density in patients with adolescent idiopathic scoliosis. *J Bone Joint Surg Br*. 2010 Aug;92(8):1118-22. [Abstract]

> *These 2 parallel studies from the same group examined the association between bone mass and polymorphisms in two osteoporosis candidate genes in 198 Korean girls diagnosed with adolescent idiopathic scoliosis (AIS). Mean LS BMD and FN BMD in AIS patients are lower than in age- and sex-matched healthy controls. In the first paper, the VDR BsmI, FokI, and Cdx2 polymorphisms were studied. Only the BsmI polymorphism significantly differed in genotype frequencies between AIS patients and controls; a significant association was found between this polymorphism and LS BMD.*
>
> *In the second paper, 3 polymorphisms of IL6 (-597 G→A, -572 G→C, and -174 G→A) were studied. IL6-572 G→C showed a statistically significant difference between AIS patients and controls and was also associated with LS BMD.* —DK

Bone Modeling, Remodeling, and Repair

Krause C, Korchynskyi O, de Rooij KE, Weidauer SE, de Gorter DJ, van Bezooijen RL, Hatsell S, Economides AN, Mueller TD, Lowik CW, Ten Dijke P. Distinct modes of inhibition by Sclerostin on bone morphogenetic protein and Wnt signaling pathways. *J Biol Chem*. 2010 Oct 15. [Epub ahead of print] [Abstract]

> *Whether sclerostin inhibits Wnt-LRP signaling and/or BMP signaling remains unclear. This study shows that it binds weakly to both LRP6 and BMP7, but inhibits their signaling through different mechanisms, i.e., direct inhibition of Wnt3a-induced signaling in vitro, whereas it prevents BMP7 signaling by inducing its proteosomal degradation when both molecules are produced in the same cell.* —SF

Oury F, Yadav VK, Wang Y, Zhou B, Liu XS, Guo XE, Tecott LH, Schutz G, Means AR, Karsenty G. CREB mediates brain serotonin regulation of bone mass through its expression in ventromedial hypothalamic neurons. *Genes Dev*. 2010 Oct 15;24(20):2330-42. [Abstract]

> *Gut-derived serotonin decreases bone accrual, while brain serotonin increases it. Gut-derived serotonin binds to the Htr1b receptor on osteoblasts, culminating in cAMP response element-binding protein (CREB) regulation of osteoblast proliferation. Brain-derived serotonin favors accrual by binding to the Htr2c receptor on neurons of the hypothalamic ventromedial nucleus (VMH). This study reports that after binding to the Htr2c receptor on VMH neurons, serotonin uses a calmodulin kinase (CaMK)-dependent signaling cascade involving CaMKKβ and CaMKIV to decrease the sympathetic tone and increase bone accrual. The transcriptional mediator of these events is CREB phosphorylation on Ser 133 that is increased by CaMKIV following serotonin treatment of hypothalamic explants. A microarray experiment identified two genes necessary for optimum sympathetic activity whose expression is regulated by CREB. These results identify CREB as a determinant of serotonin signaling in hypothalamic neurons to regulate bone mass accrual, although through different mechanisms depending on the cell type, neuron, or osteoblast in which it is expressed.* —ES

Schulte FA, Lambers FM, Kuhn G, Müller R. In vivo micro-computed tomography allows direct three-dimensional quantification of both bone formation and bone resorption parameters using time-lapsed imaging. *Bone*. 2010 Oct 13. [Epub ahead of print] [Abstract]

> *In vivo microCT has sometimes been called "virtual bone biopsy", which was*

erroneous since it did not provide dynamic indices of bone remodeling...so far. Now the pioneering team of the microCT shows that by superimposing very precisely (by a procedure called registration) a later measurement of an in vivo mouse onto an earlier measurement of the same animal, areas of bone formed and resorbed can be evaluated, and correlate well to histomorphometrical indices of bone turnover. —SF

Syed FA, Mödder UI, Roforth M, Hensen I, Fraser DG, Peterson JM, Oursler MJ, Khosla S. Effects of chronic estrogen treatment on modulating age-related bone loss in female mice. *J Bone Miner Res*. 2010 Nov;25(11):2438-46. [Abstract]

