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NOT TO BE MISSED

Clinical and Basic Research Papers – June 2007 Selections

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

Bone Modeling and Remodeling

Buckbinder L, Crawford DT, Qi H, Ke HZ, Olson LM, Long KR, Bonnette PC, Baumann AP, Hambor JE, Grasser WA, Pan LC, Owen TA, Luzzio MJ, Hulford CA, Gebhard DF, Paralkar VM, Simmons HA, Kath JC, Roberts WG, Smock SL, Guzman-Perez A, Brown TA, Li M. Proline-rich tyrosine kinase 2 regulates osteoprogenitor cells and bone formation, and offers an anabolic treatment approach for osteoporosis. *Proc Natl Acad Sci U S A*. 2007 Jun 19;104(25):10619-24. [Abstract] [Full Text]

> *Coupling mechanisms are not well-defined. Proline-rich tyrosine kinase 2 (PYK2) mediates osteoclast function. PYK2(-/-) mice have increases in bone formation. Marrow cultures show that PYK2 deficiency enhances the differentiation and activity of osteoprogenitor cells, as does expressing a PYK2-specific short hairpin RNA or dominantly interfering proteins in human mesenchymal stem cells. Administration of a PYK2 inhibitor increases bone formation. PYK2 regulates the differentiation of early osteoprogenitor cells. Inhibitors of PYK2 may have potential as anabolic agents*. —ES

Chen S, Takanashi S, Zhang Q, Xiong W, Zhu S, Peters EC, Ding S, Schultz PG. Reversine increases the plasticity of lineage-committed mammalian cells. *Proc Natl Acad Sci U S A*. 2007 Jun 19;104(25):10482-7. [Abstract] [Full Text]

> *Reversine is a protein that reverses lineage-committed murine myoblasts to a more primitive multipotent state. The authors report that reversine increases the plasticity of C2C12 myoblasts and that reversine-treated cells gain the ability to differentiate into osteoblasts and adipocytes*. —ES

Tatsumi S, Ishii K, Amizuka N, Li M, Kobayashi T, Kohno K, Ito M, Takeshita S, Ikeda K. Targeted ablation of osteocytes induces osteoporosis with defective mechanotransduction. *Cell Metab*. 2007 Jun;5(6):464-75. [Abstract]

> *When osteocytes are modified by targeting diphtheria toxin receptors to them, using the DMP-1 promoter, and then ablated, there is loss of trabecular and cortical bone and increased cortical porosity. The synthetic and mineralizing function of osteoblasts is impaired. Moreover, bone is no longer lost in response to tail suspension, suggesting that osteocytes play a key role in mechanotransduction in this model.* —GJS

Epidemiology

Kalkwarf HJ, Zemel BS, Gilsanz V, Lappe JM, Horlick M, Oberfield S, Mahboubi S, Fan B, Frederick MM, Winer K, Shepherd JA. The bone mineral density in childhood study: bone mineral content and density according to age, sex, and race. *J Clin Endocrinol Metab*. 2007 Jun;92(6):2087-99. [Abstract] [Full Text]

In 2000, the NIH launched an initiative to collect normative BMD data for children. This publication now reports BMD for several skeletal sites (and whole body BMC) measured by Hologic DXA in healthy children aged 6-16 yrs from various ethnic groups across the US. With more than 100 non-black subjects for each year of age for both males and females, this publication will serve as the new reference data for BMD (and WB BMC) in children and should be implemented by the manufacturers to calculate Z-scores by age. A strong debate now will be to determine whether or not BMD (and WB BMC) Z-scores should be further corrected for body and/or bone size and shape to account (or not) for low Z-scores in children who are relatively small for their age. —SF

Pathophysiology

Ochi S, Shinohara M, Sato K, Gober HJ, Koga T, Kodama T, Takai T, Miyasaka N, Takayanagi H. Pathological role of osteoclast costimulation in arthritis-induced bone loss. *Proc Natl Acad Sci U S A*. 2007 Jul 3;104(27):11394-99. [Abstract] [Full Text]

Costimulation by Ig-like receptors and their cognate adaptor proteins is important for osteoclast function. This paper reports that bone loss in a mouse model of arthritis induced by expression of human TNF-α is dependent upon induction of the Ig-like receptor paired Ig-like receptor-A (PIR-A). Erosions and bone loss were ameliorated in mice deficient in Fc receptor common γ-subunit or β_2-microglobulin, in which the expression of PIR-As and PIR-A ligands, respectively, is impaired. Some of the effects of TNF-α on osteoclasts are mediated by costimulation. —GJS

