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NOT TO BE MISSED

Clinical and Basic Research Papers – November 2006 Selections

Serge Ferrari, Associate Editor
Ego Seeman, Clinical Editor
Gordon J. Strewler, Editor

Bone Modeling and Remodeling

Gupta HS, Seto J, Wagermaier W, Zaslansky P, Boesecke P, Fratzl P. Cooperative deformation of mineral and collagen in bone at the nanoscale. *Proc Natl Acad Sci U S A*. 2006 Nov 21;103(47):17741-6.[Abstract] [Full Text]

> *The ability to absorb energy imposed by a load without cracking arises at the nanometer scale from motifs like the stiff inorganic mineral component reinforcing the organic collagen matrix. Strains are transferred between mineral apatite particles via shearing in collagen layers with mineral particles and fibril deforming elastically. Tissue, fibrils, and mineral particles take up successively lower levels of strain (ratio 12:5:2). The maximum strain in mineral nanoparticles (0.15-0.20%) reaches up to twice the fracture strain for bulk apatite, a mechanism of fibril-matrix decoupling for protecting the brittle mineral while redistributing the strain energy in bone tissue.* —ES

Lee SH, Rho J, Jeong D, Sul JY, Kim T, Kim N, Kang JS, Miyamoto T, Suda T, Lee SK, Pignolo RJ, Koczon-Jaremko B, Lorenzo J, Choi Y. v-ATPase V(0) subunit d2-deficient mice exhibit impaired osteoclast fusion and increased bone formation. *Nat Med*. 2006 Dec;12(12):1403-9. [Abstract]

> *The d2 subunit of v-ATPase is a minor component in osteoclasts; mRNA levels of the new subunit are 10-fold lower than the dominant d1 subunit in osteoclasts and 200-fold lower than d1 in other tissues. Yet removal of the gene for the d2 subunit has a profound bone phenotype, with reduced multinucleated osteoclasts and increased mononuclear TRAP+ cells. Bone formation rate, osteoblast surface and BV/TV are markedly increased, though the d2 subunit is not expressed in osteoblasts. In culture, osteoclasts from d2-null precursors are smaller but have normal v-ATPase activity and form pits normally. The fusion defect can be rescued by expression of the d2 subunit and partially rescued by the proteases ADAM12 or ADAM8, whose expression is reduced in d2-null preosteoclasts. The d2 subunit functions both in osteoclast fusion and indirectly in osteoblast formation and function.* —GJS

Li M, Pan LC, Simmons HA, Li Y, Healy DR, Robinson BS, Ke HZ, Brown TA. Surface-specific effects of a PPARgamma agonist, darglitazone, on bone in mice. *Bone*. 2006 Oct;39(4):796–806. [Abstract]

> *This study demonstrates that darglitazone, a PPARγ agonist, has surface-specific effects, producing bone loss on the endosteal surface, with decreased trabecular bone density, decreased bone formation, decreased mineralizing surface, increased osteoclast surface and number, but increased periosteal mineral apposition rate and bone formation rate.* —ES

Sato K, Suematsu A, Nakashima T, Takemoto-Kimura S, Aoki K, Morishita Y, Asahara H, Ohya K, Yamaguchi A, Takai T, Kodama T, Chatila TA, Bito H, Takayanagi H. Regulation of osteoclast differentiation and function by the CaMK-CREB pathway. *Nat Med*. 2007 Jan;12(12):1410-6. [Abstract]

> *RANKL is an indispensable activator of osteoclastogenesis. This study provides novel insights into the downstream signaling events of RANK (the RANKL receptor) activation through calcium/calmodulin-dependent kinase 4 (CAMK4) and CREB. CAMK4 KO mice have fewer osteoclasts, decreased bone resorption and a 30% increase in trabecular bone volume. Systemic adminisration of KN-93, a CAMK inhibitor, prevented bone loss due to OVX, low-calcium diet and LPS-induced inflammation.* —SF

Tsuji K, Bandyopadhyay A, Harfe BD, Cox K, Kakar S, Gerstenfeld L, Einhorn T, Tabin CJ, Rosen V. BMP2 activity, although dispensable for bone formation, is required for the initiation of fracture healing. *Nat Genet*. 2006 Dec;38(12):1424-9. [Abstract]