This is an important study for all of those using mice with the C57/BL6 background to understand the principles of bone turnover and/or the effects of treatments on bone loss. This strain is well-known to spontaneously lose a great deal of trabecular bone with age. This study shows that long-term estrogen-supplementation in OVX C57/BL6 mice does not prevent trabecular bone loss, although it improved cortical bone loss. It also shows that osteoblast numbers in bone decrease with age, but the osteogenic potential of progenitor bone marrow cells increases – rather than decreases – with age. Hence estrogen could play a greater role in the maintenance of cortical than trabecular bone mass. The mechanisms for the profound remodeling of trabecular bone in this strain remain to be elucidated. —SF

Molecular and Cell Biology

Bozec A, Bakiri L, Jimenez M, Schinke T, Amling M, Wagner EF. Fra-2/AP-1 controls bone formation by regulating osteoblast differentiation and collagen production. *J Cell Biol*. 2010 Sep 20;190(6):1093-106. [Abstract] [Full Text]

Fra-2 (Fosl2), a Fos-related protein of the AP-1 family, is expressed in bone cells, and Fosl2(-/-) newborn mice exhibit defects in chondrocytes and osteoclasts. This study demonstrates that Fosl2(-/-) osteoblasts display a differentiation defect both in vivo and in vitro, while Fra-2-overexpressing mice were osteosclerotic because of increased osteoblast differentiation. The osteoblast-specific osteocalcin and collagen1α2 genes were direct transcriptional targets of Fra-2 in both murine and human bone cells, and Fra-2-ATF-4 dimers and Fra-2-c-Jun or JunB dimers positively regulated this gene transcription. These findings identify Fra-2, in addition to the previously found Fra-1 and ΔFosB, as a novel transcriptional regulator of bone matrix production and osteoblast differentiation. —TM

Nishikawa K, Nakashima T, Takeda S, Isogai M, Hamada M, Kimura A, Kodama T, Yamaguchi A, Owen MJ, Takahashi S, Takayanagi H. Maf promotes osteoblast differentiation in mice by mediating the age-related switch in mesenchymal cell differentiation. *J Clin Invest*. 2010 Oct 1;120(10):3455-65. [Abstract]

McCauley LK. c-Maf and you won't see fat. *J Clin Invest*. 2010 Oct 1;120(10):3440-2. [Abstract]

The authors performed a genome-wide screening of mRNAs for transcription factors that were increased by > 4-fold during osteoblastogenesis, and from bone marrow stromal cells (BMSCs) that were decreased with aging by > 2-fold. The authors identified Maf as the most highly expressed in the BMSCs. Maf regulated mesenchymal cell bifurcation into osteoblasts and adipocytes by cooperating with the osteogenic transcription factor Runx2 and inhibiting the expression of the adipogenic transcription factor Pparg. Results showed delayed bone formation in perinatal Maf(-/-) mice and accelerated fatty marrow formation that was associated with bone loss in

aged Maf(+/-) mice. These observations may provide novel therapeutic strategies against age-related bone loss. Also see a Commentary on this study by L. McCauley in the same issue of JCI. —TM

Omatsu Y, Sugiyama T, Kohara H, Kondoh G, Fujii N, Kohno K, Nagasawa T. The essential functions of adipo-osteogenic progenitors as the hematopoietic stem and progenitor cell niche. *Immunity*. 2010 Sep 24;33(3):387-99. [Abstract]

Kincade PW. Plasticity of supporting cells in a stem cell factory. *Immunity*. 2010 Sep 24;33(3):291-3. [Abstract]

The authors created mice in which a diphtheria toxin (DT) receptor-GFP fusion protein transgene was knocked into the Cxcl12 locus, allowing conditional ablation of CXCL12/SDF-1-abundant reticular (CAR) cells by DT administration. Short-term ablation of CAR cells severely impaired the adipo-osteogenic differentiation potential of marrow cells as well as SCF and CXCL12 production, leading to a marked reduction in circulating lymphoid and erythroid progenitors. Hematopoietic stem cells (HSCs) were more quiescent with reduced number and size, and showed high early myeloid selector gene expression, similar to the phenotype of wild-type HSCs without a niche. These results demonstrate the importance of the niche composed of adipo-osteogenic progenitors for proliferation and maintenance of HSCs and lymphoid and erythroid progenitors. Also see an analysis of this paper by P. Kincade in the same issue of Immunity. —TM