Physiology and Metabolism

Imura A, Tsuji Y, Murata M, Maeda R, Kubota K, Iwano A, Obuse C, Togashi K, Tominaga M, Kita N, Tomiyama K, Iijima J, Nabeshima Y, Fujioka M, Asato R, Tanaka S, Kojima K, Ito J, Nozaki K, Hashimoto N, Ito T, Nishio T, Uchiyama T, Fujimori T, Nabeshima Y. alpha-Klotho as a regulator of calcium homeostasis. *Science*. 2007 Jun 15;316(5831):1615-8. [Abstract] [Full Text]

When it comes to calcium and phosphate metabolism, there is no doubt that klotho is a partner of FGF23, but does it have additional roles? Imura et al. report that in choroid plexus, parathyroids and kidney, klotho is secreted in response to a low extracellular calcium concentration. Moreover, klotho is involved in recruiting a fraction of Na^+,K^+-ATPase to the plasma membrane and, possibly through this mechanism, is required for robust secretion of PTH in response to hypocalcemia. It isn't clear from all of this whether klotho has a significant role independent of FGF23 in calcium homeostasis. —GJS

Treatment and Drug Effects

Amanat N, McDonald M, Godfrey C, Bilston L, Little D. Optimal timing of a single dose of zoledronic acid to increase strength in rat fracture repair. *J Bone Miner Res*. 2007 Jun;22(6):867-76. [Abstract]

Most orthopedic surgeons are afraid of early administration of a bisphosphonate, which could be deleterious to fracture repair. In this nice rat model, the distribution of zoledronic acid at the fracture repair site (callus) is shown, together with an increase in strength after a single injection. These data are of interest in anticipation of the results from a recently completed human study. —SF

Bruyere O, Roux C, Detilleux J, Slosman DO, Spector TD, Fardellone P, Brixen K, Devogelaer JP, Diaz-Curiel M, Albanese C, Kaufman JM, Pors-Nielsen S, Reginster JY. Relation between bone mineral density changes and fracture risk reduction in patients treated with strontium ranelate. *J Clin Endocrinol Metab*. 2007 Jun 12; [Epub ahead of print]

> *No more than 4-30% of the risk reduction is explained by the increase in BMD following anti-resorptive therapy. Bruyere et al. report that in women receving strontium ranelate, after 3 years, changes in femoral neck and total proximal femur BMD explained 76% and 74%, respectively, of the reduction in vertebral (but not non-vertebral) fractures. Three-year changes in spine BMD were not associated with vertebral fracture. The mechanism may relate to the incorporation of strontium into hydroxyapatite, perhaps contributing in part to its anti-fracture efficacy. These issues will need further study. Whether patients who do not have a rise in BMD with strontium ranelate have a fracture risk reduction is not clear.* —ES

Guo RT, Cao R, Liang PH, Ko TP, Chang TH, Hudock MP, Jeng WY, Chen CK, Zhang Y, Song Y, Kuo CJ, Yin F, Oldfield E, Wang AH. Bisphosphonates target multiple sites in both cis- and trans-prenyltransferases. *Proc Natl Acad Sci U S A*. 2007 Jun 12;104(24):10022-7. [Abstract] [Full Text]

> *Bisphosphonates may not all be the same. Some inhibit farnesyl diphosphate synthase (FPPS), thus decreasing prenylation of GTPases. Others also inhibit geranylgeranyl diphosphate synthase (GGPPS), as well as undecaprenyl diphosphate synthase (UPPS), a cis-prenyltransferase. For GGPPS, there are three bisphosphonate-binding sites, consisting of FPP or isopentenyl diphosphate substrate-binding sites together with a GGPP product- or inhibitor-binding site. In UPPS, there are four binding sites. These results provide the structures of GGPPS- and UPPS-inhibitor complexes, potentially important drug targets, in addition to revealing a broad spectrum of binding modes not seen in FPPS inhibition.* —ES

Samadfam R, Xia Q, Goltzman D. Pretreatment with anticatabolic agents blunts but does not eliminate the skeletal anabolic response to parathyroid hormone in oophorectomized mice. *Endocrinology*. 2007 Jun;148(6):2778-87. [Abstract] [Full Text]

> *Experiments in rats and mice have shown that, combined with intermittent PTH, alendronate or osteoprotegerin (OPG), two potent inhibitors of bone resorption and/or osteoclastogenesis, have additive effects on bone mass and microarchitecture. Others, however, have provided arguments that some osteoclastic functions might be useful for PTH anabolic effects. This study now shows that pre-treatment with OPG blunted the activity of later PTH treatment, particularly when OPG was continued during PTH treatment. These results differ from the combined effects of the two molecules added simultaneously at the beginning of treatment, i.e., when osteoclastogenesis has not yet been abated by the antiresorptive agent. In this study, moreover, biochemical bone turnover markers and histomorphometrical indices of bone formation in response to PTH were suppressed in the presence of OPG. Although the osteoclastic function(s) that is actually needed for full-blown PTH activity remains unclear, this study adds some arguments in favor of osteoclast-osteoblast coupling for PTH activity*. —SF