> *BMP2 KO embryos fail to develop due to amnion and cardiac abnormalities, precluding proper assessment of the role of BMP2 on the skeleton. In this study, targeted ablation of BMP2 in the limbs led to viable newborn mice with few skeletal abnormalities, demonstrating that BMP2 has a limited role during skeletal development. During growth, however, conditional KO mice have decreased bone mass in the limbs, spontaneous fractures, and delayed fracture healing. In a standardized fracture model, the healing defect was shown to be due to complete failure of periosteal reaction and the absence of callus formation. While BMP4 and BMP7 are normally expressed at the fracture site in BMP2 KO mice, these results demonstrate that BMP2 is necessary to initiate fracture repair. Of note, local BMP2 delivery in a large randomized clinical trial on open tibia fractures has been demonstrated to accelerate fracture healing and decrease the rate of non-union.* —SF

Genetics

Cohen MM Jr. The new bone biology: pathologic, molecular, and clinical correlates. *Am J Med Genet A*. 2006 Dec 1;140(23):2646-706. [Abstract]

> *This is a review, rather a compendium (virtually exhaustive) of most recently discovered biological pathways and related mutations in bone biology. An enormous amount of work, with great illustrations, like a book...only better updated. Must see.* —SF

Green RE, Krause J, Ptak SE, Briggs AW, Ronan MT, Simons JF, Du L, Egholm M, Rothberg JM, Paunovic M, Paabo S. Analysis of one million base pairs of Neanderthal DNA. *Nature*. 2006 Nov 16;444(7117):330-6. [Abstract]

Noonan JP, Coop G, Kudaravalli S, Smith D, Krause J, Alessi J, Chen F, Platt D, Paabo S, Pritchard JK, Rubin EM. Sequencing and analysis of Neanderthal genomic DNA. *Science*. 2006 Nov 17;314(5802):1113-8. [Abstract] [Full Text]

> *May not be directly related to our interest in bone but....First, these may be the two most important scientific papers of the early 21st century. Second, it is really an amazing technological achievement. Third, think of a Neanderthalian female meeting with a Homo sapiens male (or vice-versa)...and mixing their genomes....* —SF

Physiology and Metabolism

Bianco SD, Peng JB, Takanaga H, Suzuki Y, Crescenzi A, Kos CH, Zhuang L, Freeman MR, Gouveia CH, Wu J, Luo H, Mauro T, Brown EM, Hediger MA. Marked disturbance of calcium homeostasis in mice with targeted disruption of the Trpv6 calcium channel gene. *J Bone Miner Res*. 2006 Nov 27; [Epub ahead of print] [Abstract]

> *A dominant calcium channel in intestinal and renal epithelia was removed from mice. Knockout mice have a reduction in intestinal calcium absorption, secondary hyperparathyroidism, high urinary calcium, an inability to concentrate the urine, and alopecia associated with a loss of the calcium gradient across the epidermis. They also have osteoporosis. Interpretation of the phenotype is considerably complicated by the fact that the knockout strategy also removed the EphB6 gene, which is expressed in osteoblasts and is a member of a family that was recently shown to traffic signals between osteoclasts and osteoblasts.* —GJS

Masuyama R, Stockmans I, Torrekens S, Van Looveren R, Maes C, Carmeliet P, Bouillon R, Carmeliet G. Vitamin D receptor in chondrocytes promotes osteoclastogenesis and regulates FGF23 production in osteoblasts. *J Clin Invest*. 2006 Dec;116(12):3150-9. [Abstract] [Full Text]

> *Using Col2-cre, the vitamin D receptor (VDR) was removed from chondrocytes. This led to a mild temporary delay in the terminal differentiation of chondrocytes and a marked increase in trabecular BMD at 15 days. Blood vessel invasion of the growth plate and osteoclast number were reduced, possibly because of reduced expression of VEGF and RANKL, respectively. WT chondrocytes expressed RANKL and supported osteoclast differentiation in vitro in a vitamin D-dependent manner; knockout chondrocytes could not support osteoclast differentiation in vitro. Surprisingly, knockout mice had increased serum phosphate and 1,25(OH)$_2$D concentrations at 15 days, together with a reduction in FGF23 mRNA levels in osteoblasts and serum FGF23 levels. Although most rachitic changes induced by loss of the VDR are reversed by calcium supplementation, the VDR in chondrocytes signals transiently to blood vessels, osteoblasts and, via bone cells, to the kidney.* —GJS