Schlesinger N, Thiele RG. The pathogenesis of bone erosions in gouty arthritis. *Ann Rheum Dis*. 2010 Nov;69(11):1907-12. [Abstract]

Lee B, Kim TH, Jun JB, Yoo DH, Woo JH, Choi SJ, Lee YH, Song GG, Sohn J, Park-Min KH, Ivashkiv LB, Ji JD. Direct inhibition of human RANK+ osteoclast precursors identifies a homeostatic function of IL-1beta. *J Immunol*. 2010 Nov 15;185(10):5926-34. [Abstract]

I put these two papers together to illustrate the complexity of cytokine action on bone. On one side the review by Schlesinger et al. on the mechanisms of osteolysis in gout underscores the key role of IL-1β in the activation of osteoclasts. On another side, Lee et al. show that IL-1β added to monocytes inhibits RANKL-mediated osteoclastogenesis, partly by triggering the proteolysis of c-Fms (the M-CSF receptor) that is required for the expression of RANK. Hence, depending on the context in which it is produced (local inflammatory response as in RA or gout, or inflammatory/immune response as in the presence of bacteria or LPS), IL-1β can favor differentiation of monocytes into macrophages or osteoclasts (also see April 2010 BoneKEy Commentary by S. Ferrari-Lacraz and D. Burger). —SF

Pathophysiology

Gonzalez-Suarez E, Jacob AP, Jones J, Miller R, Roudier-Meyer MP, Erwert R, Pinkas J, Branstetter D, Dougall WC. RANK ligand mediates progestin-induced mammary epithelial proliferation and carcinogenesis. *Nature*. 2010 Sep 29. [Epub ahead of print] [Abstract]

Schramek D, Leibbrandt A, Sigl V, Kenner L, Pospisilik JA, Lee HJ, Hanada R, Joshi PA, Aliprantis A, Glimcher L, Pasparakis M, Khokha R, Ormandy CJ, Widschwendter M, Schett G, Penninger JM. Osteoclast differentiation factor RANKL controls development of progestin-driven mammary cancer. *Nature*. 2010 Sep 29. [Epub ahead of print] [Abstract]

Here are two papers on RANKL, progestins, and breast cancer. Mammary glands of RANK- and RANKL-deficient mice fail to form lobuloalveolar structures during pregnancy because of defective proliferation of mammary epithelium. RANKL causes the proliferative response to progesterone during mammary lactational morphogenesis, and in mouse models, activation of the RANK/RANKL pathway produces mammary proliferation. In the first study by Gonzalez-Suarez et al., accelerated pre-neoplasias and increased mammary tumor formation were observed in mouse mammary tumor virus (MMTV)-RANK transgenic mice after multiparity or treatment with carcinogen and progesterone. Pharmacological inhibition of RANKL attenuated mammary tumor development in hormone- and carcinogen-treated MMTV-RANK and wild-type mice and in the MMTV-neu transgenic spontaneous tumor model. RANKL inhibition acts directly on hormone-induced mammary epithelium at early stages in tumorigenesis, and the permissive contribution of progesterone to increased mammary cancer incidence is due to RANKL-dependent proliferative changes in the mammary epithelium.

Medroxyprogesterone acetate (MPA) increases the risk of breast cancer. In the second paper by Schramek et al., the authors show that the in vivo administration of MPA triggers massive induction of RANKL in mammary gland epithelial cells. Genetic inactivation of the RANKL receptor RANK in mammary gland epithelial cells prevents MPA-induced epithelial proliferation, impairs expansion of the CD49f^{hi} stem cell-enriched population, and sensitizes these cells to DNA damage-induced cell death. Deletion of RANK from the mammary epithelium results in a markedly decreased incidence and delayed onset of MPA-driven mammary cancer. These results show that the RANKL/RANK system controls the incidence and onset of progestin-driven breast cancer. —ES

Reviews, Perspectives and Editorials

Heard E, Tishkoff S, Todd JA, Vidal M, Wagner GP, Wang J, Weigel D, Young R. Ten years of genetics and genomics: what have we achieved and where are we heading? *Nat Rev Genet*. 2010 Oct;11(10):723-33. [Abstract]

Sellmeyer DE. Atypical fractures as a potential complication of long-term bisphosphonate therapy. *JAMA*. 2010 Oct 6;304(13):1480-4. [Abstract]