Reviews, Perspectives and Editorials

Canalis E, Mazziotti G, Giustina A, Bilezikian JP. Glucocorticoid-induced osteoporosis: pathophysiology and therapy. *Osteoporos Int*. 2007 Jun 14; [Epub ahead of print] [Abstract]

Holick MF. Vitamin D deficiency. *N Engl J Med*. 2007 Jul 19;357(3):266-81. [Info]

Horton WA, Hall JG, Hecht JT. Achondroplasia. *Lancet*. 2007 Jul 14;370(9582):162-72. [Abstract]

Manolagas SC, Almeida M. Gone with the Wnts: beta-catenin, TCF, FOXO, and oxidative stress in age-dependent diseases of bone, lipid, and glucose metabolism. *Mol Endocrinol*. 2007 Jul 10; [Epub ahead of print]

Nemere I. The ins and outs of phosphate homeostasis. *Kidney Int*. 2007 Jul;72(2):140-2. [Abstract]

Other Studies of Potential Interest

Aguirre JI, Plotkin LI, Gortazar AR, Martin Millan M, O'brien CA, Manolagas SC, Bellido T. A novel ligand-independent function of the estrogen receptor is essential for osteocyte and osteoblast mechanotransduction. *J Biol Chem*. 2007 Jul 3; [Epub ahead of print]

Berndt T, Thomas LF, Craig TA, Sommer S, Li X, Bergstralh EJ, Kumar R. Evidence for a signaling axis by which intestinal phosphate rapidly modulates renal phosphate reabsorption. *Proc Natl Acad Sci U S A*. 2007 Jun 26;104(26):11085-11090. [Abstract] [Full Text]

Datta NS, Pettway GJ, Chen C, Koh AJ, McCauley LK. Cyclin D1 as a target for the proliferative effects of PTH and PTHrP in early osteoblastic cells. *J Bone Miner Res*. 2007 Jul;22(7):951-64. [Abstract]

Dvorak MM, Chen TH, Orwoll B, Garvey C, Chang W, Bikle DD, Shoback DM. Constitutive activity of the osteoblast Ca2+-sensing receptor promotes loss of cancellous bone. *Endocrinology*. 2007 Jul;148(7):3156-63. [Abstract] [Full Text]

Fulzele K, Digirolamo DJ, Liu Z, Xu J, Messina JL, Clemens TL. Disruption of the IGF-1 receptor in osteoblasts enhances insulin signaling and action. *J Biol Chem*. 2007 Jun 6; [Epub ahead of print]

Hamrick MW, Shi X, Zhang W, Pennington C, Thakore H, Haque M, Kang B, Isales CM, Fulzele S, Wenger KH. Loss of myostatin (GDF8) function increases osteogenic differentiation of bone marrow-derived mesenchymal stem cells but the osteogenic effect is ablated with unloading. *Bone*. 2007 Jun;40(6):1544-53. [Abstract]

Park SJ, Kim SJ, Rhee Y, Byun JH, Kim SH, Kim MH, Lee EJ, Lim SK. Fidgetin-like 1 gene inhibited by basic fibroblast growth factor regulates the proliferation and differentiation of osteoblasts. *J Bone Miner Res*. 2007 Jun;22(6):889-96. [Abstract]

Plotkin LI, Manolagas SC, Bellido T. Glucocorticoids induce osteocyte apoptosis by blocking focal adhesion kinase-mediated survival: Evidence for inside-out signaling leading to anoikis. *J Biol Chem*. 2007 Jun 20; [Epub ahead of print]

Wang G, Woods A, Agoston H, Ulici V, Glogauer M, Beier F. Genetic ablation of Rac1 in cartilage results in chondrodysplasia. *Dev Biol*. 2007 Jun 15;306(2):612-23. [Abstract]

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Yagi M, Ninomiya K, Fujita N, Suzuki T, Iwasaki R, Morita K, Hosogane N, Matsuo K, Toyama Y, Suda T, Miyamoto T. Induction of DC-STAMP by alternative activation and downstream signaling mechanisms. *J Bone Miner Res*. 2007 Jul;22(7):992-1001. [Abstract]

Zwerina J, Redlich K, Polzer K, Joosten L, Krönke G, Distler J, Hess A, Pundt N, Pap T, Hoffmann O, Gasser J, Scheinecker C, Smolen JS, van den Berg W, Schett G. TNF-induced structural joint damage is mediated by IL-1. *Proc Natl Acad Sci U S A*. 2007 Jul 10;104(28):11742-7. [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 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.