Urakawa I, Yamazaki Y, Shimada T, Iijima K, Hasegawa H, Okawa K, Fujita T, Fukumoto S, Yamashita T. Klotho converts canonical FGF receptor into a specific receptor for FGF23. *Nature*. 2006 Dec 7;444(7120):770-4. [Abstract]

> *When injected, FGF23 induces early gene responses in kidney, parathyroid and pituitary, but not other tissues. These target tissues express the "aging gene" klotho, and Klotho protein directly binds FGF23; moreover, coexpression of Klotho converts one of the canonical FGF receptors, FGFR1(IIIc), to a specific receptor for FGF23. The klotho(-/-) mouse has a syndrome of hyperphosphatemia, high levels and hypercalcemia identical to the FGF23(-/-) mouse, and a similar phenotype can be induced by injection of Klotho antibodies. Klotho is thus a coreceptor for FGF23 and most known aspects of Klotho function are consequences of FGF23 deficiency.* —GJS

Reviews, Perspectives and Editorials

Asagiri M, Takayanagi H. The molecular understanding of osteoclast differentiation. *Bone*. 2006 Nov 10; [Epub ahead of print] [Abstract]

Bilezikian JP. Osteonecrosis of the jaw — do bisphosphonates pose a risk? *N Engl J Med*. 2006 Nov 30;355(22):2278-81. [Info]

Harper KD, Krege JH, Marcus R, Mitlak BH. Osteosarcoma and teriparatide? *J Bone Miner Res*. 2006 Nov 27; [Epub ahead of print] [Info]

Hofbauer LC, Brueck CC, Shanahan CM, Schoppet M, Dobnig H. Vascular calcification and osteoporosis-from clinical observation towards molecular understanding. *Osteoporos Int*. 2006 Dec 7; [Epub ahead of print] [Abstract]

Rauch F, Glorieux FH. Treatment of children with osteogenesis imperfecta. *Curr Osteoporos Rep*. 2006 Dec;4(4):159-64. [Abstract]

Superti-Furga A, Unger S. Nosology and classification of genetic skeletal disorders: 2006 revision. *Am J Med Genet A*. 2006 Nov 21; [Epub ahead of print] [Abstract]

Other Studies of Potential Interest

Abdelmagid SM, Barbe MF, Arango-Hisijara I, Owen TA, Popoff SN, Safadi FF. Osteoactivin acts as downstream mediator of BMP-2 effects on osteoblast function. *J Cell Physiol*. 2007 Jan;210(1):26-37. [Abstract]

Bodine PV, Seestaller-Wehr L, Kharode YP, Bex FJ, Komm BS. Bone anabolic effects of parathyroid hormone are blunted by deletion of the Wnt antagonist secreted frizzled-related protein-1. *J Cell Physiol*. 2007 Feb;210(2):352-7. [Abstract]

Chen Y, Whetstone HC, Youn A, Nadesan P, Chow EC, Lin AC, Alman BA. beta-catenin signaling pathway is crucial for bone morphogenetic protein 2 to induce new bone formation. *J Biol Chem*. 2006 Nov 3; [Epub ahead of print]

De Benedetti F, Rucci N, Del Fattore A, Peruzzi B, Paro R, Longo M, Vivarelli M, Muratori F, Berni S, Ballanti P, Ferrari S, Teti A. Impaired skeletal development in interleukin-6-transgenic mice: a model for the impact of chronic inflammation on the growing skeletal system. *Arthritis Rheum*. 2006 Nov;54(11):3551-63. [Abstract]

Feng Y, Zhao H, Luderer HF, Epple H, Ross FP, Teitelbaum SL, Longmore GD. The LIM protein, LIMD1, regulates AP-1 activation through an interaction with TRAF6 to influence osteoclast development. *J Biol Chem*. 2006 Nov 8; [Epub ahead of print]