Stockton KA, Mengersen K, Paratz JD, Kandiah D, Bennell KL. Effect of vitamin D supplementation on muscle strength: a systematic review and meta-analysis. *Osteoporos Int*. 2010 Oct 6. [Epub ahead of print] [Abstract]

Other Studies of Potential Interest

Hassan MQ, Gordon JA, Beloti MM, Croce CM, van Wijnen AJ, Stein JL, Stein GS, Lian JB. A network connecting Runx2, SATB2, and the miR-23a~27a~24-2 cluster regulates the osteoblast differentiation program. *Proc Natl Acad Sci U S A*. 2010 Oct 27. [Epub ahead of print] [Abstract]

Jönsson B, Ström O, Eisman JA, Papaioannou A, Siris ES, Tosteson A, Kanis JA. Cost-effectiveness of Denosumab for the treatment of postmenopausal osteoporosis. *Osteoporos Int*. 2010 Oct 9. [Epub ahead of print] [Abstract]

Judson RN, Wackerhage H, Hughes A, Mavroeidi A, Barr RJ, Macdonald HM, Ratkevicius A, Reid DM, Hocking LJ. The functional ACTN3 577X variant increases the risk of falling in older females: results from two large independent cohort studies. *J Gerontol A Biol Sci Med Sci*. 2010

Oct 21. [Epub ahead of print] [Abstract]

Jules J, Shi Z, Liu J, Xu D, Wang S, Feng X. The receptor activator of NF-kappa B (RANK) cytoplasmic IVVY535-538 motif plays an essential role in tumor necrosis factor-alpha (TNF)-mediated osteoclastogenesis. *J Biol Chem*. 2010 Sep 24. [Epub ahead of print] [Abstract]

Millard SM, Louie AM, Wattanachanya L, Wronski TJ, Conklin BR, Nissenson RA. Blockade of receptor-activated G(i) signaling in osteoblasts in vivo leads to site-specific increases in cortical and cancellous bone formation. *J Bone Miner Res*. 2010 Oct 11. [Epub ahead of print] [Abstract]

Ortuño MJ, Ruiz-Gaspà S, Rodríguez-Carballo E, Susperregui AR, Bartrons R, Rosa JL, Ventura F. p38 regulates expression of osteoblast-specific genes by phosphorylation of osterix. *J Biol Chem*. 2010 Oct 15;285(42):31985-94. [Abstract] [Full Text]

Patel CJ, Bhattacharya J, Butte AJ. An Environment-Wide Association Study (EWAS) on type 2 diabetes mellitus. *PLoS One*. 2010 May 20;5(5):e10746. [Abstract]

Shireman TI, Almehmi A, Wetmore JB, Lu J, Pregenzer M, Quarles LD. Economic analysis of cinacalcet in combination with low-dose vitamin D versus flexible-dose vitamin D in treating secondary hyperparathyroidism in hemodialysis patients. *Am J Kidney Dis*. 2010 Oct 14. [Epub ahead of print] [Abstract]

Stein EM, Dempster DW, Udesky J, Zhou H, Bilezikian JP, Shane E, Silverberg SJ. Vitamin D deficiency influences histomorphometric features of bone in primary hyperparathyroidism. *Bone*. 2010 Oct 13. [Epub ahead of print] [Abstract]

Su JL, Chiou J, Tang CH, Zhao M, Tsai CH, Chen PS, Chang YW, Chien MH, Peng CY, Hsiao M, Kuo ML, Yen ML. CYR61 regulates BMP-2-dependent osteoblast differentiation through the alphavbeta3 integrin/integrin-linked kinase/ERK pathway. *J Biol Chem*. 2010 Oct 8;285(41):31325-36. [Abstract] [Full Text]

Teixeira CC, Liu Y, Thant LM, Pang J, Palmer G, Alikhani M. Foxo1, a novel regulator of osteoblast differentiation and skeletogenesis. *J Biol Chem*. 2010 Oct 1;285(40):31055-65. [Abstract] [Full Text]

Thi MM, Suadicani SO, Spray DC. Fluid flow-induced soluble vascular endothelial growth factor isoforms regulate actin adaptation in osteoblasts. *J Biol Chem*. 2010 Oct 1;285(40):30931-41. [Abstract] [Full Text]

Conflict of Interest: 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 and Dr. Karasik report no conflicts of interest.