Frishberg Y, Ito N, Rinat C, Yamazaki Y, Feinstein S, Urakawa I, Navon-Elkan P, Becker-Cohen R, Yamashita T, Araya K, Igarashi T, Fujita T, Fukumoto S. Hyperostosis - hyperphosphatemia syndrome: a congenital disorder of O-glycosylation associated with augmented processing of fibroblast growth factor 23. *J Bone Miner Res*. 2006 Nov 27; [Epub ahead of print] [Abstract]

Gujral TS, Singh VK, Jia Z, Mulligan LM. Molecular mechanisms of RET receptor-mediated oncogenesis in multiple endocrine neoplasia 2B. *Cancer Res*. 2006 Nov 15;66(22):10741-9. [Abstract]

Iwaniec UT, Wronski TJ, Liu J, Rivera MF, Arzaga RR, Hansen G, Brommage R. Parathyroid hormone stimulates bone formation in mice deficient in Lrp5. *J Bone Miner Res*. 2006 Dec 5; [Epub ahead of print] [Abstract]

Kiel DP, Ferrari SL, Cupples LA, Karasik D, Manen D, Imamovic A, Herbert AG, Dupuis J. Genetic variation at the low-density lipoprotein receptor-related protein 5 (LRP5) locus modulates Wnt signaling and the relationship of physical activity with bone mineral density in men. *Bone*. 2006 Nov 28; [Epub ahead of print] [Abstract]

Liu Y, Bhat RA, Seestaller-Wehr LM, Fukayama S, Mangine A, Moran RA, Komm BS, Bodine PV, Billiard J. The orphan receptor tyrosine kinase Ror2 promotes osteoblast differentiation and enhances ex vivo bone formation. *Mol Endocrinol*. 2006 Nov 9; [Epub ahead of print]

Meadows NA, Sharma SM, Faulkner GJ, Ostrowski MC, Hume DA, Cassady AI. The expression of chloride channel 7 (CLCN7) and OSTM1 in osteoclasts is co-regulated by microphthalmia transcription factor. *J Biol Chem*. 2006 Nov 14; [Epub ahead of print]

Olivotto E, Vitellozzi R, Fernandez P, Falcieri E, Battistelli M, Burattini S, Facchini A, Flamigni F, Santi S, Facchini A, Borzi' RM. Chondrocyte hypertrophy and apoptosis induced by GROalpha require three-dimensional interaction with the extracellular matrix and a co-receptor role of chondroitin sulfate and are associated with the mitochondrial splicing variant of cathepsin B. *J Cell Physiol*. 2007 Feb;210(2):417-27. [Abstract]

Ramnaraine ML, Mathews WE, Donohue JM, Lynch CM, Goblirsch MJ, Clohisy DR. Osteoclasts direct bystander killing of bone cancer. *Cancer Res*. 2006 Nov 15;66(22):10929-35. [Abstract]

Riancho JA, Valero C, Zarrabeitia MT. MTHFR polymorphism and bone mineral density: meta-analysis of published studies. *Calcif Tissue Int*. 2006 Nov;79(5):289-93. [Abstract]

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Xiao Z, Camalier CE, Nagashima K, Chan KC, Lucas DA, Cruz MJ, Gignac M, Lockett S, Issaq HJ, Veenstra TD, Conrads TP, Beck GR Jr. Analysis of the extracellular matrix vesicle proteome in mineralizing osteoblasts. *J Cell Physiol*. 2007 Feb;210(2):325-35. [Abstract]

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Zhang Y, Ge G, Greenspan DS. Inhibition of bone morphogenetic protein 1 by native and altered forms of alpha 2-macroglobulin. *J Biol Chem*. 2006 Dec 22;281(51):39096-104. [Abstract] [Full Text]

Conflict of Interest: Dr. Ferrari reports that he receives research support from Amgen and consultancy/speaker's fees from Merck Sharp & Dohme, Eli Lilly, and Amgen. Dr. Seeman reports that he is an advisory committee member for

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Sanofi-Aventis, Eli Lilly, Merck Sharp & Dohme, Novartis, and Servier, and that he lectures occasionally at conference symposia for those companies. Dr. Strewler reports that no conflict of interest exists.